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Original Article

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

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ABSTRACT

Background: Brain iron deficiency has been implicated in the pathophysiology of RLS, and current RLS treatment guidelines recommend iron treatment when peripheral iron levels are low. In order to assess the evidence on the oral and intravenous (IV) iron treatment of RLS and periodic limb movement disorder (PLMD) in adults and children, the International Restless Legs Syndrome Study Group (IRLSSG) formed a task force to review these studies and provide evidence-based and consensus guidelines for the iron treatment of RLS in adults, and RLS and PLMD in children.

Methods: A literature search was performed to identify papers appearing in MEDLINE from its inception to July 2016. The following inclusion criteria were used: human research on the treatment of RLS or periodic limb movements (PLM) with iron, sample size of at least five, and published in English. Two task force members independently evaluated each paper and classified the quality of evidence provided.

Results: A total of 299 papers were identified, of these 31 papers met the inclusion criteria. Four studies in adults were given a Class I rating (one for IV iron sucrose, and three for IV ferric carboxymaltose); only Class IV studies have evaluated iron treatment in children. Ferric carboxymaltose (1000 mg) is effective for treating moderate to severe RLS in those with serum ferritin <300 μg/l and could be used as first-line treatment for RLS in adults. Oral iron (65 mg elemental iron) is possibly effective for treating RLS in those with serum ferritin ≤75 μg/l. There is insufficient evidence to make conclusions on the efficacy of oral iron or IV iron in children.

Conclusions: Consensus recommendations based on clinical practice are presented, including when to use oral iron or IV iron, and recommendations on repeated iron treatments. New iron treatment algorithms, based on evidence and consensus opinion have been developed.

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1. Introduction

Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED), is a common neurological disorder, which significantly impacts quality of life, sleep, and health [1,2]. There is substantial evidence implicating brain iron deficiency in the pathophysiology of RLS [3,4], and current RLS treatment guidelines recommend the assessment of iron status and iron treatment when peripheral iron levels are low [5–8]. In recent years there has also been an increase in the number of scientific and clinical studies on the oral and intravenous (IV) iron treatment of RLS and periodic limb movement disorder (PLMD). In order to assess these data, the International Restless Legs Syndrome Study Group (IRLSSG) formed a task force to review these studies and provide, in this paper, updated evidence-based and consensus guidelines for the iron treatment of RLS in adults, and RLS and PLMD in children.

2. Iron regulation pertinent to understanding the role of iron treatment in RLS

Before establishing iron treatment guidelines for RLS, it is first necessary to recognize several unique features of iron biology and homeostasis, which affect treatment goals, methods of delivery, treatment response times, and the need for repeated treatment.

2.1. Iron biology

Iron in biological material exists in one of two forms: ferric (Fe^{3+}) and ferrous (Fe^{2+}), the latter being the most reactive (for a review see, Aisen et al. [9]). Iron transported in blood is primarily bound to transferrin, while cellular iron is stored primarily in the large globular protein, ferritin [10]. Serum ferritin appears to be secreted mostly by monocytic/macrophage cells [11] and may function to provide high volume iron loads to selected organs, such as the brain, independently of the transferrin-based iron transport system [12,13]. Serum ferritin, which is usually a reasonable measure of erythron[1]/macrophage iron status, is commonly used to guide oral iron therapy for iron deficiency (ID) anemia [14]. However, as an acute phase reactant, serum ferritin increases independently of iron status with any level of inflammation [14], often returns to normal range at 4 weeks but may remain elevated for more than 5 weeks after onset of inflammation [15,16]. Serum ferritin also increases, independently of iron status, with age and decreasing glomerular filtration rate [17,18]. While adequate body iron levels are required to support essential functions in all cells, iron overload causes serious toxic responses in cells and organs. Thus, iron homeostasis is highly regulated [10].

2.2. Iron homeostasis

Iron regulation in humans relies mainly on recycling body iron and controlling iron uptake (see reviews [10,17,19]). Approximately 10% of the usual daily 10–20 mg of dietary oral iron consumption is absorbed into the body. Dietary iron is actively controlled at the level of the intestinal epithelium and vascular endothelium. Once in the blood, the vast majority of iron (75% or more) goes to the erythron for red blood cell (RBC) production, with about 10–20% going to iron storage pools (mostly to liver, reticuloendothelial system [macrophages] and muscle). The macrophage is the primary source of iron, which is recycled to other organs, including brain, whether obtained directly from the blood or from iron recycled from senescent red blood cells [10]. Only 5–15% of newly absorbed iron (0.5–1.5% of the iron consumed orally), is available for transport to organs such as in the kidneys, heart or brain [10,17]. The rate of iron absorption is primarily regulated by hepcidin that serves to block the uptake of iron from the gastrointestinal mucosa, macrophages, and from the liver into the blood [20]. Increases in blood or liver iron stimulate the production of hepcidin, as does an increase in inflammatory factors [20]. This causes a reduction in gastrointestinal iron absorption, thereby limiting the utility of oral non-heme iron in further increasing body iron stores (see Fig. 1) [10].

Iron homeostatic mechanisms are, however, organ specific and under the control of complex genetics [21–23], this complicates the determination of the iron status of an organ. Iron status first became clinically relevant as an indication of anemia, and later, to a lesser extent, iron overload. Efforts to produce reliable measures of iron status have been exclusively based on the iron status of the erythron [18]. The clinical use of the term “iron deficiency” (ID) is based on bone-marrow-determined iron concentrations with hemoglobin (Hgb) and other serum measures of iron status developed as correlates of bone-marrow iron. Thus, clinical measures of body iron stores, including serum iron, transferrin saturation, and serum ferritin, reflect primarily the iron status of the erythron [18]. When ID is defined by a conservative serum-based, bone-marrow-defined measure (e.g., transferrin saturation <16%), then the prevalence of ID, with or without anemia, is reported to be 16% in menstruating women in the USA [24]. However, if liver iron stores are used, autopsy data indicate that ID among menstruating women is 50% in the USA [25]. Serum measures and criteria used in clinical practice to define “iron deficiency” provide a good to very good measure of the iron status in the erythron, but serum measures have not been validated as measures of iron status in other organs.

Iron homeostasis in the brain is regionally regulated through an interaction of local cellular energy demand and blood brain barrier accessibility [26]. All of these mechanisms are subservient to complex genetic determinants, circadian processes and, most importantly, the availability of iron in the body [27–29]. Iron is actively taken up into the brain on a minute by minute basis [30], even in areas with apparently adequate iron stores [28]. This “demand” for more iron appears to be under the influence of circadian dynamics [28,31] and thus presumably follows circadian fluctuations in energy/metabolic demand [32]. Despite the existence of general concepts of the mechanisms involved in homeostatic regulation of iron in the brain, there are no adequate measures of local cellular brain iron requirements, and no measure on an individual-by-individual basis of how any one of these mechanisms or genetic factors affect brain iron stores. Animal data have shown that serum iron and related indices reflect brain iron status very poorly, with genetic variations producing large differences in the blood–brain iron regulation for individual animals [27]. Measures of iron-related serum factors provide information about their primary source: erythron, macrophage, and liver, but bear minimal, if any, relation to regional brain iron. Extrapolating from animal data it can be said for humans that (1) systemic ID will reduce brain iron in select regions in some individuals, (2) some individuals with normal serum iron levels may still have relatively insufficient regional brain iron, and (3) serum measures of peripheral iron status are unlikely to be related to regional brain iron, and thus poorly related to RLS expression.

2.3. Rationale for iron treatment of RLS

Several studies have shown that lower ferritin is associated with increased RLS severity [33,34]. Severe ID to the point of anemia is

[1] Erythron is the name given to the collection of all stages of erythrocytes throughout the body and this includes the developing precursors in bone marrow and the circulating mature erythrocytes in the peripheral blood, therefore erythron is the entirety of erythroid cells in the body.

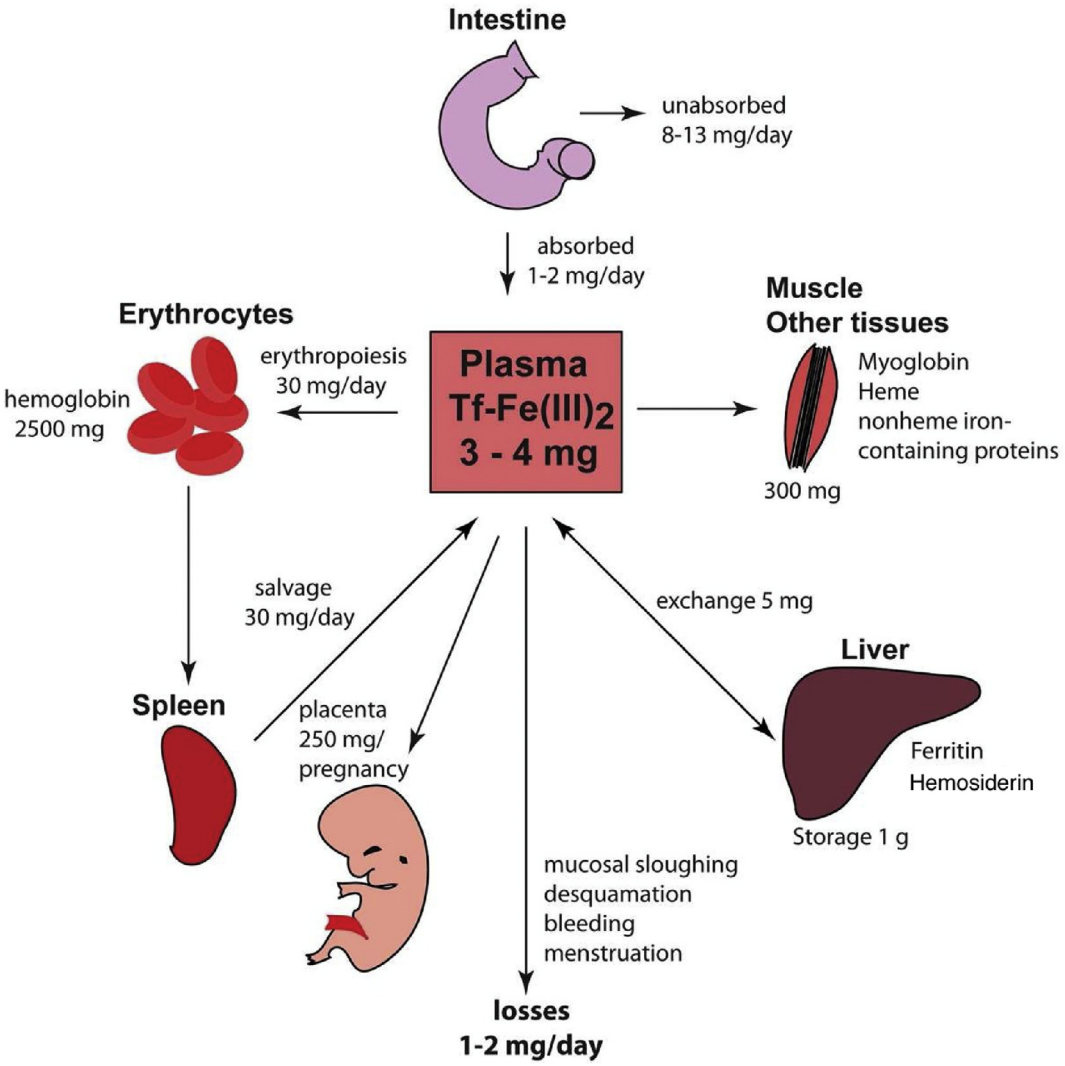


Fig. 1. Iron absorption, distribution, and recycling in the body and quantitative exchange of iron between body iron sources. Reprinted with permission from Ref. [10]. Copyright (2017) American Chemical Society. Body iron levels are maintained by daily absorption of ~1–2 mg of dietary iron to account for obligatory losses of a similar amount of iron through sloughing of mucosal and skin cells, hemorrhage, and other losses. Approximately 4 mg of iron is found in circulation bound to Tf, which accounts for 0.1% of the total body iron. The majority of the body iron is found in the erythroid compartment of bone marrow and in mature erythrocytes contained within the heme moiety of the hemoglobin. Splenic reticuloendothelial macrophages, which recycle iron from senescent red blood cells, provide iron for the new red blood cell synthesis. Tf delivers iron to developing erythroid precursors, as well as to other sites of iron utilization. Liver hepatocytes store iron in ferritin shells. During pregnancy, 250 mg of iron is transported across the placenta to the fetus. The distribution of iron in the body is altered in iron deficiency and iron overload.

associated with a six-fold increase in the prevalence of RLS [35]. Patients with RLS who are not anemic and have normal peripheral iron stores, have been found to have reductions in brain iron relative to normal controls [36–38]. This brain-specific alteration in iron homeostasis is also considered a putative cause of dopamine abnormalities seen in RLS [39]. Therefore, unlike current FDA-approved medications for RLS, which only treat symptoms, iron therapy seeks to correct the underlying relative brain iron deficiency and thus correct a putative major cause of RLS [39]. RLS symptoms may reflect an underlying brain iron deficiency in some patients, but the decisions regarding iron treatment involve multiple factors as described below.

2.3.1. Oral iron

The benefits of oral iron are limited by lack of compliance often due to gastrointestinal upset [14] and by restriction on absorption under certain conditions [40]. As iron absorption is highly correlated with erythropoiesis [41], as long as there are sufficient iron stores for red blood cell (RBC) production, there will be hepcidin-dependent limitations on iron absorption [20]. As an example of the effects of iron stores (as determined by serum ferritin levels) on iron absorption, approximately 20% of oral non-heme iron is absorbed when ferritin is about 10 μg/l but as little as 1–2% absorption when ferritin is between 50 and 75 μg/l [42]. Therefore, administering oral iron when serum ferritin is greater than 75–100 μg/l is likely to have very limited benefits within a reasonable, clinically meaningful period of time.

2.3.2. Intravenous (IV) iron

IV iron bypasses the gastrointestinal-based regulation of oral iron absorption. Iron given intravenously is taken up predominately by the erythron, liver and macrophages [43]. As the macrophages are the primary source of redistributing iron to the other organs [17], including brain, the amount of iron taken up by the macrophages during the initial iron loading period may be relevant in determining when and/or how much iron reaches the brain. There

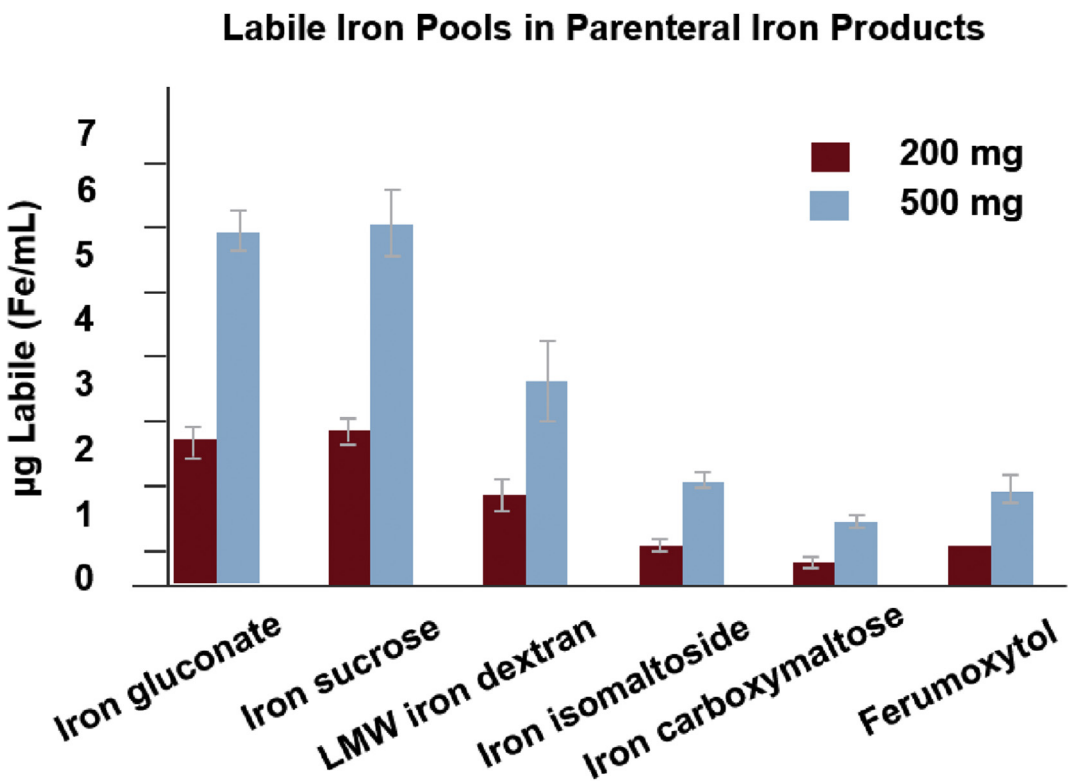


Fig. 2. Labile 'free' iron pool in serum for currently available IV iron formulations: averages and variances from at least 4 measures. Note that the labile iron for 500 mg of the slower release formulations (isomaltoside, carboxymaltose, ferumoxytol) is less than that for the 200 mg faster release formulations (gluconate, sucrose). Reprinted with permission from Ref. [109].

are differences in the uptake of the different IV formulations by the macrophages [44], as well as different rates at which the iron is released from the carrier carbohydrate into the blood. Those with faster release (iron sucrose and iron gluconate) require administration at lower doses in order to avoid overwhelming available transferrin, and thereby producing excessive, and toxic, free or labile iron. The lower doses are repeated over several days to obtain the desired total dose. Conversely, compounds that release iron more slowly over many hours (low molecular weight iron dextran, ferric carboxymaltose, ferumoxytol, and iron isomaltoside) allow more iron to be taken up by transferrin, and produce less labile iron (Fig. 2). The slow-release compounds also show greater increases in macrophage iron concentrations compared to the fast-release compounds [44]. The slow-release compounds can be given in one or two repeated administrations (see Table 1 for a list of available IV iron formulations and their basic characteristics).

Although the first documented use of IV iron for RLS treatment was by Nordlander in 1953 [45], this treatment, despite remarkable success, was largely forgotten. More recent cerebrospinal fluid (CSF) ferritin studies provided a scientific rationale reviving interest in IV iron treatment of RLS [36,37]. CSF ferritin was found to be lower in RLS than controls, and also positively correlated with serum ferritin [37]. The serum-CSF ferritin correlation in RLS was shown to shift downwards and have a slightly lower slope (Fig. 3). This correlation suggests that if serum ferritin values could be increased to more than 200 µg/l in RLS patients, iron concentrations in the brain might reach levels seen in normal controls (Fig. 3). These data are, however, only cross-sectional with large individual variations limiting the use of serum or CSF values in guiding treatment on an individual basis. Moreover, CSF ferritin is likely to have a limited relation to regional brain iron. These data, nonetheless, support the concept that increasing peripheral iron stores could potentially lead to an increase in brain iron with a subsequent reduction of symptoms. These higher levels of peripheral iron, which appear to be required, could be achievable with IV iron but are unlikely to be attainable with oral iron given the highly regulated absorption of iron at the level of the gastrointestinal tract. This led to studies using IV iron treatment for RLS described in this report.

Some strains of mice have been found to have normal Hgb concentrations and normal peripheral iron stores, yet have lower brain iron concentrations similar to that seen in RLS [27]. These animals have been used as a model for understanding the discordant relation between peripheral iron and the region-specific brain iron concentrations seen in RLS pathology [39]. A study using this animal model demonstrated the ability of 1000-mg-human-dose-equivalency of IV iron to correct brain-region-specific iron deficiency without affecting other brain regions and without causing iron overload [28]. This study supports the concept of increasing peripheral iron stores in RLS in order to selectively improve brain-region-specific iron deficiency and helps temper concerns about non-specific brain iron overload.

3. Methods for establishing recommendations

A panel of experts was approved in July 2016 by the IRLSSG Executive Committee to provide recommendations on the iron treatment of RLS in children and adults. The task force was composed of the 12 authors of this paper, with emphasis on broad representation, including clinical sleep medicine, RLS research, hematology, neuroscience, pediatrics, and international sleep medicine. The committee had extensive e-mail correspondence, telephone conferences, and a single face-to-face meeting in Bilbao, Spain, in September 2016. A conflict of interest statement of each of the members can be consulted in Appendix 1.

Table 1
Intravenous iron formulations currently available.

Trade name(s)	INFeD[a]	Ferrlecit[b]	Venofer[c]	Feraheme[d] (Ferumoxytol)	Monofer[e]	USA: Injectafer[f,*] Not USA: Ferinject[g]
Generic name	LMW dextran	Iron gluconate	Iron sucrose	Ferumoxytol	Iron isomaltoside 1000	Ferric carboxymaltose
Distributor	Watson Pharmaceuticals Inc.	Sanofi Aventis Inc.	American Regent Inc.	AMAG Pharmaceuticals	Pharmacosmos A/S **Europe Only**	USA: American Regent Inc Not USA: Vifor Pharma
Molecular weight measured by manufacturer (Da)	165,000 Low-Molecular-weight iron dextran	289,000–444,000	34,000–60,000	750,000	150,000	150,000
Labeled dosage (mg)	100	125	Adult: 200 Pediatric: 100	510	20 mg/kg	USA: 750 mg Europe: 1000 mg
Doses for RLS	1000 mg single dose	100 mg 8 doses 5–7 days apart	1000 mg 5 doses 3–4 days apart	1000 mg single dose	1000 mg single dose	USA: 1500 mg (if weight >50 kg) 2 doses: 5–7 days apart Europe: single dose 1000 mg
Dose administration	IV infusion 1 h (usually with 250 ml normal saline)	Slow IV 10 m	Slow IV 2–5 m	Slow IV 1–2 m	Slow IV 15 m	Slow IV 7.5 m
Test dose required	Yes	No	No	No	No	No
Iron concentration (mg/ml)	50	12.5	20	30	100	50
Vial volume (ml)	2	5	5	17	1, 5 & 10 in Europe	2 and 10 in Europe, 15 US
Black box warning	Yes	No	No	Yes	N/A	No
Preservative	None	Benzyl alcohol	None	None	None	None

Abbreviations: N/A, not available; TDI, total-dose infusion. *Injectafer is marketed outside the US under the brand name Ferinject.
[a] INFeD Prescribing Information. Morristown, NJ: Watson Pharmaceuticals, Inc.
[b] Ferrlecit Prescribing Information. Bridgewater, NJ: Sanofi Aventis, Inc, Venofer Prescribing Information. Shirley, NY: American Regent, Inc.
[c] Venofer Prescribing information http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/pediatricadvisorycommittee/ucm437786.pdf downloaded 30 Jan 17.
[d] Feraheme Prescribing Information. Lexington, MA: AMAG, Inc, Monofer data on file. Holbaek, Denmark: Pharmacosmos A/S.
[e] Monofer FDA Advisory Committee Briefing Document, Drug Safety and Risk Management Committee, February 1, 2008.
[f] Injectafer prescribing information from http://www.injectafer.com/pdf/pi.pdf downloaded 30 Jan 17.
[g] Ferinject prescribing information from http://www.ferinject.co.uk/prescribing-information/downloaded 30 Jan 17.

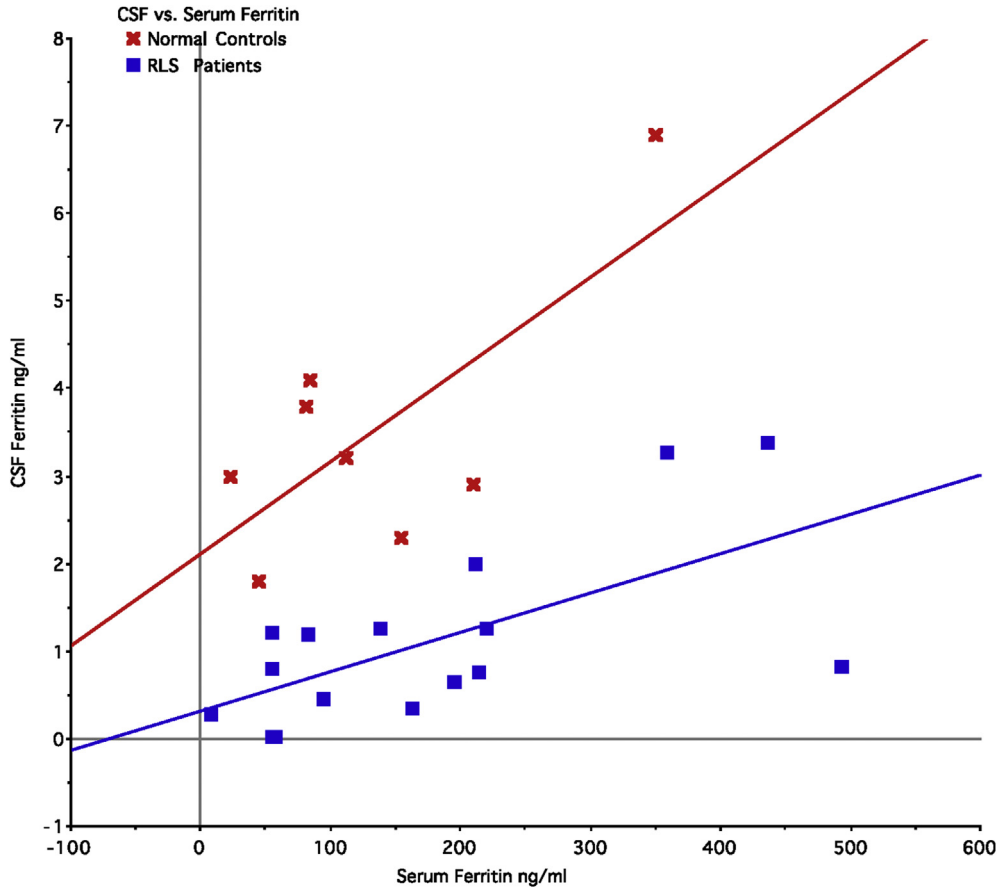


Fig. 3. CSF vs. serum ferritin for RLS patients and age and gender matched healthy adults without RLS. Reprinted with permission from Ref. [37]. Note significant correlations between CSF and serum ferritin for controls ($r = 0.72$, $p < 0.05$) and RLS ($r = 0.64$, $p < 0.01$) but also the wide individual variability. Overall increased serum ferritin indicates higher values for CSF ferritin, but the lowest normal CSF ferritin range occurs for those with serum ferritin >200 μg/l.

A formal literature review was performed to identify published papers (meta-analyses, randomized trials, cohort studies, case–control, and observational studies) appearing in the National Library of Medicine's MEDLINE database from its inception to July 15, 2016 using the MeSH search phrase "("restless legs" OR "periodic limb movement") AND iron AND treatment". In addition, expert panel members were asked if they were aware of any submitted papers. One paper [46] identified by the panel as "submitted" but only available as a program abstract was accepted and reviewed based on an available "in press" version. This search strategy identified 299 articles. Abstracts were reviewed to determine if the following inclusion criteria were met: human research on the treatment of RLS or periodic limb movements (PLM) with iron, sample size of at least five, and published in English. Based on the literature search and checking of reference sections for any articles otherwise missed ("pearling"), 31 papers were retained: 24 reported iron treatment of adult RLS (four oral, 20 IV) and seven of pediatric RLS and/or periodic limb movements (six oral, 1 IV). An in-depth review of the safety of oral and IV iron treatments was also performed. The age of the subjects was 11 months to 82 years.

Two task force members independently evaluated each paper using a data template created specifically for this purpose by the task force. American Association of Neurology (AAN) rules were used to classify each article according to the quality of the evidence provided (e-Table 1) [47] and to make evidence-based recommendations—with Level A reflecting strong evidence, Level B reflecting moderate evidence, Level C reflecting weak evidence, and Level U representing insufficient evidence to support or refute the use of an intervention (e-Table 1). Any disagreements in classification were identified and resolved by the two primary reviewers. A listing of the major findings for each paper evaluated is provided in evidence (e-Table 2) for adults, and (e-Table 3) for children. In addition to evidence-based recommendations, the task force made clinical recommendations based on expert clinical opinion. Evidence-based and expert-consensus recommendations were discussed at the face-to-face meeting, and guidelines were established. A consensus was considered to be a majority of the 10 task force members present at the face-to-face meeting.

After approval of the written report by all task force members, the recommendations were forwarded to the IRLSSG executive committee for review.

4. Diagnosis, disease severity and outcomes used in treatment studies

4.1. RLS diagnosis

RLS is a clinical diagnosis based on the guidelines provided by the IRLSSG as published in 2003 [48] for older studies, or the updated version published in 2014 [49], for newer studies. In almost all studies, clinicians responsible for the study made the diagnosis following these guidelines. Clinicians in some very old studies, however, relied on a preliminary version of the RLS diagnosis published in 1995 [50] or on general clinical descriptions in the literature such as that provided by Ekbom's seminal work describing RLS [51]. Information about each study's diagnostic standards is included in the tables.

4.2. RLS severity and impact assessment

Treatment efficacy was determined for each study based on the *a priori* primary treatment outcome(s) evaluated in the study. The efficacy evaluation, therefore, differs somewhat according to the outcomes used. Fortunately, most studies had a primary outcome of either the IRLS severity scale completed by the patient with clinician supervision [52,53], or one of the clinical global impression scales (CGI) completed by the clinician [54]. These scales base efficacy primarily on reduction of the main RLS sensory symptoms, but also include some consideration of changes in the impact of RLS on sleep and quality of life (one question for each among the 10 on the IRLS). Often, sleep was assessed by various scales, the most common being the Medical Outcomes Study (MOS) sleep scale [55,56]. Sleep lab evaluation was also used in a few studies, usually with a focus on changes in the primary motor sign of RLS, i.e., periodic leg movements of sleep (PLMS). PLMS provide the only objective evaluation of treatment response related to the primary features or RLS. For children, in particular, PLMS are obtained for diagnosis as well as treatment evaluation, since, unlike adults, PLMS are both sensitive and specific for RLS diagnosis. e-Tables e2 and e3 indicate the primary outcomes used to evaluate efficacy for each study.

5. Evidence- and consensus-based guidelines: adults

5.1. Guidelines for oral iron treatment for adults with RLS

5.1.1. Evidence-based guidelines

Oral iron as ferrous sulfate 325 mg (65 mg elemental iron) twice a day with 100 mg Vitamin C twice a day is possibly effective (level C) for treating RLS for patients with a serum ferritin $\leq$75 μg/l, but possibly not effective (level C) for the treatment of RLS in adults who have a serum ferritin >75 μg/l.

The literature search identified two Class II studies [57,58], one Class III study [59], and one Class IV study [33] of oral iron in adults. One of the Class II studies [57] (small sample size) assessed the efficacy of oral ferrous sulfate 325 mg (65 mg elemental iron) and vitamin C 100 mg, bid for 12 weeks in 18 non-anemic RLS patients who met entry requirements of an IRLS score $\geq$11, and a serum ferritin between 15 and 75 μg/l. There was a significant decrease in IRLS score for the 11 subjects randomized to oral iron vs. nine who received placebo (mean ± SD: −10.3 ± 7.4 vs. −1.2 ± 5.6, $p = 0.01$). Mean serum ferritin rose from 40.6 to 65.7 μg/l ($p < 0.04$) for those in the active treatment arm. The other Class II study [58] (<80% of subjects completed the study) assessed the efficacy of oral ferrous sulfate 325 mg (65 mg elemental iron) bid for 12 weeks in 28 non-anemic patients (Hgb $\geq$10 g/dl) who did not have hemochromatosis and were on treatment for RLS. There were no study entry restrictions on iron status and the mean and range of serum ferritin for those treated with iron was 134.8 μg/l (range 9–680 μg/l). Those completing the study included eight on iron and 13 on placebo. The study found no significant benefit from iron treatment for RLS symptoms or sleep quality as measured on visual analogue scales. The Class III study [59] (unmasked, no primary outcome and <80% completers) compared the efficacy of oral ferrous sulfate 325 mg bid (65 mg elemental iron) to pramipexole (0.125–0.75 mg at bedtime) over 12 weeks in 30 RLS patients who had a study entry requirement of a serum ferritin between 15 and 50 μg/l (mean 35.5 ± 11.62 in the iron group, and 36.6 ± 7.11 μg/l in the pramipexole group). Compared to baseline, both oral iron and pramipexole significantly improved IRLS scores ($p = 0.001$), and no differences were reported between the two treatment arms. Serum ferritin rose by an average of 50.8 μg/l (±20.69) in those on iron vs. a decrease of −4 μg/l (±12.56) in those on pramipexole. One open-label Class IV study [33] assessed the efficacy of oral ferrous sulfate 200 mg (40 mg elemental iron) three times a day over 2 months in 15 RLS patients aged between 70 and 87 years who had a median serum ferritin 32.5 μg/l (range: 6–100 μg/l). At 2 months RLS symptoms had improved according to a study-specific RLS rating score, and all showed an increase in serum ferritin of 34 μg/l (range 10–69 μg/l).

5.1.2. Safety and tolerability

The most commonly reported side effects were nausea and constipation. In the one Class II study that reported adverse effects to oral iron [58] 21% of the patients discontinued because of the adverse effects and 36% of the patients receiving iron reported nausea and constipation. No serious adverse events were reported. Gastrointestinal side effects are thus a limiting factor for oral iron. One Class IV study, provides insufficient evidence (Level U) to indicate that oral iron adversely affects gut bacterial diversity and composition in patients with inflammatory bowel disease [60].

5.1.3. Evidence-based efficacy conclusions

Oral iron as ferrous sulfate 325 mg (65 mg elemental iron) twice a day with 100 mg Vitamin C is possibly effective for treating RLS for patients with serum ferritin ≤75 μg/l. This conclusion is supported by one Class II study [57] that provides Level C evidence showing oral ferrous sulfate 325 mg (65 mg elemental iron) and vitamin C 100 mg were more effective than placebo for patients with serum ferritins between 15 and 75 μg/l. In addition, a Class III and a Class IV study, both using slightly different serum ferritin entry values (≤50 and ≤ 100 μg/l), support this recommendation.

Oral iron as ferrous sulfate 325 mg (65 mg elemental iron) twice a day is possibly not effective for the treatment of RLS in adults who have a serum ferritin >75 μg/l. This conclusion is supported by one Class II study [58] providing Level C evidence showing that oral ferrous sulfate 325 mg (65 mg elemental iron) was ineffective in adults not limited to serum ferritin values ≤ 75 μg/l.

5.1.4. Expert-consensus clinical recommendations

In RLS patients with a serum ferritin ≤75 μg/l, oral iron equivalent to ferrous sulfate 325 mg should be considered. The dosing regimen in the study supporting possible efficacy was twice a day with 100 mg vitamin C (ascorbic acid). Ascorbic acid enhances iron uptake by an intracellular reductive mechanism, and is also capable of regulating iron-responsive element-binding proteins (IRP-IRE) and the hypoxia inducible factor (HIF) systems. These mechanisms are important in systemic and cellular iron homeostasis [61]. New research also indicates that oral iron given once a day is almost equally effective as twice-daily dosing due to greater hepcidin induction with more frequent dosing [62]. Therefore, according to clinical consensus the task force recommends once- or twice-daily dosing. If the medication is not well tolerated it can be taken with food but this will likely decrease absorption. Once-a-day dosing may be somewhat preferred to twice-a-day dosing since it reduces adverse reactions with little loss of benefit for increasing peripheral iron status. Dosing once every other day may be considered but seems likely to decrease compliance.

5.2. Guidelines for IV iron treatment of RLS in adults

As noted in the introduction, there are several IV iron formulations available (see also Table 1). The high molecular weight iron dextran used in the past (but no longer available) can, rarely, produce significant life-threatening anaphylaxis. The currently available iron formulations, including low molecular weight (LMW) iron dextran, appear to be relatively free from these reactions except for a few very rare cases that have been reported [63]. A test dose is, however, still required before administration of the full dose of LMW iron dextran but not for the other formulations.

5.3. Ferric carboxymaltose

5.3.1. Evidence-based guidelines

Ferric carboxymaltose 1000 mg is considered effective (Level A) for the treatment of moderate to severe RLS in patients with a serum ferritin <300 μg/l and transferrin saturation < 45%.

Three Class I [46,64,65], and three Class IV studies [66–68] have assessed the efficacy of ferric carboxymaltose 500–1000 mg for the treatment of RLS in adults who were not anemic. Patients in the Class I studies were off any RLS medications and had serum ferritin levels <300 μg/l and transferrin saturation <45%. In the first study by Allen et al. [64] (n = 46) patients were randomized to receive ferric carboxymaltose in two 500 mg infusions 5 days apart (n = 24) or placebo (n = 19). RLS patients in the active treatment arm had a significant improvement compared to placebo at the planned outcome evaluation at 4 weeks after treatment for both primary outcomes: the IRLS scale ($p < 0.04$) and the CGI scale ($p < 0.004$). The second Class I study by Cho et al. [65] (n = 64; 32 each for iron and placebo), required patients to not be anemic. The patients who received ferric carboxymaltose (1000 mg infusion over 15 min) had a significant improvement in both primary outcomes at the planned outcome evaluation at 6 weeks after treatment compared to those in the placebo arm: IRLS scale ($p < 0.03$) and a visual analog scale for severity ($p < 0.001$).

The third Class I study by Trenkwalder et al. [46] differed from the two earlier studies in that patients (n = 110, 58 ferric carboxymaltose, 52 placebo) were required to have indications for low peripheral iron with either serum ferritin <75 μg/l, or transferrin saturation <20% and serum ferritin <300 μg/l. This study failed to confirm statistically significant differences between ferric carboxymaltose and placebo for the primary outcome variable of change in IRLS at the planned outcome evaluation at 4 weeks after treatment. However, at 12 weeks after treatment there was a statistically significant improvement in IRLS score for ferric carboxymaltose compared to placebo. At week 12, 27% of subjects had discontinued the study (14 of 59 on ferric carboxymaltose and 16 of 51 on placebo). Last observation carried forward (LOCF) was used for analyses. 27% of patients in the iron group reported treatment-emergent adverse events, with the most common reported adverse event being headache (12%).

Allen et al. [64] reported more remission of RLS (IRLS ≤10) with ferric carboxymaltose compared to placebo (29% vs. 5%, $p = 0.051$), and a higher percentage of responders (IRLS decrease ≥40%) 45% vs. 14.3% at 4 weeks. This study also provides Class II data from its follow-up phase, where, at 20 weeks after initial treatment, 25% of those who had received ferric carboxymaltose and 60% of the responders continued to have no need for further RLS treatment. Similarly, Cho et al. [65] reported higher percentages for ferric carboxymaltose than placebo for both responders at 6 weeks after treatment (IRLS scale decrease >40%; 59.4% vs. 28.1%) and symptom remitters (IRLS ≤10; 37.5% vs. 9.4%). Class II data from the follow-up phase of this study showed that about one-third (37.5%) of the patients treated with iron remained free of further RLS medications 30 weeks after treatment. No pre-treatment measure predicted response to IV iron in these studies. The Trenkwalder et al. study [46] reported significantly more responders (IRLS decrease ≤ 50%) for ferric carboxymaltose than placebo at week 12 using LOCF (22 of 59 on iron, 37% vs. 10 of 51 on placebo, 20%, $p = 0.042$).

In the first two Class I studies [64,65] RLS patients had a wide range of serum ferritin levels. The mean (±SD) serum ferritin prior to treatment was 28.1 ± 22.9 μg/l in women (range 4.7–79.0) and 70 ± 22.8 μg/l in men (range 29.9–113.3) in the study by Allen et al. and mean ± SD of 53.5 ± 41 μg/l in the treatment group in the study conducted by Cho et al. [65]. There was no relation of outcome to

pre-treatment serum ferritin levels in either study within the studied range of 5–153 μg/l. Notably, in the study by Cho et al. [65] six patients in the treatment arm had serum ferritin levels >100 μg/l; of these, three responded to treatment (serum ferritin range 102.61–153.34, TSAT range 25–43%), while three did not (serum ferritin range 108.65–116.55 μg/l, TSAT range 16–43%) [personal communication].

Two Class IV studies reported that ferric carboxymaltose was effective in improving RLS symptoms at 8 days [66] and at both 2 and 12 weeks [67] after treatment. A Class IV study, which assessed the efficacy of ferric carboxymaltose during pregnancy, reported RLS symptoms to improve progressively over 28 days after treatment [68].

5.3.2. Safety and tolerability

The most commonly reported side effects for ferric carboxymaltose include nausea (3–5%) and headache (3–12%), but these were mostly mild to moderate and did not lead to dropping out of the study. No serious adverse events were reported.

5.3.3. Evidence-based efficacy conclusions

Two Class I studies [64,65] provide Level A evidence to recommend ferric carboxymaltose 1000 mg as effective for the treatment of moderate to severe RLS in patients with serum ferritin levels < 300 μg/l and transferrin saturation <45%. Efficacy was reported at primary end points of 4 and 6 weeks after treatment.

One Class I study [46] failed to confirm that ferric carboxymaltose 1000 mg provides effective treatment for moderate to severe RLS in patients with serum ferritin <75 μg/l or transferrin saturation < 20% with serum ferritin <300 μg/l when these patients were evaluated at the primary end point of 4 weeks post-treatment. This study reported efficacy at a later evaluation 12 weeks after treatment but with a >20% drop out rate.

5.3.4. Expert-consensus clinical recommendations

Ferric carboxymaltose should be considered as one of the first-line treatments in patients with RLS. IV iron treatment should not be given to patients with serum ferritin levels >300 μg/l or transferrin saturation >45%. It was noted that the mean serum ferritin was <154 μg/l in these Class I studies. These studies do not provide information about response of patients with higher serum ferritin values. Moreover, only six patients in one of the Class I studies [65] had serum ferritin levels > 100 μg/l. There is, however, no evidence that those with higher serum ferritin levels would not respond. Nonetheless, given the lack of significant experience with higher serum ferritin levels the expert-based recommendations are to limit the initial IV iron treatment to patients with serum ferritin levels ≤100 μg/l. Patients with ID anemia, while not evaluated in the above studies, are expected to respond well to oral iron treatment and have also been shown to respond very well to IV iron treatment particularly if their anemia is corrected [69].

5.4. IV Iron sucrose

5.4.1. Evidence-based guidelines

Iron sucrose, at a dose of 200 mg administered in five infusions is probably not effective (Level B) for treatment of RLS in patients with serum ferritin <45 μg/l; and at a dose of 500 mg given in two infusions over 24 h is possibly not effective (Level C) for the treatment of RLS with serum ferritin <300 μg/l.

One Class I study [70], one Class II study [71], two Class III studies [72,73], and one Class IV study [74] assessed the efficacy of iron sucrose for the treatment of RLS. The Class I study [70] assessed the efficacy of iron sucrose administered in five doses of 200 mg over 3 weeks (n = 60, 29 iron sucrose, 31 placebo) in RLS patients with a pre-treatment IRLS score of ≥10 (the majority of other treatment trials in RLS include patients with an IRLS score of ≥15) and a serum ferritin <45 μg/l. They were off all RLS medications for at least 4 days prior to treatment. There was no significant difference between iron and placebo treatments in the primary outcome: absolute IRLS score (rather than the usual change from baseline) at 11 weeks after initial treatment (median [range] 7 [0–31] for iron sucrose vs. 17 [0–33] for placebo, p > 0.1). There were some secondary outcome measures showing greater improvement with iron sucrose than placebo. At the primary evaluation 11 weeks after treatment initiation, there were significantly more responders (>50% decrease in IRLS score) for iron than for placebo treatment (65% vs. 35%, p = 0.02). The absolute IRLS scores were significantly less (p < 0.05) for iron than placebo treatment at seven but not 3 weeks after starting treatment. During the continued blinded evaluation 12 months after treatment (providing Class II data) the number of subjects who dropped out due to lack of treatment efficacy was greater for the placebo (70%) than the iron sucrose treatment (31%) groups (p < 0.001).

The Class II study [71] (lower class due to small sample size) used a more rapid administration of iron sucrose than in the Class I study (i.e., 500 mg in two doses in 24 h) in RLS patients with a PLM index (PLMI) ≥15, Hgb ≥12 g/dl, and serum ferritin <300 μg/l who had been off all RLS medications for at least 7 days. Iron sucrose significantly improved RLS symptoms according to the global rating score compared to placebo (p = 0.02) at 2 weeks after treatment but there were no significant differences between RLS and placebo treated groups according to PLMI (mean ± SD decrease 24.8 ± 89.4 vs. 11.7 ± 32.9, respectively, p > 0.05) or in IRLS severity score (mean ± SD, 30.8 ± 9.2 vs. 29.7 ± 2.9, p > 0.05).

Of the three Class III studies, one [73] assessed the efficacy of two dosing regimens i.e., 1000 mg given as either two high doses (500 mg × 2) or five lower doses (200 mg × 5). IRLS scores were significantly (p < 0.05) improved compared to baseline for both dose schedules at 2, 4 and 6 weeks after treatment (p < 0.05), and at 6 weeks IRLS scores were significantly better for the 5- than the 2-dose schedule. Another Class III study [72] assessed the efficacy of iron sucrose (200 mg) compared to oral iron sulfate (100 mg od × 20) in 120 patients who had been blood donors more than five times in the previous 2 years. Twenty-two of these were reported to have RLS (eight in the iron sucrose arm and 14 in the iron sulfate treatment arm). The mean serum ferritin levels (all patients, mean ± SD: 33.8 ± 19 μg/l) were low for adults. The IRLS scores were significantly higher for iron sucrose compared to oral iron-treated patients at 4 and 8 weeks after treatment, and also at the second and fourth, but not the third donation after treatment. The third Class III study [74], a “letter to the editor”, assessed the efficacy of iron sucrose (200 mg once weekly until iron parameters increased) in 35 patients with congestive heart failure. Those with RLS (n = 15) were reported to have lower serum ferritin levels compared to those without RLS (mean ± SD: 109.4 ± 76.6 vs. 260.9 ± 218.5 μg/l, p = 0.045). No change in the prevalence and frequency of RLS was seen in these patients at 3 or 12 months.

5.4.2. Safety and tolerability

The most commonly reported side effects following treatment with IV iron sucrose included dysesthesia (7.1%) [70], taste perversion (4.8%) [70], edema in hands/feet (36%) [71], and nausea/vomiting (36%) [71].

5.4.3. Evidence-based efficacy conclusions

One Class I study [70] provides Level B evidence that iron sucrose 200 mg given in five doses over 3 weeks is probably not effective for the treatment of RLS in iron deficient patients without anemia when evaluated at 11 weeks and 12 months after treatment.

One Class II study [71] provides Level C evidence that iron sucrose 500 mg given in two doses within 24 h is possibly not effective at 2 weeks after treatment in iron deficient patients without anemia.

5.4.4. Expert-consensus clinical recommendations

The one Class I study indicated that iron sucrose was efficacious at 7 weeks, but not at any other time point. This planned analysis, however, was not adjusted for baseline scores. The change from baseline measured as number of responders (>50% decrease in IRLS) at the time for primary outcome evaluation (11 weeks after treatment started) was significantly greater for iron sucrose than placebo (65% vs. 35%, $p < 0.02$). Iron sucrose was considered by expert consensus to be effective for treatment of RLS but less so than ferric carboxymaltose or LMW iron dextran. The reduced efficacy of iron sucrose was seen as related to faster dissociation of the iron from the carbohydrate leading to more rapid release into the blood with more rapid distribution and storage for iron sucrose than ferric carboxymaltose. This may reduce the time when increased serum iron is available for transport to the brain. The iron taken up into the macrophages for tissue redistribution is also less for iron sucrose than for ferric carboxymaltose or LMW iron dextran [44]. These distribution differences were considered to be part of the reason for the putative lesser efficacy of iron sucrose compared to ferric carboxymaltose. The faster dissociation also limits the maximum dose of each infusion to avoid excessive “free” iron in the blood (see Fig. 1). This then requires multiple infusions repeated 2–3 days apart to reach the usual 1000 mg minimum dose. Iron sucrose is therefore less convenient to administer compared to the one or two doses required to administer ferric carboxymaltose or LMW iron dextran (see Table 1).

5.5. Low molecular weight iron dextran

5.5.1. Evidence-based guidelines

There is inadequate evidence to make any conclusions on the efficacy or safety of low molecular weight (LMW) iron dextran for the treatment of RLS (Level U).

Only two Class IV studies [69,75] have assessed the efficacy of LMW iron dextran in RLS. In a retrospective evaluation of cases ($n = 42$), Mehmood et al. [69] reported that 76% of subjects with ID anemia receiving a single infusion of LMW iron dextran (1000 mg) reported a reduction in RLS symptoms, while 65% of patients had an improvement in symptoms lasting over 6 months. The second Class IV study [75] was a prospective open-label case series of 25 non-anemic RLS patients. LMW iron dextran was administered as a 250 mg infusion once a week for 4 weeks as an add-on treatment to the patient's current RLS treatment. Twenty-four of the 25 patients were on dopamine treatment for RLS with one having no previous RLS treatment. Some patients decreased or discontinued their oral RLS medications 1 week after the last IV treatment. There was a significant reduction in IRLS scores 3 weeks after treatment compared to baseline before treatment ($p = 0.001$). Moderate to complete symptom improvement was described for 68% ($n = 17$) and symptom remission (IRLS ≤ 10) was reported for 32% ($n = 8$) including four patients who stopped oral medications. RLS symptom improvement began between 1 and 6 weeks after the last IV LMW iron dextran treatment.

5.5.2. Safety and tolerability

No clinically relevant toxicity or persisting adverse effects were observed.

5.5.3. Evidence-based efficacy conclusions

The two Class IV [69,75] studies do not provide enough data (Level U evidence) to make any recommendations regarding efficacy of LMW iron dextran for the treatment of RLS.

5.5.4. Expert-consensus clinical recommendations

There is a lack of data on LMW iron dextran for the treatment of RLS, but there is substantial clinical experience that shows it to be clinically effective in both anemic and non-anemic RLS patients. Its cost and accessibility vary worldwide, however, in the countries where it is available it is often used in clinical practice as it is frequently more cost effective than alternative IV iron formulations. It can be given as a single 1000 mg infusion. Since this is a dextran formulation there is some concern about anaphylaxis, although this seems rare. A small test dose infusion of 25 mg is required at 10–30 min before the full treatment dose.

5.6. Iron gluconate

5.6.1. Evidence-based guidelines

There is inadequate evidence to make any conclusions on the efficacy or safety of iron gluconate for the treatment of RLS (Level U).

One Class IV study [76], a prospective case series of five RLS patients who had responded to 1000 mg IV iron dextran, assessed the efficacy of IV iron gluconate (150 mg administered in three infusions) given when RLS symptoms returned, and provided serum ferritin <300 μg/l. This dosing of iron gluconate was repeated as needed over a 2-year observation period. One to four repeated treatments were given to these patients. All patients showed some improvement in RLS global severity score after the iron gluconate treatment.

5.6.2. Expert-consensus clinical recommendations

There was inadequate clinical experience to make any clinical consensus on use of iron gluconate for the treatment of RLS.

5.7. High molecular weight iron dextran

This formulation is no longer available and therefore efficacy was not evaluated.

Four Class IV studies [77–80] are available that assess the efficacy of high molecular weight iron dextran (see e-Table 2 for an overview), however, this IV iron formulation is no longer available and therefore no evidence-based or clinical recommendations have been made on its use.

5.8. Other iron formulations: ferumoxytol and isomaltoside

5.8.1. Evidence-based guidelines

There is inadequate evidence to make any conclusions on the efficacy or safety of ferumoxytol and isomaltoside for the treatment of RLS (Level U).

There are no studies available that assess the efficacy of either ferumoxytol or isomaltoside for treatment of RLS.

5.8.2. Expert-consensus clinical recommendations

Clinical consensus noted that like LMW iron dextran and ferric carboxymaltose, the iron in ferumoxytol and isomaltoside is slowly released from the carbohydrate bond and therefore a 1000 mg dose can be provided using one or possibly two injections. These formulations are often used in clinical practice for treating ID. The clinical consensus was that 1000 mg IV of these formulations given as one single or two divided doses is possibly effective for the treatment of RLS.

5.9. Repeated dosing of intravenous iron

5.9.1. Evidence-based guidelines

There is inadequate evidence to make any conclusions on the efficacy or safety of repeated IV iron doses for the treatment of RLS (Level U).

One Class IV study [76] (see also above under iron gluconate) provides insufficient evidence (Level U) to support repeated iron infusions for the maintenance of symptomatic improvements achieved after an initial successful IV iron treatment. Patients who responded to an initial dose of 1000 mg of dextran were followed for 2 years after treatment. If a patient's symptoms returned and serum ferritin <300 μg/l then 450 mg IV iron gluconate was administered in three separate doses of 150 mg delivered over a 5–10 day period. Five patients received two to four repeated doses. Two of the five patients were symptom free 2 years after the initial treatment and each had received two repeated treatments over the 2-year period. The other three subjects had one to four repeated treatments and had a 50% improvement in symptoms at the end of the 2-year period.

5.9.2. Expert-consensus clinical recommendations

The clinical consensus was that repeated treatment for recurring symptoms may be effective for maintaining or restoring an initial positive clinical response to IV iron but further clinical studies are needed to evaluate safety and efficacy of repeated IV iron treatments.

5.10. Expert-consensus clinical recommendations: IV Iron administration and safety for currently used formulations

The usual 500–1000 mg total IV iron dose for RLS or ID is given as one or as a series of treatments over a few days. Estimates are that serious adverse effects (SAEs) with the administration of these doses of IV iron are exceedingly rare, occurring in less than 1:250,000 administrations [81]. Pre-medication, particularly with diphenhydramine, is not generally recommended. All IV formulations have a risk of minor infusion reactions. Like many IV formulations, IV iron is a vesicant and care should be taken to avoid extravasation, which can cause skin discoloration. Minor infusion reactions for IV iron, due to the release of labile free iron, are infrequent, occurring in approximately 1% of administrations [82]. It is important to distinguish between the extremely rare severe hypersensitivity reaction, which can lead to anaphylaxis, and the minor infusion reactions due to labile free iron. Severe hypersensitivity should be associated with wheezing, stridor, periorbital edema, and shock, while in contrast minor infusion reactions due to labile free iron are associated with myalgia of the chest or back, facial flushing or tickling in the throat [83]. The possibility of severe hypersensitivity reactions, irrespective of rarity, requires that interventions to deal with impending anaphylaxis are in place before IV iron infusion is initiated. The minor infusion reactions, in contrast, resolve spontaneously without therapy. Once resolved, empiric treatment with a corticosteroid but not an anti-histamine, is sometimes given prior to further IV iron. This is based on the proven efficacy of corticosteroids in preventing next day myalgia [84]. Recurrence of the minor infusion reaction symptoms is rare, but if it happens a different formulation should be used.

Given these two different potential adverse reactions to IV iron, its administration should begin slowly with observation. If no signs of hypersensitivity or a minor infusion reaction are observed within the first few minutes, they are very unlikely to occur. LMW iron dextran may, in some places, have a requirement for a test dose as described in the section on LMW dextran above and in Table 1.

Prior studies have observed the patient for 30 min after IV iron treatment to detect development of adverse effects. There is, however, no physiologic evidence to support the benefit of observing the patient for adverse effects after the completion of an iron infusion [85].

5.11. Summary expert consensus clinical recommendations for IV iron treatment

FDA-approved guidelines for administration of any of the IV formulations should be followed. The Class I studies [46,64,65] indicate that IV ferric carboxymaltose, and presumably similar formulations, provide significant symptom improvement and could be used as first-line treatment for RLS. The improvement in RLS symptoms beyond placebo effect, however, may not occur until 4–6 weeks after treatment. Patient management needs to plan for this delayed response to treatment. A full iron panel should be obtained from an initial morning fasting blood sample prior to treatment to assess appropriateness for treatment with this approach. Obtaining a repeat iron panel from a morning fasting blood sample is recommended at 8 weeks after IV iron treatment and then repeated 8 weeks later. The recommended delay of 8 weeks is due to acute phase reactions that cause serum ferritin levels to be falsely elevated after IV iron treatment.

6. Evidence- and consensus-based guidelines: children

6.1. Oral iron in children

6.1.1. Evidence-based guidelines

There is inadequate evidence to make any conclusions on the efficacy of oral iron for the treatment of RLS in children (Level U).

Six Class IV open-label case series [86–91], which included a total of 261 participants, have assessed various oral iron formulations and regimens for the treatment of RLS and/or PLMD in children (e-Table 3). Four studies focused on RLS, one on RLS and PLMD, and one on PLMD; two were prospective and four retrospective. Except for the study by Furudate et al. [87], none of the studies were randomized, blinded or controlled. Patients included were aged 11 months to 18 years. The entry requirements included serum ferritin <50 μg/l in three studies, and <40 μg/l in one study.

The largest study (n = 105), by Dye et al. [86], evaluated 105 children (mean age of 10 ± 5.3 years) with RLS or PLMS (PLMD) and serum ferritin <50 μg/l. Oral ferrous sulfate 3 mg/kg/day was effective in reducing objectively measured PLMS at 3–6 months, at 1–2 years, and after 2 years follow-up in children. This coincided with serum ferritin increases from an average baseline of 27.4 to average values of 45.6, 52.0, and 54.7 μg/l respectively. In addition, 63% of the children had sustained subjective improvement in clinical symptoms. Another PLMD study, by Simakajornboon et al. [91], evaluated response to 3 months of treatment using ferrous sulfate (3 mg/kg/day) for 25 children (mean age 7.5 ± 3.1 years) with subjective sleep complaints, PLMS index > 5/hr and serum ferritin <50 μg/l. Subjective clinical improvement in sleep and objective decrease in PLMS was reported for 19 of the 25 (76%). These studies support setting a therapeutic target for serum ferritin ≥50 μg/l for oral iron in PLMD.

These studies in pediatric RLS reported that oral iron at doses ranging from 3 to 8.5 mg/kg/day [88–90] consistently increased serum ferritin levels. Subjective RLS symptoms were reduced in 80%–100% of these children. Another case series reported 50% of 16 RLS children (age mean, range: 12.3, 7–18 years) treated with

50–100 mg/day of ferrous citrate resulted in ≥50% improvement in IRLS scores [87].

Children sometimes show aversion to the taste of ferrous sulfate elixir. Consequently, a preparation containing an iron polysaccharide has been developed, which is more pleasant tasting. In a recent double-blind trial in subjects aged 9–48 months (n = 80), ferrous sulfate was, however, superior to the iron polysaccharide complex in improving Hgb concentration at 12 weeks [92].

6.1.2. Safety and tolerability

Adverse effects were either not reported (four studies) or not found (two studies).

6.1.3. Expert-consensus clinical recommendations

Oral iron treatment maintained for 3 months was considered likely effective in reducing clinical sleep disturbance and PLMS in children with RLS and PLMD, and also RLS symptoms. It is unclear if oral iron can be stopped when symptoms improve or if it needs to be continued to avoid return of symptoms.

The benefits of oral iron treatment may be limited for children with RLS or PLMD if they have systemic comorbidities that interfere with absorption of orally administered iron, e.g., eosinophilic esophagitis, gastro-esophageal reflux, celiac disease, bowel resections related necrotizing enterocolitis, etc. As in adults, gastrointestinal side effects can also be a limiting factor for oral iron therapy in this population. A Class IV study found insufficient evidence (Level U) that oral iron affects gut bacterial diversity and composition in patients with inflammatory bowel disease [60].

6.2. Intravenous iron in children

6.2.1. Evidence-based guidelines

There is inadequate evidence to make any conclusions on the efficacy or safety of IV iron sucrose for the treatment of RLS in children (Level U).

Iron sucrose is the only IV iron formulation that has been assessed in children, and only in a Class IV study. In this study [93] iron sucrose 1.2–6.6 mg/kg (max total dose 120 mg) was administered over 2 h in 16 children (mean age 6.6 [2–16] years) with RLS or PLMD. Sleep improved in 62.5% of the patients, and mean ferritin rose significantly for the group from 15.3 μg/l to 45.7 μg/l (p = 0.0001).

6.2.2. Safety and tolerability

The most common adverse events were transient gastrointestinal symptoms (anorexia, nausea, and vomiting). Two patients experienced difficulty with peripheral IV catheter placement. No clinically relevant toxicity or persisting adverse effects were observed.

6.2.3. Expert-consensus clinical recommendations

Many children with RLS/PLMD have significant comorbidities and suffer for many months before they are diagnosed [94–96]. IV iron sucrose was found to be safe and effective in the above Class IV study, as well as in another Class IV study in 45 children with ID anemia who had been refractory to oral iron [97]. Additional efficacy and safety data for pediatric IV iron therapy to treat ID anemia is summarized in a recent review [98]. A lack of evidence has no doubt contributed to the hesitancy of practitioners administering IV iron in children with RLS and PLMD. The IRLSSG task force, based on clinical experience and solid data in adult RLS, recommends that IV iron sucrose (3–6 mg/kg) (max 120 mg) can be considered for pediatric RLS/PLMD if performed in the setting of an infusion center with pediatric experience provided the following occur: a prior oral iron treatment of at least 3 months has not produced an adequate benefit or was discontinued because of adverse effects and there has been no appreciable rise in serum ferritin levels with 3 months of oral iron treatment. IV iron can be considered without a prior oral iron trial if significant comorbidity is present that will impair iron absorption. A serum ferritin ≥50 μg/l is considered an adequate therapeutic target in children [86].

Caution should be exercised in children with mitochondrial disorders, or when there is an active significant systemic inflammatory process as there are theoretical reasons to be concerned that infections might worsen following iron treatment. Great care should also be taken to prevent the risk of IV drug extravasation. Children with hemochromatosis should not be treated with iron for RLS.

7. Special populations

RLS with ID anemia has been shown to respond well to 1000 mg of IV LMW iron dextran [69]. The World Health Organization (WHO) defines anemia as: Hgb < 13 g/dl in men over 15 years of age, < 12 g/dl in non-pregnant women over 15 years of age, and <11 g/dl in pregnant women [99,100].

The guidelines for treating ID in specific disease conditions would also apply to treating RLS with ID in these conditions. These guidelines are available for chronic kidney disease [101], pregnancy [102,103], and gastroenterology [99,104]. Specific recommendations about using iron for treatment of RLS during pregnancy were developed by the IRLSSG [105] and should be considered for that special population.

8. Clinical consensus on when to use oral iron vs. IV iron for treatment of RLS

8.1. Use oral iron when both a and b below apply (see treatment algorithms Figs. 4–6)

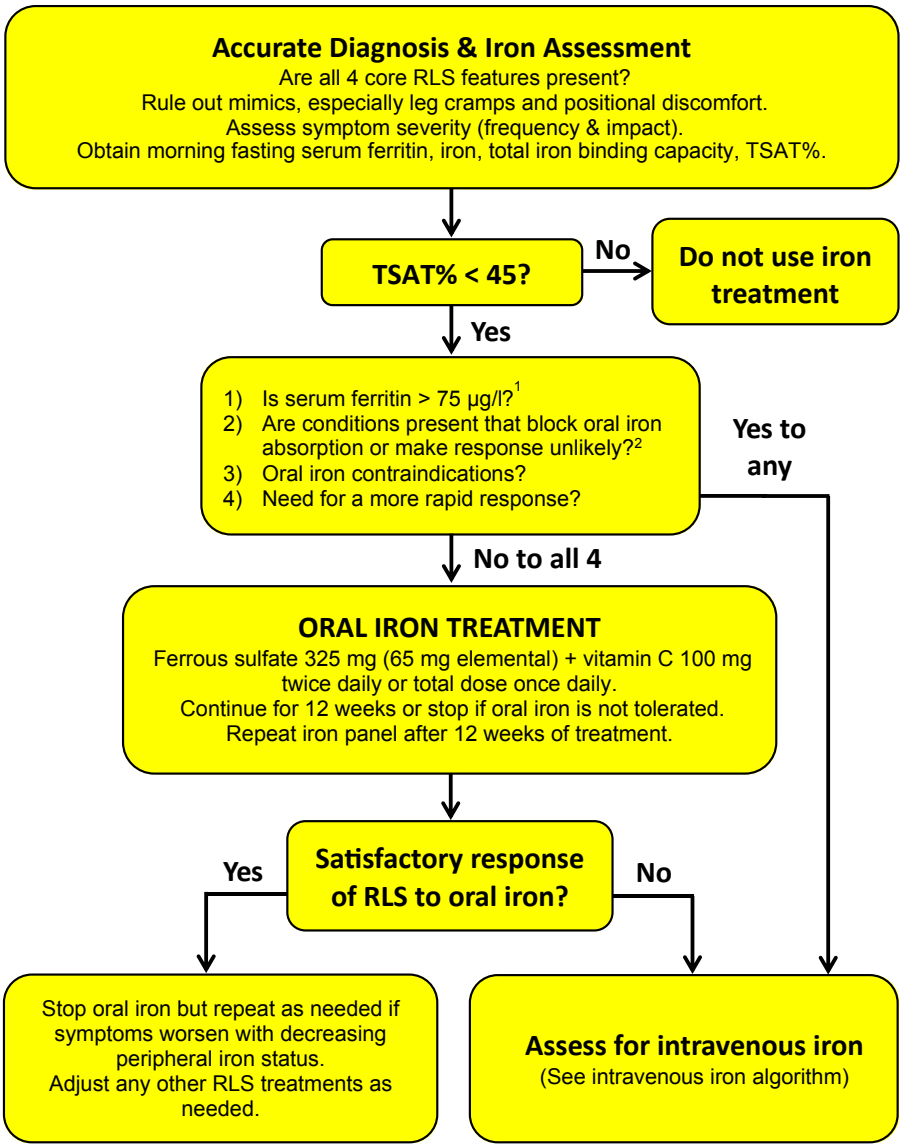
a Serum ferritin ≤75 μg/l in an adult or <50 μg/l in a child, AND
b There are no conditions: 1) that are exacerbated by oral iron (e.g., inflammatory bowel disease), 2) where oral iron cannot be absorbed (e.g., bariatric surgery), 3) where oral iron cannot keep up with rapid iron losses (e.g., heavy uterine bleeding, hereditary hemorrhagic telangiectasia or other acquired angiodysplasia).

8.2. Switch from oral to IV iron

a If oral iron is not tolerated
OR
b If after 12 weeks with oral iron the RLS symptoms remain clinically significant and the serum ferritin or other iron measures are within acceptable values for giving IV iron for RLS (For children, if symptoms have shown significant improvement and serum ferritin <50 μg/l, then a further 12 weeks of oral iron treatment is recommended).

8.3. Start with IV and not oral iron for

a Adults and children with moderate to severe RLS: if there is a medical contraindication for use of oral but not IV iron.
b Adults (18 years and older) only if <u>any one</u> of the following are present:
1 Serum ferritin 75–100 μg/l (or, if serum ferritin is elevated due to the presence of inflammation, then treatment with IV iron should only be considered if transferrin saturation is <20%.)



[1]Serum ferritin can be falsely elevated in the presence of acute or chronic inflammation.

[2]Such as a heavy uterine bleeding, bariatric surgery, malabsorption syndrome, inflammatory bowel disease, rheumatic diseases, etc.

Abbreviations: RLS, restless legs syndrome; TSAT%, percentage transferrin saturation.

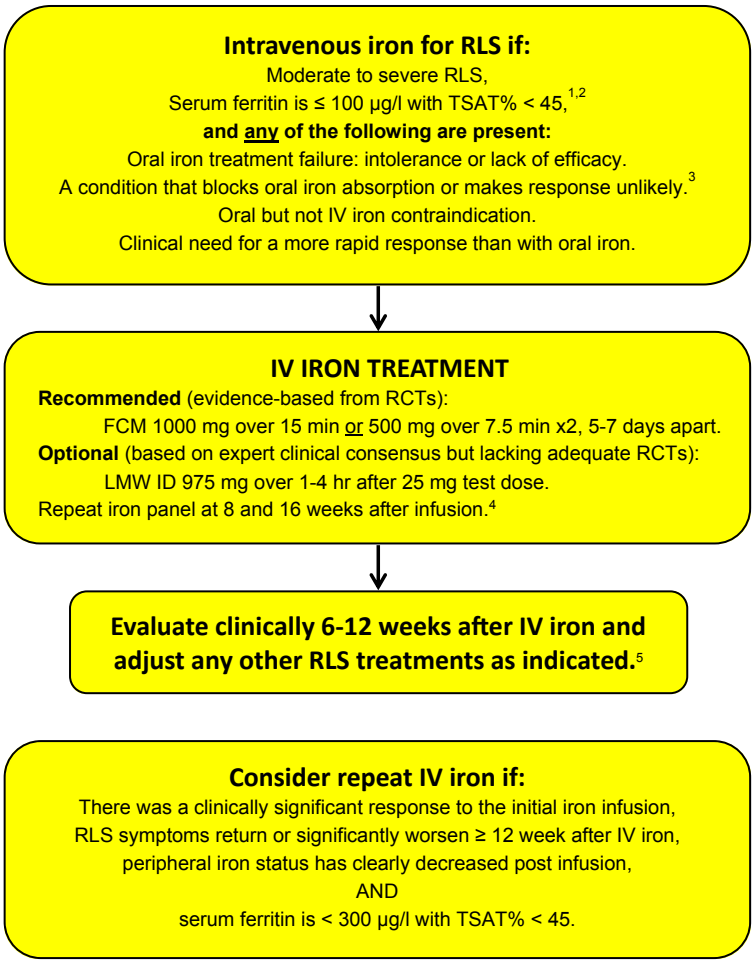
Fig. 4. Algorithm for oral iron treatment of adult RLS.

2 There are significant systemic comorbidities that might interfere with oral iron absorption (e.g., inflammatory conditions, rheumatoid arthritis).
3 There was a prior failure with oral iron treatment.
4 There is a clinical need for a more rapid symptom relief than is likely to be achieved with oral iron.

9. General comments and considerations

9.1. Tests for peripheral iron status

Because (1) of the distinct circadian changes in serum iron (highest in the morning and lowest in the evening) [106], (2) of increases in serum iron immediately after food intake, and (3) of serum iron's importance as an independent determinant of iron status (plus part of the calculation of percent iron saturation), serum tests of iron should be obtained in the morning after an overnight fast. Where possible, the last meal prior to the fasting period should have a limited amount of meat, particularly red meat. The full iron panel should include: serum ferritin, transferrin saturation, iron, and total iron binding capacity. Soluble transferrin receptor should not be part of the routine iron panel as it is very expensive and has limited value in non-anemic populations [14]. The population-based norms that are provided with laboratory iron tests do not exclude subpopulations with diseases or other medical conditions. Therefore, "normative" lab ranges for iron-based indices include populations of subjects with anemia and ID. As "normative" lab ranges are inclusive of these conditions, they are therefore not clinically discriminative in value. For example, serum ferritin 15 µg/l is



[1]Serum ferritin can be falsely elevated in the presence of acute or chronic inflammation.

[2]Although benefit may occur when the pre-treatment serum ferritin is 100-300 µg/L, current data and experience are incomplete.

[3]Such as a heavy uterine bleeding, bariatric surgery, malabsorption syndrome, inflammatory bowel disease, rheumatic diseases, etc.

[4] The first 8-week, post-infusion iron assessment is to establish what level of iron stores were achieved with the infusion. The second post-infusion assessment is to see how stable the levels are.

[5]The other RLS treatments may be adjusted, usually decreased prior to or at appropriate times after IV iron treatment as clinically indicated. The best effects of IV iron may not occur until 6 weeks after treatment and iron benefit for RLS augmentation is not known. The class I RCT studies were done on patients withdrawn from other RLS medications who then did not have RLS augmentation.

Abbreviations: FCM, ferric carboxymaltose; IV, intravenous; LMW ID, low molecular weight iron dextran; TSAT%, percentage transferrin saturation; RLS, restless legs syndrome; RCTs, randomized controlled trials.

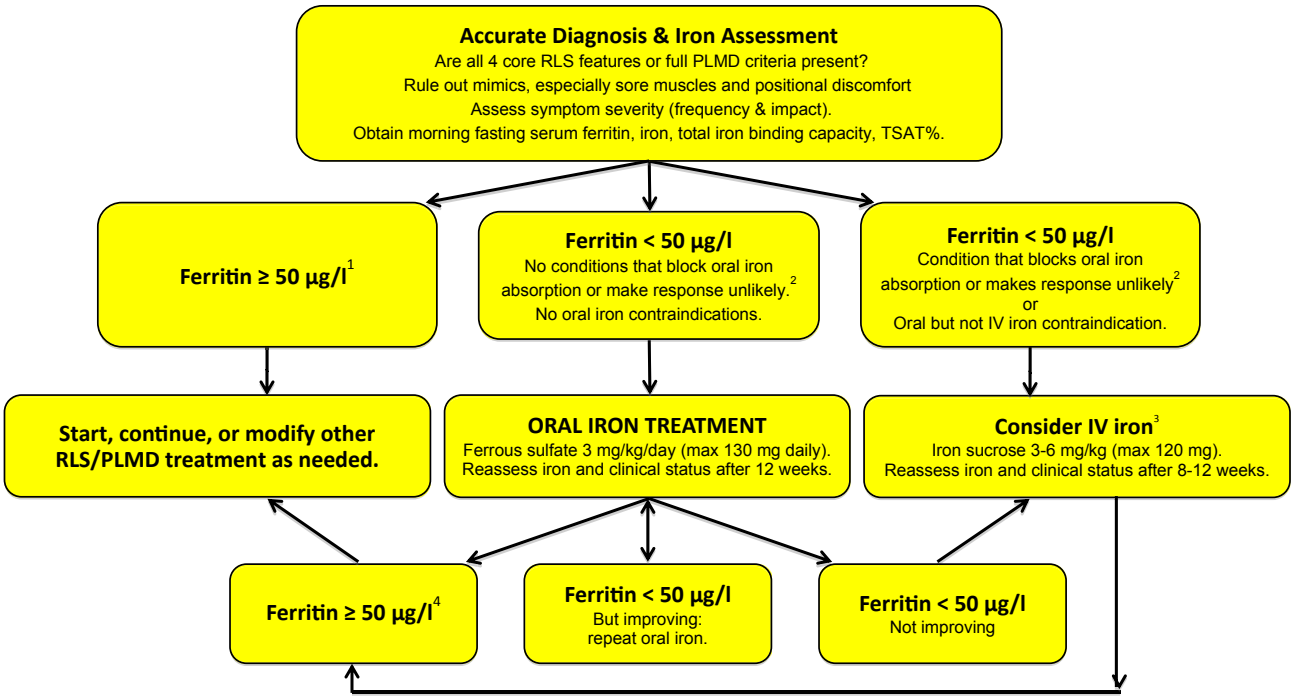
Fig. 5. Algorithm for intravenous iron treatment of adult RLS.

highly indicative of ID [14] even though that value will appear within the "normal" range for that lab result.

The full iron panel is recommended at initial evaluation of an RLS patient and every time RLS symptoms worsen without explanation. A repeat iron panel is recommended about 3 months after starting oral iron and then based on rate of change over time every 3–6 months. As long as the patient remains on oral iron, they need to have their iron indices checked regularly. The patient should not take oral iron 2 days before the repeat iron panel is performed. Iron status after IV iron should be checked at 8 weeks after IV iron infusion and again 8 weeks later. The first 8-week, post-infusion iron assessment is to establish what level of iron stores were achieved with the infusion. The second post-infusion assessment is to see how stable the levels are. The risk of peripheral iron overload is minimized by not giving iron treatment when transferrin saturation is >45% or when serum ferritin is > 300 µg/l. As serum iron concentration is one of two values used to calculate the percent iron saturation, secondarily elevated iron values (on iron pills, failure to fast, heavy meat meal the night before) will give a false estimate of the true iron saturation. Serum ferritin within the first 6 weeks after IV iron treatment will tend to show a spurious elevated value, thus the recommendation to wait 8 weeks before the initial post-infusion levels. Serum ferritin values will also be elevated by inflammatory processes, and very high values should be evaluated in relation to the other iron measures. If concerned about inflammation affecting the results, repeat the iron panel later.

9.2. IV Iron treatment response times

Clinical studies using IV iron discussed above demonstrate that the overall clinical response may be delayed, or at least the



Therapeutic target of ferritin ≥ 50 mcg/L for iron therapy.

[1] Serum ferritin can be falsely elevated in the presence of acute or chronic inflammation. IV iron treatment can then be considered if transferrin saturation is < 20%

[2] Such as a malabsorption syndrome, inflammatory bowel disease, heavy uterine bleeding, rheumatic diseases, etc.

[3] Administer at an infusion center with pediatric experience and with care taken to avoid IV drug extravasation.

[4] May need to continue oral iron to avoid return of symptoms due to decrease in iron stores with growth.

Abbreviations: IV, intravenous; PLMD, periodic limb movement disorder; RLS, restless legs syndrome; TSAT%, percentage transferrin saturation.

Fig. 6. Algorithm for iron treatment of pediatric RLS/PLMD.

maximum benefits achievable by treatment may be delayed, by at least 4–6 weeks. Yet some patients may report an immediate response. When initiating IV iron therapy it is important for the patient to be informed that symptoms may not improve until 4–6 weeks after IV iron infusion. When using IV iron as an add-on treatment, decreasing medication doses or making other changes that might increase symptoms should be undertaken cautiously or not at all during the first 4–6 weeks following IV iron treatment.

9.3. Repeated iron treatments

IV Iron treatments will definitively increase peripheral iron stores. If iron treatment improves iron status as well as the RLS symptoms, the underlying cause of the deficiency may return. Clinical factors that may be helpful in deciding about repeat iron treatments are: (1) Did the initial treatment have clear symptomatic benefits? (2) Did the initial treatment raise serum ferritin to high "normal" range or is serum ferritin still in the low to mid normal range? (3) Are symptoms now worsening because of a drop in peripheral iron stores? And (4) Are there safety concerns associated with repeat therapy? Decisions about repeating a successful oral iron treatment can be guided by serum ferritin levels dropping below 75–100 µg/l, which would indicate a possible benefit from restarting oral iron to reduce RLS symptoms. Deciding about repeating an IV iron treatment is more complicated since there is only one published Class IV study and very limited clinical experience. No clinical guidance can be provided at this time. The consensus of the committee, however, is that the treatment-exclusion limits on ferritin (≥300 µg/l) and percent iron saturation (>45%) used in the prior initial IV iron treatment trials [64,65] should not be exceeded when considering repeated IV iron treatment.

9.4. Assessment for causes of low peripheral iron

Blood loss is the most likely cause of low serum measures of iron status. Possible causes of blood loss should be considered, and a thorough medical evaluation for possible causes of blood loss is warranted in some cases, such as an abnormally low or a rapid decrease in serum iron measures. Menorrhagia is a common cause of iron deficiency, while the most serious reason for blood loss is bowel cancer, and the least elicited cause is blood donation. Malabsorption is also a common cause of ID and is commonly seen after bariatric/gastric surgery, with inflammatory bowel syndrome, and celiac disease [14].

10. Future considerations

This review of the literature and evaluation of iron treatment of RLS reveals the existence of several significant gaps in our knowledge concerning the efficacy and safety of iron treatments, in particular with regards to limitations of current clinical trials, prediction of treatment response, add-on treatment options, repeated IV iron treatments, long-term treatment outcomes, biological measures documenting benefits, developing better ways to deliver iron to the brain, and correcting or preventing the factors causing reduced brain iron.

10.1. Limitations of current clinical trials

10.1.1. Oral iron

Oral iron treatment is strongly recommended in all of the RLS treatment guidelines but there is only one very small clinical trial that lends support for this recommendation. This one trial provides insufficient evidence for oral iron to be considered as "effective" treatment according to evidence-based classifications. It would be very helpful to have at least one more controlled clinical trial evaluating oral iron treatment of RLS.

10.1.2. IV iron

There is adequate documentation of the efficacy of one IV iron formulation, ferric carboxymaltose. These studies have been relatively small, so safety conclusions rely upon the assumption that the safety determined in studies with ID anemia applies to RLS [107]. These RLS trials, while designed to accept patients with serum ferritin $\leq$300 μg/l in fact treated no one with serum ferritin >156 μg/l [64]. This has led to a consensus that usual clinical use of IV iron for RLS should be limited to those with serum ferritin $\leq$100 μg/l with allowances for conditions where serum ferritin is not a reliable measure of body iron stores. Certainly larger and longer studies are needed, with a wider range of serum ferritin levels, in order to have a more secure understanding of the benefits and limitations of this treatment for RLS. It would also be helpful to evaluate some of the other IV iron formulations, and in particular a relative evaluation for safety and efficacy of the formulations with more vs. less release of free iron, e.g., iron sucrose vs. ferric carboxymaltose.

10.1.3. Predicting treatment response

Predicting treatment response would be very helpful for guiding IV iron treatments. The puzzling 50% response rate does not appear to occur because the usual 1000 mg dose is inadequate [64], but rather represents some difference between patients. Moreover, the response to IV iron tends to be bi-phasic with either a good response or very little response at all [64]. However, none of the studies to date have identified any reliable and reproducible pre-treatment variable(s) that would predict response to iron treatment. Given the apparent large genetic variation in brain iron regulation and its changes with iron deprivation, there may not be any relation between peripheral iron status and IV iron treatment response, except for more extreme ID. There may, however, be some other aspect of iron status, clinical history especially regarding ID, or other subject variables including past RLS medications and dopaminergic RLS augmentation that would identify those likely or not likely to respond. This would guide treatment, clinical trial methods, and also research into better methods for delivery of iron.

10.1.4. IV iron as add-on treatment

Add-on treatments are often needed for RLS patients who need better treatment benefit or reduction of adverse events from ongoing treatment. Oral iron is always considered in those with low serum ferritin, but IV iron should also be considered as offering a treatment, which is not limited to those with serum ferritin levels $\leq$75 μg/l. This approach to treatment may lead to a reduction of the doses of other medications as well as an improvement in overall treatment outcomes.

10.1.5. Repeating IV iron treatments

Repeating iron treatments is easy to manage for oral iron formulations. A serum ferritin level falling below 75 μg/l in conjunction with increased RLS symptoms can be used as a guide. IV iron treatment repetition, however, can only be based on the clinical symptoms and concerns about safety. The treatment literature indicates that the duration of IV iron treatment benefit is limited for most individuals to less than a year, and therefore, repeated treatment needs to be considered. The clinical consensus guidelines for repeated IV iron treatment presented in this paper are based on very limited published experience. Aside from one small open-label study [76] there has been no documentation of the benefits or consequences of repeated IV iron treatments. This clearly needs further study.

10.1.6. Long term IV iron treatment outcome

Long-term outcomes, particularly with repeated IV iron treatments, need to be evaluated. The studies to date report some outcomes of up to 6–12 months, but little information is available beyond that. This becomes an important safety as well as long-term efficacy issue.

10.1.7. Biological markers for changes with iron treatments

Biological markers of treatment outcomes have curiously not been evaluated to date, except for one good study showing that the post-treatment increase in CSF ferritin related to RLS treatment outcome [65]. Clearly, it would be useful to have more specific measures of brain iron, such as magnetic resonance imaging (MRI), to evaluate changes after iron treatment in relation to clinical benefits. MRI and other brain iron measures have limited sensitivity and may not be able to reliably detect changes with iron treatment, but they certainly should be studied as a first step to documenting iron treatment effects. Studies could also evaluate post treatment changes of iron-related biology in various peripheral tissue, e.g., iron regulatory proteins in lymphocytes [108].

10.1.8. Methods for delivery of iron to the brain

The putative goal for iron treatment of RLS is to improve brain iron status. The current oral and IV iron treatments, while effective, tend to have a significant number of non-responders. This has been better studied for IV iron where it appears in most studies that about 40–50% of the patients fail to show significant clinical benefit. Development of alternate ways to improve brain iron status could possibly improve iron treatment of RLS.

11. Summary: conclusions

Both the evidence-based conclusions and the clinical consensus indicate iron should be one of the options for first-line treatment for RLS. Oral iron treatment will often be the first choice. IV iron should, however, be considered whenever serum ferritin levels are too high for oral iron absorption, when oral iron is not tolerated or contraindicated, or when there is an inadequate response of serum iron levels to oral iron. Iron treatments add an important dimension to managing RLS. There are, unfortunately, no studies on the long-term benefits or safety of iron treatments in RLS. Patients treated with iron, particularly those given IV iron, should be followed regularly to ensure long-term safety.

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Disclaimer

These guidelines are not inclusive of all proper approaches to care or exclusive of others. They are based on data available at the time of this review. Practitioners and patients should be vigilant for further research that may alter these guidelines. It should be noted that neither oral nor IV iron formulations currently have specific approval for RLS by the United States Food and Drug Administration

or the European Medicines Agency, and are therefore considered "off-label" treatments for RLS.

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Appendix A. Supplementary data

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