The Use of Iron in the Treatment of Restless Legs Syndrome

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Abstract

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Methods: Wide-ranging search of available medical literature. The keywords: Iron, Anemia, Treatment, Restless Legs Syndrome, and Clinical Trial were used in the MEDLINE, CINAHL, Evidence-Based Medicine Reviews Multifile and Web of Science databases.

Results: The search revealed over 25 articles. The literature used in this systematic literature review was limited to randomized, double-blind, placebo controlled, studies published after 2000. In a majority of these studies iron supplementation was shown to produce a statistically significant reduction in patient symptoms.

Conclusion: Intravenous (IV) iron supplementation combined with sleep hygiene counseling, is a potential first-line treatment option for patients with Restless Legs Syndrome. Serum ferritin must be monitored before initiating treatment and quarterly once treatment is underway to ensure Hemocromatosis is avoided. Oral dosage of iron requires proper dosage techniques to allow for effective absorption. Attention to this important factor proved lacking in some trials showing no benefit in oral iron supplementation. More information regarding oral and IV iron effectiveness and dosing requirements is necessary for iron to become a universally recognized 1st line treatment option.

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Degree Name
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Annjanette Sommers MS, PAC

Keywords
Iron, Anemia, Treatment, Restless Legs Syndrome, Clinical Trial

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The Use of Iron in the Treatment of Restless Legs Syndrome

Joshua A. Rafkind

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
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Faculty Advisor: Rob Rosenow PharmD, OD
Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC &
Rob Rosenow PharmD, OD
Biography

Joshua Rafkind is a native of Idaho, *The Gem State*, where he lived and guided seasonally on the Middle Fork of the Salmon River for the last 10 years. He graduated with distinction from Whitman College receiving an ‘Honors’ Bachelor Degree in Arts & Science. Since graduating he has studied wilderness medicine, worked with Habitat for Humanity, lived abroad, and most recently held a Medical Assistant position at a small rural clinic in Potlatch, Idaho. He plans to help save the world once he graduates.
Abstract

Background: A growing body of research is addressing the role iron plays in Restless Legs Syndrome (RLS) pathology and treatment. Caring for patients suffering from this disease, one sees the interruption to, and tangible frustration in, the lives of these patients. Consensus for treatment modalities is incomplete. The goal of this systematic review of literature is to provide a complete picture of the role iron plays in the treatment of RLS.

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To Andrew and Deborah, the two most important people in my life, the gifts you have given me are timeless and I owe every breath, accomplishment and joy wholly to you.

To all those in the medical community giving their time to the invaluable work of providing patient care.
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List of Abbreviations

RLS………………………………………………………. Restless Legs Syndrome

IRLS................................................................................ International Restless Legs Scale

IRLSSG…………………………… International Restless Legs Study Group

SFL……………………………………………………… Serum Ferritin Levels

IV……………………………………………………………… Intravenous

CBC……………………………………….. Complete Blood Count

BID……………………………………………………… Twice Daily

PO…………………………………………………………. Taken Orally
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BACKGROUND

Overview

“…So great a restlessness and tossing of their members ensue that the diseased are no more able to sleep than if they were in a place of greatest torture”.1 This clinical depiction, from Sir Thomas Willis in 1685 English Medical Literature, describes a condition that has since echoed through the adult population only recently gleaning the attention it deserves from the medical research community. For 10% of the adult population the symptoms of restless legs syndrome (RLS) resonate today.2 Sufferers are mostly over 45 and predominantly women.3 Many patients encountered in the clinic describe in great detail, and with frustration, an interruption to their night that so consumes them they will choose to ignore other more critical health problems preferring to have this specific discomfort addressed.4

Frequently during office visits, patients suffering from RLS also describe the repercussions of a poor night’s sleep. The impact of this disease carries through to their day to day activities. They are preoccupied with finding relief; once this goal is met the improvement in quality of life is appreciated.5

Through the work of Swedish neurologist Karl Ekbom in 1945, the clinical diagnosis of RLS began to take shape. His work entitled Restless Legs was so influential in describing this disease clinically, that RLS became known, for a period of time, as Ekbom syndrome. The first proposal that iron deficiency played a role in RLS was put forth by Norlander in
Since 1980, a concerted effort has been made to further the understanding of both, the hypothesis that iron plays an integral role in RLS pathology and of, the outcomes of treatment with supplemental iron.

Central iron deficiency has been implicated in the underlying pathology of RLS. A 2006 MRI imaging study found brain iron concentrations are lower than average in early onset RLS patients. Two years later, another MRI imaging survey found multi-regional (global) brain iron deficiency in patients with RLS. During the last 10 years, through the use of Ultrasound B-mode imaging and autopsy, brain iron insufficiency has been implicated in RLS.

Peripheral iron deficiency, which is considered to be levels of serum ferritin < 50 ng/ml, figures prominently in patients with RLS. The most commonly studied populations with RLS include, pregnant women in their third trimester, those with end stage renal disease requiring dialysis, and patients with anemia.

There is now a universally recognized set of criteria established by the International Restless Legs Study Group (IRLSSG) to aid providers in the clinical diagnosis and evaluation of the severity of the patients’ RLS (see table II). In the last 10 years much time has been invested in exploring the physiology and treatment of this common condition.

There are 2 major classifications of RLS – Primary and Secondary. Studies have provided many inroads toward understanding both Primary and Secondary RLS. However, today the pathophysiology is not completely understood. Primary RLS, as compared to Secondary etiologies of RLS, typically exhibit varying ages of onset, and rates of disease progression. Patients with Primary RLS are affected earlier in life and have symptoms that
progress slowly with age. Primary or Idiopathic RLS is thought to follow an autosomal dominant inheritance pattern. Secondary RLS is commonly abrupt in onset. It occurs in conjunction with, or due to, iron deficiency. Secondary RLS is most common among pregnant, or renal insufficient patients undergoing hemodialysis, or patients suffering blood loss. These groups experience the greatest resolution of symptoms with iron treatment.

This systematic review will answer the clinical question “how affective is treatment of RLS with iron?” This important question will be answered by analyzing the most current findings from randomized, double-blind, placebo controlled trials.

**PURPOSE OF STUDY**

The best research would address the diversity in the patient population suffering from RLS. Different treatment modalities would then be applied to each specific patient population. A specific proven treatment regimen could then be fitted to each of the subcategories, primary or secondary, under the umbrella of RLS. This ideal has not been completely achieved by a single study up to this point. By compiling the information provided by the most appropriate studies, exemplary in their methods, a picture greater than the individual sum of its parts emerges. The aim of this project is to concentrate on iron as one of the treatment options for patients suffering from RLS. This process includes discussion of the safety, the efficacy, the adverse-effects, and dosage forms of iron in the treatment of RLS. Once illuminated, treatment recommendations for RLS patients, based on the most current and well performed studies, will be made in order to determine the most beneficial use of iron supplementation.
CLINICAL QUESTION

The question being proposed is: how effective is treatment of RLS with iron? For this condition commonly encountered in the primary care setting, practitioners must have a full quiver of treatment options. Each patient must be treated as an individual in order to receive the most appropriate plan of care for their specific needs, conditions, and values. Answering the question, is iron an effective treatment for patients suffering from RLS will forge another treatment modality for clinical use.

METHODS

This work extends the evolving understanding of RLS by synthesizing the most recent information available with an eye toward treating RLS patients with iron supplementation.

SEARCH STRATEGY

A systematic literature review of studies focusing on iron for the treatment of Restless Legs Syndrome was performed using the MEDLINE, CINAHL, Evidence-Based Medicine Reviews Multifile and Web of Science databases. The review of literature on this topic was
not limited by date so as to include historical writing on this topic and trace the ongoing progression of understanding and treatment of RLS. When considering efficacy of the treatment, critically appraised literature was excluded if published before 2000. Only original research of the highest standard, randomized double-blind placebo controlled trials, the highest standard in research modalities, was included.

**INCLUSIONS / EXCLUSIONS**

Only studies published in the English language were considered. Studies with a focus solely on treatments other than iron were excluded. Any study not using randomized, double-blind, placebo controlled was excluded, although details from articles were used to provide a broader historical context.

**RESULTS**

Three studies focusing on the treatment of RLS with IV iron were included in this article review. They are all randomized, double-blind, placebo controlled trials with populations varying in size, gender, age, and ethnicity. The following is an overview of their methods and findings.

Turning attention first to a multicenter study conducted in Sweden and Germany by Grote et al.\textsuperscript{13} This randomized, double-blind, placebo controlled, study of Intravenous Iron Sucrose and Placebo in the Treatment of RLS was published in 2009 by *Movement Disorders*. This corner stone of the studies involving iron in the treatment of RLS utilized the largest population size of any randomized, double-blind, placebo controlled studies on the treatment results specific to iron.\textsuperscript{13}
Following 60 patients, eleven patient visits were performed during the study. There were 2 visits each at weeks 2 & 3 for drug infusion as well as subsequent visits at weeks 7, 11, months 5, 8, and 12. RLS disease severity was assessed using the IRLS at each visit. Safety and tolerance of IV iron treatment were evaluated by documentation of adverse reactions and by blood samples taken at the intervals listed above. No patients experienced changes in their hematology, iron status, and C-reactive protein that required cessation of iron treatment or any medical intervention. The paper lists in its findings no adverse affects resulting from the study and that the iron sucrose was well tolerated.

In total, 30 patients withdrew before the 12 month completion of the study. The patient population who withdrew and their stated reasons for withdrawal are a significant part of this study’s findings. The single most common reason for discontinuing involvement was “lack of efficacy”. Nineteen patients in the placebo group and 5 in the treatment group bowed out prematurely for this reason.

The methods and scoring values for findings utilized the highest of study standards. The outcome was analyzed for the “intention to treat” population (n=60). Missing values were replaced applying the last observation carried forward. This process weighs the results toward a negative outcome. With the findings weighed towards a negative outcome, the positive findings that IRLS is decreased in patients are even more significant. (Treatment: 1000 mg IV iron sucrose dosed at 200 mg spread evenly over a 3 week period in patients with serum ferritin <45nl/l before treatment. Visually identical placebo: normal saline).

Grote et al found evidence that IV iron sucrose reduced RLS symptoms both in the acute phase of the study (at 7 weeks) and during long term follow up (12-20 weeks). These
findings were within a patient population with varying degrees of iron deficiency at initiation of iron treatment. The population was between 18-70 years old, >10 IRLS, had the four cardinal RLS diagnostic criteria, and had serum ferritin >45 nl/l. Median IRLS score decreased from 27 to 7 (week 11) after iron sucrose and from 26 to 17 after placebo. The other scores at weeks 7, 12, 20 and 12 months, found this treatment modality provided significant long term RLS symptom control.\textsuperscript{13}

Complementing this body of work is a smaller population randomized, double-blind, placebo controlled study performed in 2008 and published in \textit{Sleep Medicine} in 2009. This study looked at the efficacy of oral iron in patients with RLS and a low-normal ferritin. Wang et al\textsuperscript{14} utilized the Madigan Army Medical Center as a study location. A patient population was generated from current patients at the facility who met diagnostic criteria for RLS (IRLS >10). The group was further screened and only patients with a ferritin level of 15-75 ng/l were included. 18 patients remained, 11 were randomized to iron therapy and 7 to placebo.\textsuperscript{14}

Patients were followed over 12 weeks. The treatment group was administered ferrous sulfate 325mg orally, twice daily. The placebo group was given an appearance matched placebo on the same schedule. All patients were also asked to take vitamin C concurrently (100 mg. PO). This is common, as an acidic environment in the GI tract facilitates absorption of iron taken orally. Patients were followed at 6 and 12 weeks during which they were asked to complete IRLS scoring questionnaires. They were also monitored for adverse events. There were no events requiring cessation of iron treatment or medical intervention during the course of the trial.\textsuperscript{14}
The findings of this study demonstrate statistically significant improvements in RLS symptoms using oral iron therapy in patients with low-normal serum ferritin levels. The mean baseline IRLS scores for iron and placebo groups were 24.8 and 23. Mean decreases in IRLS after 12 weeks for the 325 mg BID iron group was 10.3 and in the placebo 1.14. (p-score = .00045)

The outcome of Davis et al\textsuperscript{2} randomized, double-blind, placebo controlled study conducted in 1999, and published in *European Neurology* in 2000, reached a different result than the previously discussed studies. It concluded there were no significant differences in outcome between their iron treatment and placebo groups. In this study, conducted by the department of neurology at the University of Iowa, participants were followed at University of Iowa Hospitals and Clinics Iowa City, Iowa. The patient population included 2 groups of 14 patients administered either 325mg ferrous sulfate or placebo, orally, twice daily (PO, BID).\textsuperscript{2}

Patients included in the study had to have “symptomatic RLS”, and be under treatment for RLS at the time of enrollment. Symptomatic RLS was not defined by the authors of the paper. Because the patients were selected based on the diagnosis of RLS in their medical record one assumes that symptomatic, in this instance, means positive on each of the diagnostic 4 RLS criteria. Patients were included regardless of other potential causes of RLS, such as neuropathy. Potential participants were excluded only if they had a history of treatment for RLS with iron or if they were “anemic” (hemoglobin <10).\textsuperscript{2}

Medical history, physical examination, and adverse event reporting were all performed at time of enrollment and at weeks 2,4,14, & 26. There were no events requiring cessation of iron treatment or medical intervention during the course of the trial. Adverse
events were noted in 9 patients taking iron sulfate. There was no discussion associating the adverse events directly with iron supplementation. Adverse events include: nausea/constipation (5 patients), dark colored stools (3 patients), tooth discoloration (2 patients) vertebral fracture (1 patient), worsening of RLS symptoms (1 patient) & bladder spasms. The vertebral fracture was determined to be unrelated by the authors of the study.  

The primary outcome measure was the dichotomous variable of improvement or no improvement in average quality of sleep over weeks 13-14. These findings were compared to baseline established in the 2 weeks previous to the study beginning. Patients documented the severity of their RLS on a 100mm visual analog scale ranging from “slept very well” to “impossible to sleep”. At week 14 the question was changed to how does RLS affect your life; the same scale was employed with the two poles being “does not affect my life” and “makes my life miserable”.  

DISCUSSION

Systematically reviewing the results of randomized, double-blind, placebo controlled iron trials within the last 10 years, contrasting their findings, methods, and patient population, informs a consideration of iron’s effectiveness in RLS treatment. In their trials Grote et al\textsuperscript{13} and Wang et al\textsuperscript{14} concluded that iron supplementation resulted in statistically significant improvement in RLS symptoms. The study by Davis et al\textsuperscript{2} found that “iron sulfate does not appear to be a successful empiric treatment for RLS”.  

Davis et al\textsuperscript{2} took no steps to improve the iron absorption in the treatment group, ferrous sulfate 325mg PO BID. The widely accepted understanding concerning the difficulty
of absorbing oral iron supplements was not addressed in this study. How to maximize the absorption of oral iron supplements is integral to any discussion of oral iron therapy. An acidic gastrointestinal environment is necessary for the absorption of oral iron agents. Comparing the success between 2 separate studies with identical dosing of ferrous sulfate 325mg PO BID only patients taking concurrent vitamin C 100mg appreciated a significant improvement in RLS symptoms. This adds more evidence and support to the belief that oral iron’s effectiveness is integrally linked to proper dosing technique.

It is Wang et al$^{14}$ whose findings supported the use of oral iron, who took into account the variability in absorption. Utilizing ferrous sulfate 350mg PO BID and facilitating a gastrointestinal environment suited to absorption of iron, an acidic environment via vitamin C 100 mg, produced statistically significant results in support of iron in the treatment of RLS.$^{14}$

Turning to treatment with IV iron sucrose, Grote et al$^{13}$ conducted an exemplary and flawless study with results supporting IV iron treatment in RLS patients. Their numbers are telling in their strong implication that relevant RLS symptoms were far less frequent in patients receiving iron sucrose ($p=0.0006$).$^{13}$

Iron sucrose is the preferred form of iron for IV use. This form is the most studied and utilized IV iron supplement in current literature.$^{12}$ It is associated with the least negative adverse affects of all available IV iron forms.
CONCLUSION

Before initiating iron therapy the IRLS scale (see figure I) should be used to diagnose and document a patient’s RLS severity. This tool also allows a provider to monitor treatment outcomes and tailor a treatment plan for each patient’s specific needs. In RLS patients serum transferrin saturation and ferritin levels should be monitored. Patients with a history of iron deficiency or low serum iron parameters should undergo evaluation for the underlying iron deficiency ideology. Patients who have histories suggestive of hemochromatosis, iron overload, elevated pre-treatment transferrin saturation or serum ferritin levels should undergo evaluation to determine the cause of these abnormalities before they are treated with iron. These populations are at the highest risk for serious side effects associated with iron treatment. In all persons with RLS treated with iron, serum iron parameters should be re-measured at least quarterly. Iron treatment for patients with RLS must be combined with counseling regarding sleep hygiene.

Iron appears to be an appropriate treatment for patients in the following categories: pregnant / dialysis / iron deficient patients (ferritin <45). 1000mg IV iron sucrose dosed at 200 mg over for 3 weeks or oral iron (ferrous sulfate) 325mg BID concurrently with 100 mg vitamin C PO were both shown to be successful in decreasing RLS symptom severity in a majority of the patients as opposed to placebo group.

Further studies are warranted before Iron will be universally accepted as a first line treatment. The next generation of studies must take into account target patient groups, dosing type, dosing intervals, and comparison with other treatment modalities. To this point no
comparison study has been conducted directly comparing the two preferred treatment methods - dopamine agonists and iron.

Grote et al\textsuperscript{13} did state the relief of symptoms with their treatment was in comparable order with current clinical trials supporting dopamine agonists.\textsuperscript{13} With dopamine agonists and iron commonly being prescribed for this condition, and both resulting in symptom improvement, comparing the effectiveness would be a logical next step in forming a complete consensus for a particular treatment modality.
REFERENCES


Have the patient rate his/her symptoms for the following ten questions.

The patient and not the examiner should make the ratings, but the examiner should be available to clarify any misunderstandings the patient may have about the questions.

The examiner should mark the patient's answers on the form.

<table>
<thead>
<tr>
<th>In the past week…</th>
<th>In the past week…</th>
<th>In the past week…</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Overall, how would you rate the RLS discomfort in your legs or arms</td>
<td>(6) How severe was your RLS as a whole?</td>
<td>(7) How often did you get RLS symptoms?</td>
</tr>
<tr>
<td>_ (4) Very severe</td>
<td>_ (4) Very severe</td>
<td>_ (4) Very severe</td>
</tr>
<tr>
<td>_ (3) Severe</td>
<td>_ (3) Severe</td>
<td>_ (3) Severe</td>
</tr>
<tr>
<td>_ (2) Moderate</td>
<td>_ (2) Moderate</td>
<td>_ (2) Moderate</td>
</tr>
<tr>
<td>_ (1) Mild</td>
<td>_ (1) Mild</td>
<td>_ (1) Mild</td>
</tr>
<tr>
<td>_ (0) None</td>
<td>_ (0) None</td>
<td>_ (0) None</td>
</tr>
</tbody>
</table>

(2) Overall, how would you rate the need to move around because of your RLS symptoms?

_ (4) Very severe | _ (4) Very severe |
_ (3) Severe | _ (3) Severe |
_ (2) Moderate | _ (2) Moderate |
_ (1) Mild | _ (1) Mild |
_ (0) None | _ (0) None |

(3) Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?

_ (4) Very severe | _ (4) Very severe |
_ (3) Severe | _ (3) Severe |

8) When you had RLS symptoms, how severe were they on average?

_ (4) Very severe | _ (4) Very severe |
_ (3) Severe | _ (3) Severe |
<table>
<thead>
<tr>
<th>In the past week…</th>
</tr>
</thead>
<tbody>
<tr>
<td>(4) How severe was your sleep disturbance due to your RLS symptoms? (9) Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example</td>
</tr>
<tr>
<td>_ (4) Very severe_ (3) Severe_ (2) Moderate_ (1) Mild_ (0) None</td>
</tr>
<tr>
<td>In the past week…</td>
</tr>
<tr>
<td>(5) How severe was your tiredness or sleepiness during the day due to your RLS symptoms?</td>
</tr>
<tr>
<td>_ (4) Very severe_ (3) Severe_ (2) Moderate_ (1) Mild_ (0) None</td>
</tr>
<tr>
<td>In the past week…</td>
</tr>
<tr>
<td>(10) How severe was your mood disturbance due to your RLS symptoms - for example angry, depressed, sad, anxious or irritable?</td>
</tr>
<tr>
<td>_ (4) Very severe_ (3) Severe_ (2) Moderate_ (1) Mild_ (0) None</td>
</tr>
</tbody>
</table>

**Sum of scores =**

Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40)

1. Answers for this IRLS are scored from 4 for the first (top) answer (usually ‘very severe’) to 0 for the last answer (usually none). All items are scored. The sum of the item scores serves as the scale score.
### Table II

**Summary Matrix**

<table>
<thead>
<tr>
<th>Author/ Journal</th>
<th>Yr. published</th>
<th>Patients/ Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis, Rajput A, Rajput M, <em>European Neurology</em> Vol 43, 2000 pp. 70-75</td>
<td>2000</td>
<td>28 patients</td>
<td>Ferrous sulfate 325 mg b.i.d</td>
<td>Placebo</td>
<td>Ferrous Sulfate 325 BID does not appear to be affective empiric treatment for restless legs syndrome.</td>
<td>Randomized, Double-Blind, Placebo-Controlled</td>
</tr>
</tbody>
</table>
FIGURES

Figure I: Sleep cycle, Restless Legs Syndrome

Sleep Stage

Wake
REM sleep
I
II
III
IV

Hours of Sleep
Red = RLS patient untreated, Blue = normal sleep pattern