Restless Leg Syndrome Treatment

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September 27, 2019

Objectives

- Role for Iron
- First Line Medications
- Augmentation
- Options for Intermittent Symptoms
- Role of Opiates

What is Restless Leg Syndrome (RLS)?

Neurologic disorder – clinical diagnosis

Four Essential Criteria
Urge to move legs - usually assoc. w/ uncomfortable sensations in legs
Begins/worsens during rest or inactivity
Partially or totally relieved by movement at least as long as activity continues
Occurs exclusively or predominantly in the evening/night

What is Restless Leg Syndrome (RLS)?

- Not accounted for by another medical / behavioral condition

  Leg cramps, positional discomfort, myalgia, venous stasis, leg edema, arthritis, habitual foot-tapping

- Causes concern, distress, sleep disturbance or impairment in function

- May be accompanied by involuntary / jerking movements during sleep – periodic limb movements

Epidemiology

- 1.5-15% of adults – studies mostly looked at Caucasian populations (Ohayon 2012; Ohayon 2016; Silber 2013; Yeh 2012)

- Etiology of primary RLS unknown – idiopathic CNS disorder

  May be secondary to iron deficiency, end-stage renal disease, or pregnancy

- Pathophysiology linked to abnormalities in the dopaminergic system & iron metabolism

- Insufficient sleep / sleep apnea might exacerbate

- Family history common – 92% of idiopathic RLS (Ondo 1996)

International Restless Legs Syndrome Study Group (IRLS) Rating Scale

10-item scale with scores ranging from 0 to 4 per question

- Mild: ≤10
- Moderate: 11–20
- Severe: 21–30
- Very severe: >30

Non-pharmacologic Treatment

- Avoid precipitants - caffeine, alcohol, certain meds
- Mental alerting activities at bedtime
- Moderate regular exercise (Aukerman 2006)
- Counter stimuli - hot or cold baths, compression stockings, limb massage, and pneumatic compression devices (Lettieri 2009)
- Short daily hemodialysis for ESRD patients
- Treat other sleep disorders, such as OSA (Silva 2017)

Medications & Substances associated with RLS

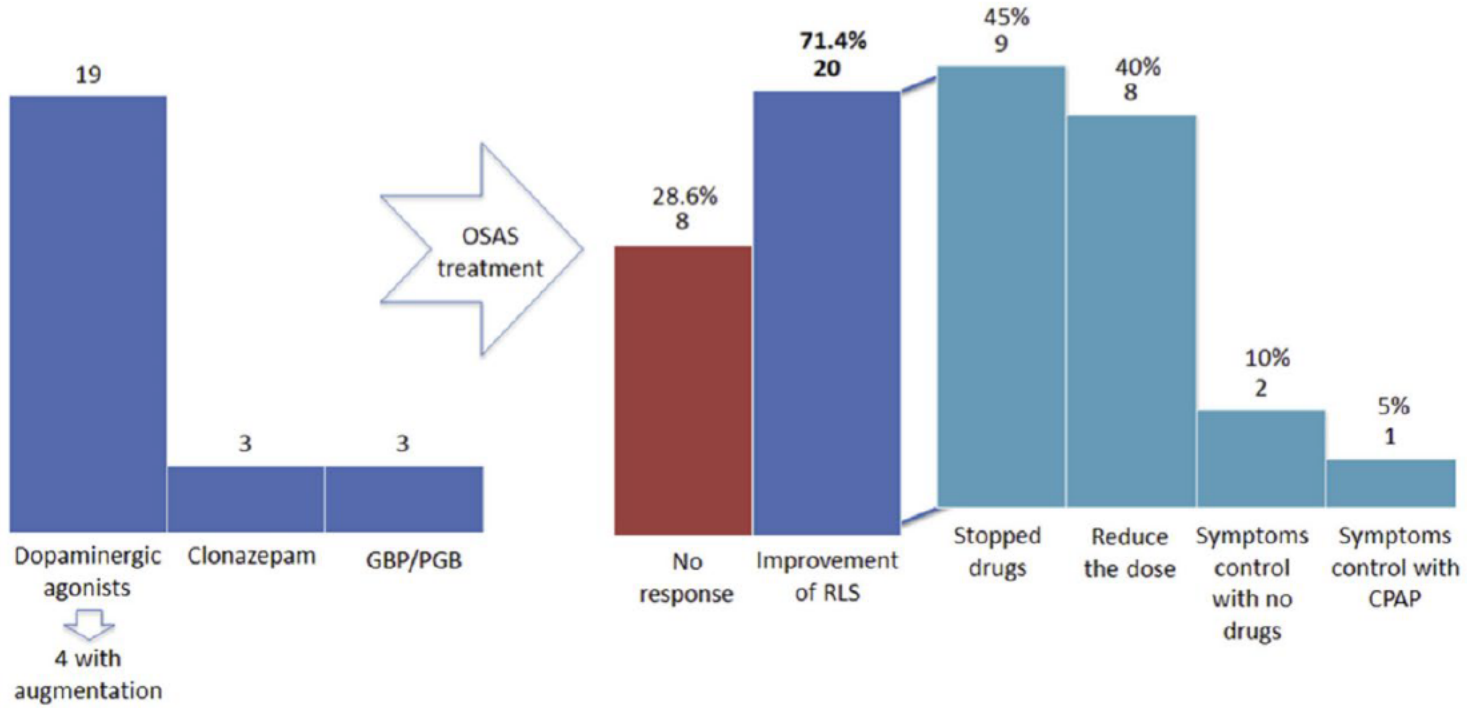
SSRIs
SNRIs
Tricyclic antidepressants
Neuroleptic / Antipsychotic Agents
Dopamine-blocking anti-emetics (i.e. metoclopramide)
Sedating centrally-acting antihistamine (i.e. diphenhydramine)
Caffeine

Buproprion NOT associated with RLS

Comorbid OSA

From a database of 97 RLS pts, 56 pts had both OSA and RLS (Silva 2017)

- 28 met the criteria for study
- Mean AHI - 19



Alternative Therapies & Novel Devices

Low quality of evidence & number of trials for any single alternative therapy (Xu 2018)

- Low-risk strategies - acupuncture and yoga

Novel devices

- Relaxis Pad - approved by FDA in May 2014
  - Vibratory stimulation to legs
  - Somewhat questionable evidence
    - Improvement was noted in the Medical Outcomes Study Sleep Problems Index II (MOS-II) scores compared to sham pads (mean improvement 13.2 vs 6.2 points, p = 0.02) (Burbank 2013)
    - MOS-II was not a primary or secondary outcome on studies and was tabulated from MOS sleep scale, which was a secondary outcome
    - No difference - active vs sham pad
      - IRLS scores (Improvement - 6.68 versus 6.39, p = 0.81)
      - RLS quality of life scores (Improvement - 11 versus 7 points, p = 0.14)

Pharmacologic Treatment

Major Classes of Medications (Scholz 2011; Aurora 2012; Wilt 2013; Trotti 2019)

- Iron Replacement
- Dopaminergic Agents
- Alpha-2-Delta Calcium Channel Ligands
- Opiates
- Benzodiazepines

Meds with FDA approval (only for moderate or severe)

- Pramipexole
- Ropinorole
- Rotigotine Patch
- Gabapentin Enacarbil

Iron & RLS

- CSF analysis - ↓ferritin & ↑transferrin in RLS patients, despite normal serum ferritin and transferrin (Earley 2000)

- MRIs - ↓iron concentrations in substantia nigra, one of the primary brain regions with dopamine-producing cells (Haba-Rubio 2005 and Allen 2001)

  Early onset (not late onset) (Earley 2006)

- Autopsy studies on brain tissue - ↓ferritin & transferrin receptor & ↑transferrin in substantia nigra - consistent with iron insufficiency (Connor 2003 and Connor 2004)

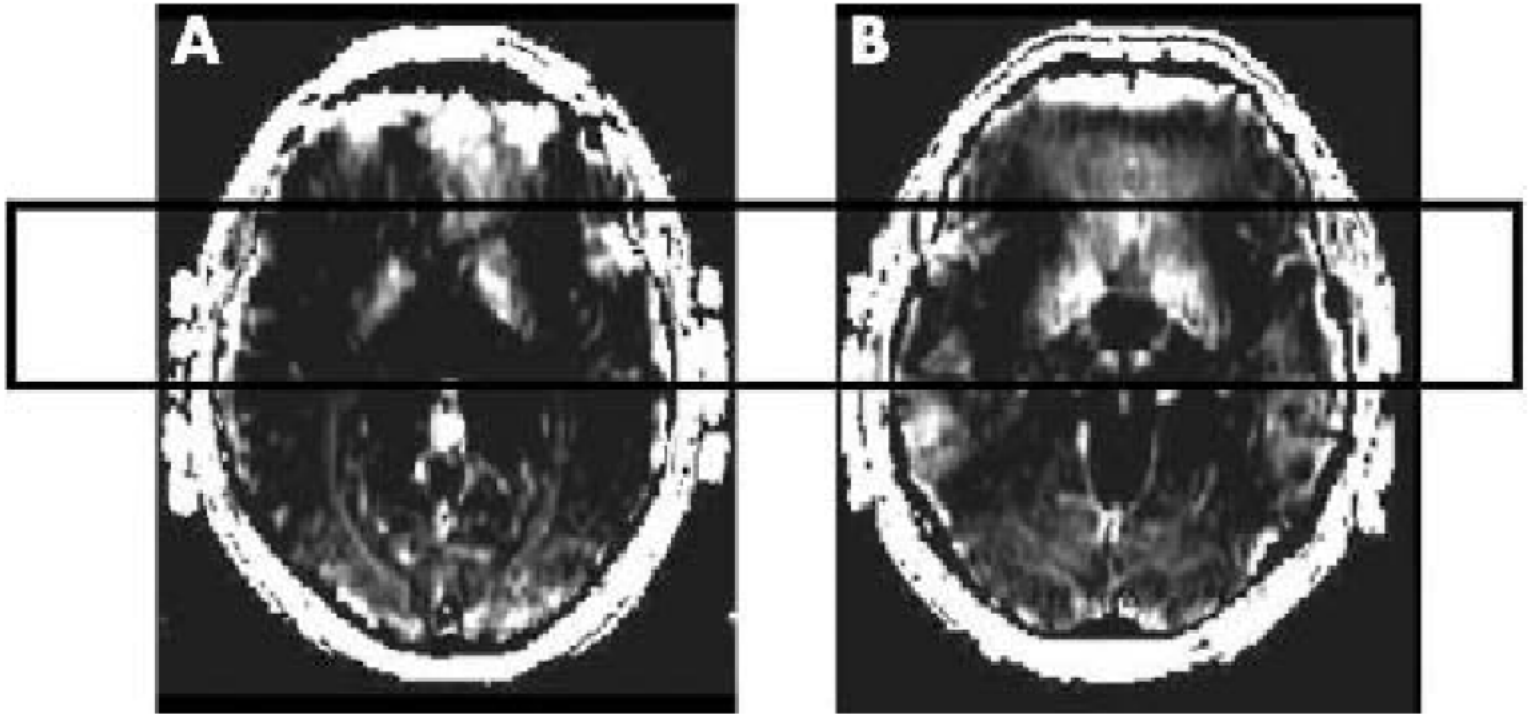


Figure 1 Quantitative analysis of different regions of interest obtained by calculating the relaxation rate R2′ (1/T2′), a pure measure of focal field inhomogeneity due to tissue iron content. Basal ganglia R2′ image in (A) a 56 year old patient with RLS and haemochromatosis (patient 2) and (B) a control subject.

Haba-Rubio J, Staner L, Petiau C, et al. Restless Leg syndrome and low brain iron levels in patients with haemochromatosis. J Nurol Neurosurg Psychiatry 2005; 76: 1009-1010.

Iron Replacement

Iron insufficiency - most consistent finding / strongest environmental risk factor associated with RLS

- Regular blood donors have increased risk of RLS (Silber 2003)
- RLS severity negatively correlates with serum ferritin (O'Keeffe 1994 and Sun 1998)
- Correcting iron status in those deficient can reduce symptoms (O'Keeffe 1994 and Davis 2000)

Serum ferritin < 45 - 50 mcg/L associated with increased severity of RLS (Silber 2013)

Oral replacement suggested if serum ferritin level ≤75 mcg/L
(Silber 2013; Winkelman 2016; Allen 2018)

Avoid empiric treatment - unsuspected hemochromatosis

Iron improves IRLS score

Cochrane Database of Systematic Reviews 2019 - 10 studies (428 participants, followed 2-16 wks)

Primary outcome - restlessness or uncomfortable leg sensations

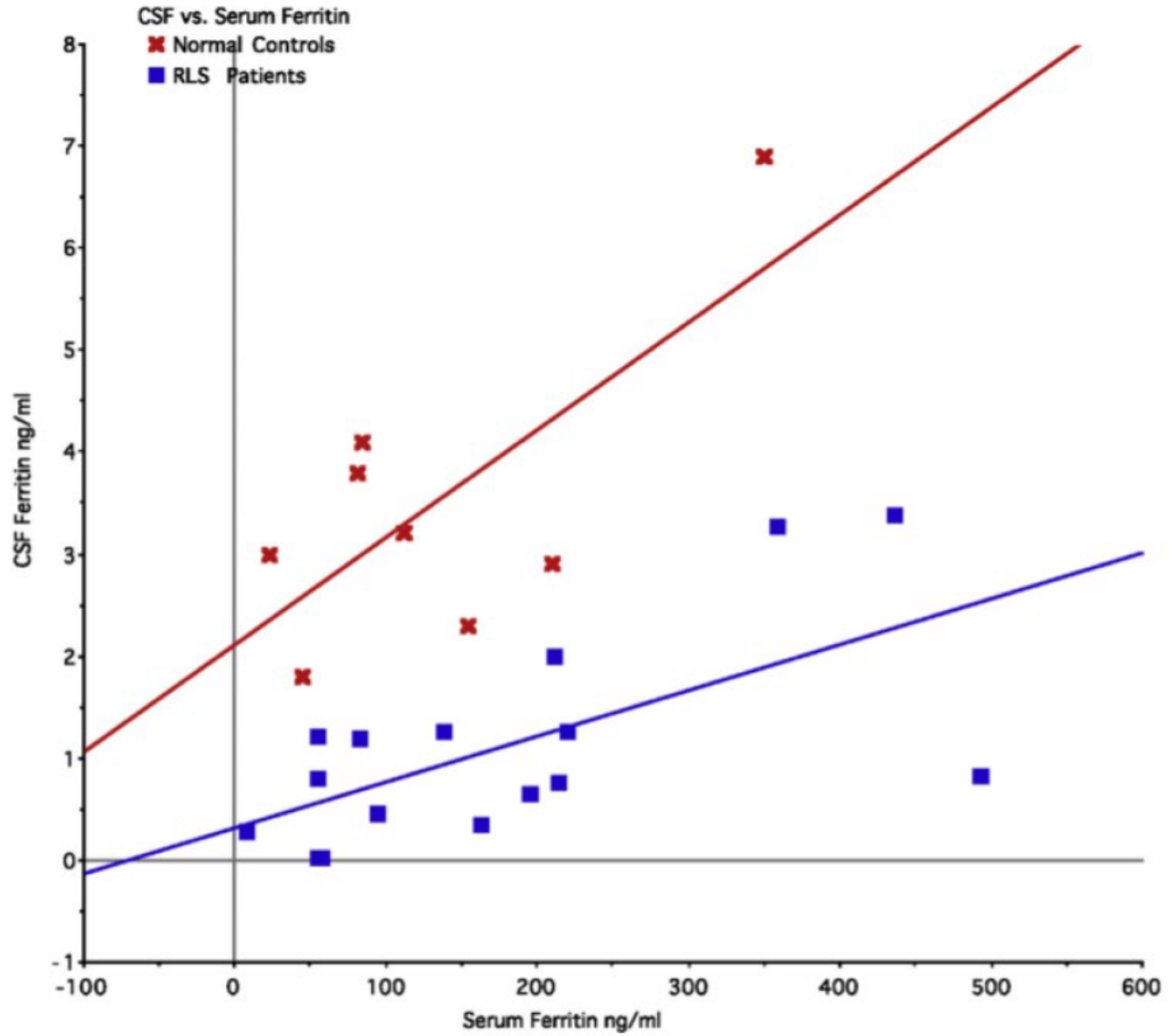
- Data from 7 trials using IRLS to compare iron and placebo, found iron resulted in greater improvement in IRLS (Mean Difference -3.78, 95% CI -6.25 to -1.31; 7 studies, 345 participants)
- GRADE assessment of certainty - moderate

Secondary outcomes

- Subjective sleep quality - no difference between groups
- PLMS - not significantly reduced
- Iron did not improve ESS but did improve the daytime tiredness item of the RLS-6 compared to placebo
- GRADE rating for secondary outcomes - low to very low

Subgroup analysis

- More improvement - dialysis patient trials
- Oral vs IV iron did not show significant subgroup differences
- Iron did not result in significantly more adverse events than placebo



Earley C, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology. 2000;54:1698-1700.

Clinical Benefit with Supplementation even with Normal Ferritin

Wang et al (Sleep Med 2009)

- Double-blind, placebo-controlled study (18 pts)
- Baseline ferritin - Similar

  Treatment Group (40.6+/-15.3ng/ml)

  Placebo Group (36.7+/-20.8ng/ml)
- After 12 weeks, Ferritin levels increased more in treatment group

  Treatment Group (25.1+/-20.3ng/ml)

  Placebo Group (7.5+/-13.7ng/ml), (p=0.04)
- After 12 weeks, IRLS scores decreased more in treatment group

  Treatment Group(10.3+/-7.40)

  Placebo Group (1.14+/-5.64), (p=0.01)

Recommended Iron Levels

If serum ferritin < 50 to 75 µg/L, oral iron supplementation should be prescribed

Consider IV iron if ferritin levels do not increase (from malabsorption or inability to tolerate po replacement)

Willis-Ekbom Disease Foundation Revised Consensus Statement on the Management of Restless Legs Syndrome

If serum ferritin is ≤75 µg/L, oral iron supplementation should be prescribed

Ferrous sulfate 325 mg with vitamin C 200 mg taken twice daily likely will improve RLS symptoms in these patients

Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

IV Iron Therapy

Christopher J. Earley et al. (Sleep 2004)

- Single 1000 mg IV infusion of iron dextran
- Improvement in mean global RLS symptom severity, TST, hours with RLS symptom, PLMS, Brain iron concentrations at 2 weeks by MRI
- Benefit in 3/10 patients with only mild side effects (except one who had an allergic response)

Yong Won Cho et al. (Sleep 2013)

- Four weekly doses of 250 mg low-molecular weight iron dextran for a total dose of 1 gram.
- 25 patients without serious adverse reactions, 17/25 showed moderate or complete improvement of all symptoms
- Response was not predicted by blood or CSF iron baseline characteristics

When to consider IV iron

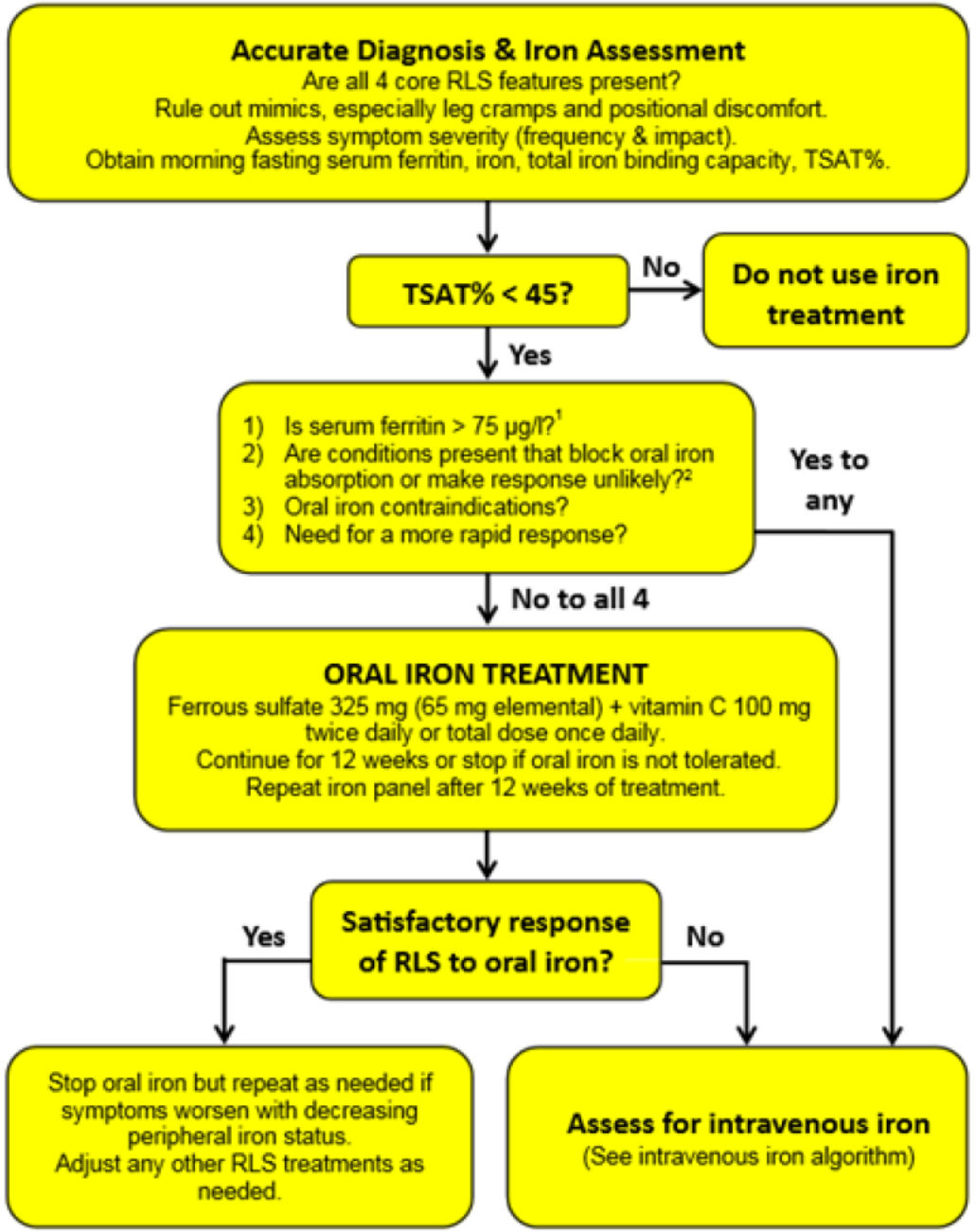
- Reserved for pts with proven low or low-normal serum ferritin levels intolerant of or resistant to oral iron (malabsorption)
- Iron gluconate, iron sucrose, iron dextran, ferric carboxymaltose, and ferumoxytol all IV preparations available in U.S.
- Iron dextran associated with risk of anaphylaxis

  Less of an issue with more recently developed low-molecular-weight iron dextran (incidence estimated to be 1 per 200,000 infusions)

Willis-Ekbom Disease Foundation Revised Consensus Statement on the Management of Restless Legs Syndrome

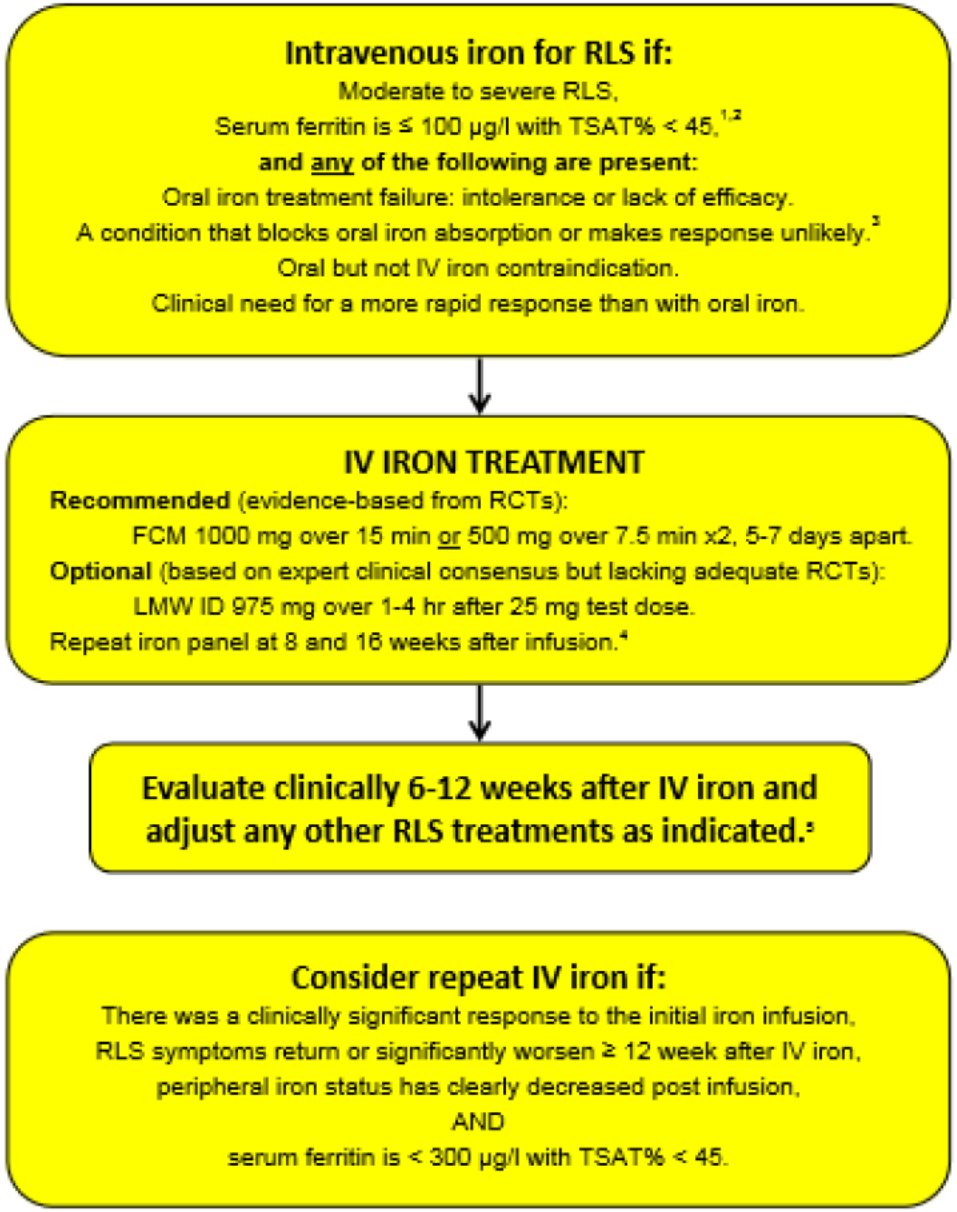
IV vs. PO Iron

- No direct comparisons of IV vs. oral iron supplementation
- Available data does not show clear superiority of one route of administration over another
- As oral iron is easier to administer and is safer – oral iron is recommended first line
- Trials of IV iron suggest effective in ~50-60% of patients (Allen 2018)



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

Richard P. Allen [a,*], Daniel L. Picchietti [b], Michael Auerbach [c], Yong Won Cho [d], James R. Connor [e], Christopher J. Earley [a], Diego Garcia-Borreguero [f], Suresh Kotagal [g], Mauro Manconi [h], William Ondo [i], Jan Ulfberg [j], John W. Winkelman [k], On behalf of the International Restless Legs Syndrome Study Group (IRLSSG)



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Selecting Medications for RLS

Chronic persistent RLS (Silber 2013)

- Frequent / Troublesome enough to warrant daily medication
- At least x2 per week
- Moderate to severe distress
- Did not respond to non-pharmacologic therapy or treatment of underlying iron deficiency

Goals of treatment

- Reduce or Eliminate Symptoms of RLS
- Improve Daytime Function
- Sleep
- Quality of Life

First-line Meds

Dopamine Agonists	Alpha-2-Delta Calcium Channel Ligands
Pramipexole	Gabapentin
Ropinirole	Gabapentin Enacarbil
Rotigotine transdermal patch	Pregabalin

Head to head comparisons limited between these two classes

Factors to Consider when Choosing Medication

Disease Severity

Patient Age

Comorbidities (Depression / Anxiety, Pain, History of Impulse Control Disorders, Pain)

Drug Side Effects

Patient Preferences

When to Choose Dopamine Agonists

When to Choose Dopamine Agonists
Increased risk for falls
Severe symptoms of RLS
Excess weight, metabolic syndrome, or OSA
Comorbid depression

Adapted from Garcia-Borreguero D, Kohnen R, Silber MH, et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep Med 2013; 14:675.

When to Choose Alpha-2-Delta Ligands

When to Choose Alpha-2-Delta Ligands
Sleep disturbance disproportionate to the other symptoms of RLS
Comorbid insomnia
Painful restless legs
Comorbid pain syndrome
History of or current impulse control disorder
Comorbid generalized anxiety disorder

Adapted from Garcia-Borreguero D, Kohnen R, Silber MH, et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep Med 2013; 14:675.

Other Factors to Consider

Factors that impact the choice of agent	Treatment choice
Time of day (daytime disturbance)	Long-acting agent (preferred) Twice a day dosing of a short-acting agent
Pregnancy risk	Avoid both dopaminergic agents and alpha-2-delta ligands Consider iron therapy
Impaired renal function	Avoid pramipexole Avoid or dose adjust alpha-2-delta ligands
Hepatic impairment	Avoid ropinirole Use caution with rotigotine patch

Adapted from Garcia-Borreguero D, Kohnen R, Silber MH, et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep Med 2013; 14:675.

Dopamine Agonists

Directly stimulate dopamine receptors

Longer half-life (4-6 hours) then levodopa (90 minutes)

Lower risk of complications then levodopa

Cochrane Database of Systematic Reviews 2011 looking at 38 trials

- Including cabergoline, lisuride, pergolide, pramipexole, ropinirole, rotigotine, and sumanirole

  All except sumanirole were superior to placebo
- Mean reduction IRLS -5.7 in dopamine agonist treatment versus placebo (95% CI -6.7 -to -4.7)
- Self rated quality of sleep were improved by a standardized mean difference (SMD) of 0.40 (95% CI 0.33 to 0.47)
- Disease specific quality of life were improved by a SMD of 0.34 (95% CI 0.23 to 0.44)

Non-Ergot Dopamine Agonists

Pramipexole, Ropinirole, Rotigotine preferred

Fewer side effects then other dopamine agonists (cabergoline and pergolide) and levodopa

American Academy of Sleep Medicine Clinical Practice Guideline – 2012 Update (Aurora 2012)

- STANDARD level of recommendation include pramipexole and ropinirole.

  STANDARD AGAINST pergolide – risk of heart valve damage

- GUIDELINE level of recommendation include levodopa with dopa decarboxylase inhibitor and cabergoline (which has additional caveats for use)

  Potential side effects use cabergoline only if other recommended agents have been tried first and failed with close clinical follow-up

Pramipexole

Meta-analysis of seven randomized placebo-controlled trials with 1398 pts

Average improvement in IRLS rating scale of 6.7 point over placebo (95% CI 4.9-8.5)

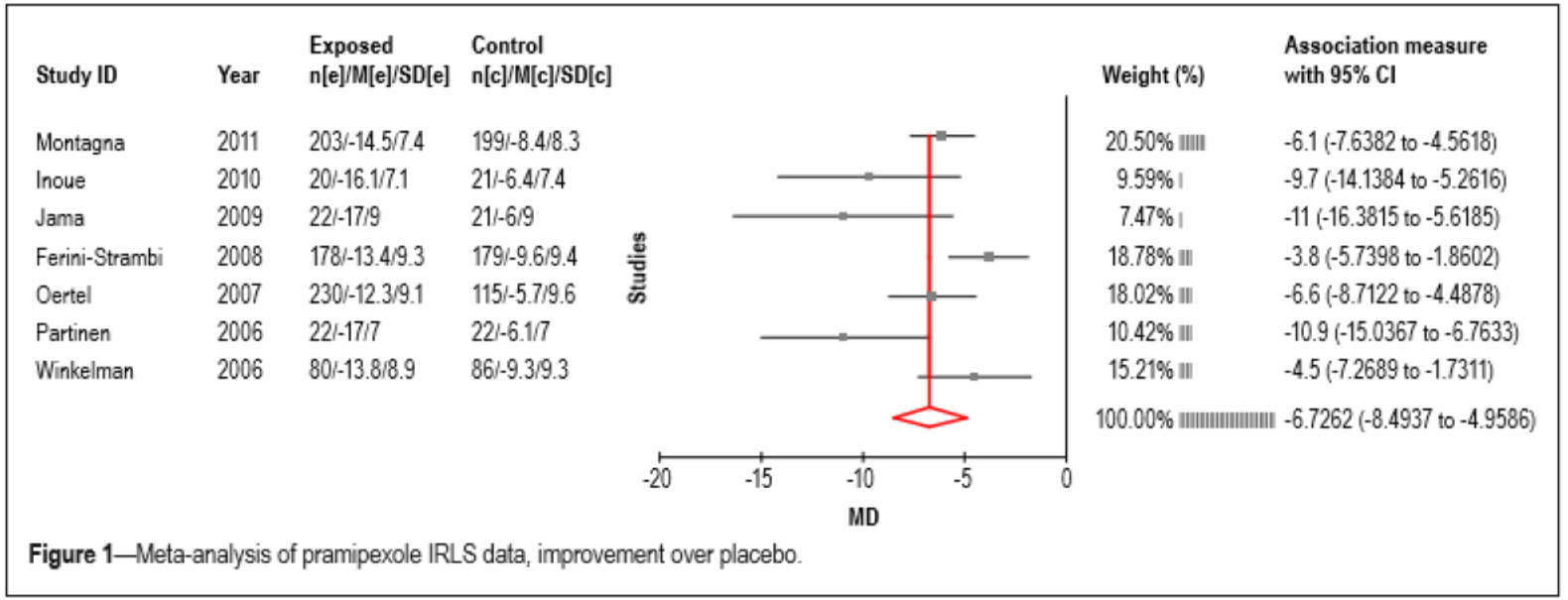


Figure 1—Meta-analysis of pramipexole IRLS data, improvement over placebo.

Aurora RN, Kristo DA, Bista SR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults--an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep 2012; 35:1039.

Ropinirole

Meta-analysis of five randomized placebo-controlled trials with 936 pts on doses of 1.5-4.6 mg

Average improvement in IRLS rating score of 4 points over placebo (95% CI 2-6)

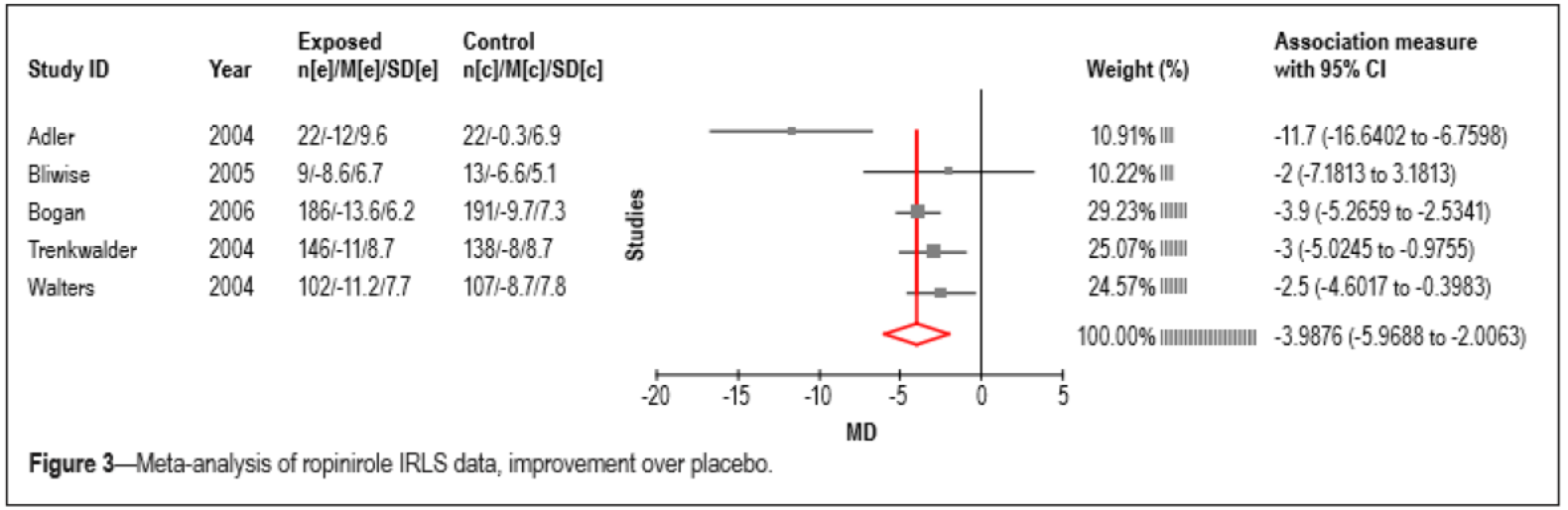


Figure 3—Meta-analysis of ropinirole IRLS data, improvement over placebo.

Aurora RN, Kristo DA, Bista SR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults--an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep 2012; 35:1039.

Dosing of Pramipexole and Ropinirole

- Onset of Action ~ 90-120 minutes
- Longer acting forms - not well studied
- Side effects - generally mild, last 10-14 days
  - Nausea, fatigue, and orthostasis
  - Excessive sleepiness (56%)/ Sleep attacks (10%) on Pramipexole (Lipford 2012)
- Pramipexole 0.125 mg daily - may increase by 0.125 mg every 2-3 days
  - Most need ≤ 0.5 mg, doses up to 0.75 may be needed
  - 52-wk, randomized, double-blind trial – 0.25 mg was no more effective then placebo, but 0.5 mg reduced the IRLS score (Allen 2014)
- Ropinirole 0.25 mg daily - may increase by 0.25 mg every 2-3 days
  - Most need 2 mg, doses up to 4 mg may be needed
  - Max ~3 mg in ESRD pts
  - Average daily dose in one large trial was 1.9 mg (Trenwalder 2004)

Other Considerations – Impulse Control Disorders

Increased risk of impulse control disorders (ICDs) (Tippmann-Peikər 2007)

- Can develop within months to years – widely variable
- Seen at both high and low doses – case series had a mean pramipexole dose of 0.46 mg and ropinirole at 0.25 mg/day

Prospective case-control study using a screening questionnaire for ICDs (mean onset 9.5 months) (Cornelius 2010)

- 9% compulsive shopping
- 5% pathologic gambling
- 11% compulsive eating
- 3% hypersexuality
- 7% punding
- 17% any ICD
- Mean dose 1.25 mg for pramipexole, 3.6 mg for ropinirole at onset

Other Considerations - Augmentation

Main complication of long-term dopaminergic therapy (Garcia-Borreguero 2016)

Worsening of RLS symptoms with stable or increasing doses of medication

- Earlier onset
- Increased intensity
- Shorter duration of drug action
- Spread of symptoms to arms

When to suspect

- Increasing severity despite appropriate treatment
- Increasing severity after a dose increase
- Dose reduction improves symptoms

Screening question for augmentation

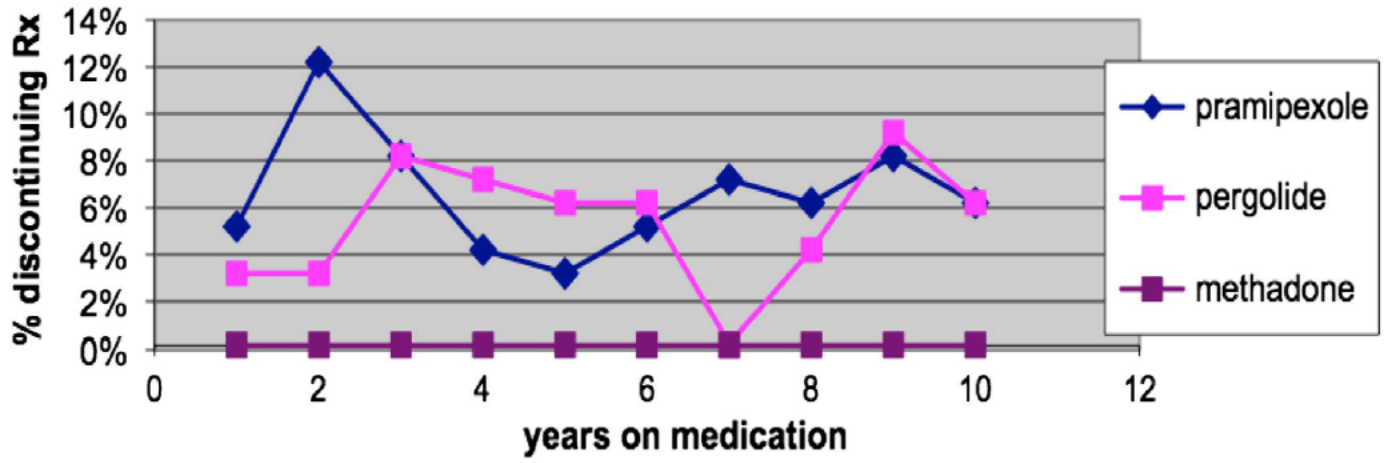
Proposed questions from International Restless Legs Syndrome Study Group Task Force in conjunction with the European Restless Legs Syndrome Study Group and the RLS Foundation:

- Not yet validated
- Affirmative answer to any question → suspect augmentation

Screening Questions
[1] Do RLS symptoms appear earlier than when the drug was first started?
[2] Are higher doses of the drug now needed, or do you need to take the drug earlier in the day to control symptoms?
[3] Has the intensity of symptoms worsened since starting the drug
[4] Have symptoms spread to other body parts (eg, arms) since starting the drug?

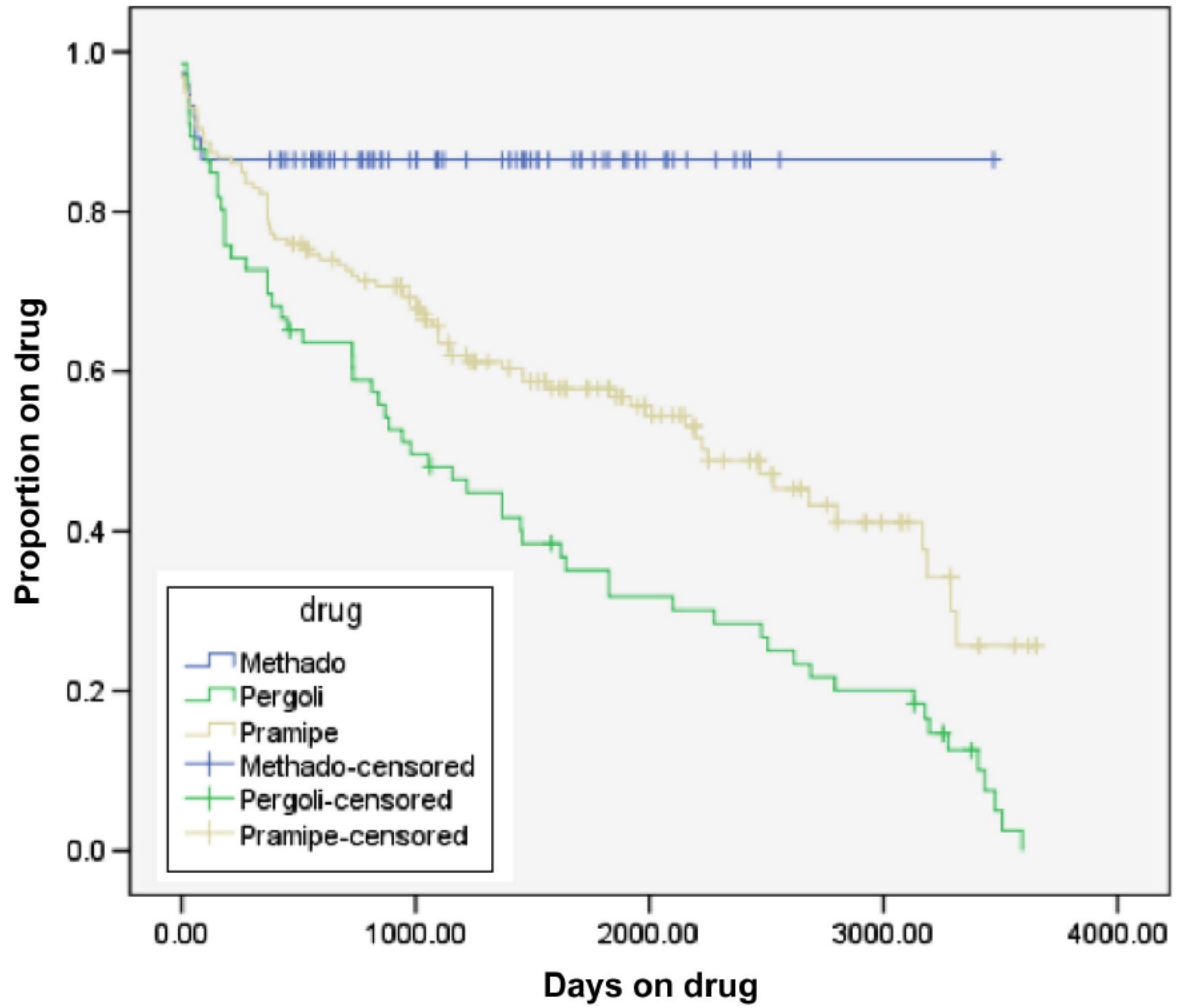
Risk of Augmentation with Time

- 5-8% taking pramipexole 40-52 weeks (Allen 2014)
- 32% taking pramipexole for 21.2 +/- 11.4 months (Winkelman 2004)
- 42-68% of patients taking pramipexole for 8-10 years (Lipford 2012; Silver 2011)



Silver N, Allen RP, Senerth J, Earley CJ. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med 2011; 12:440.

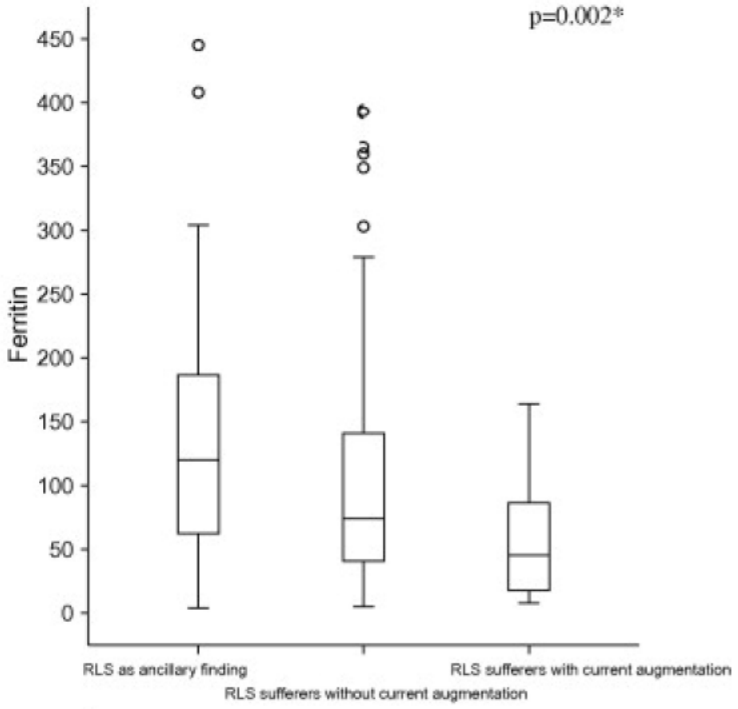
Kaplan-Meier Curve – Drug Discontinuation

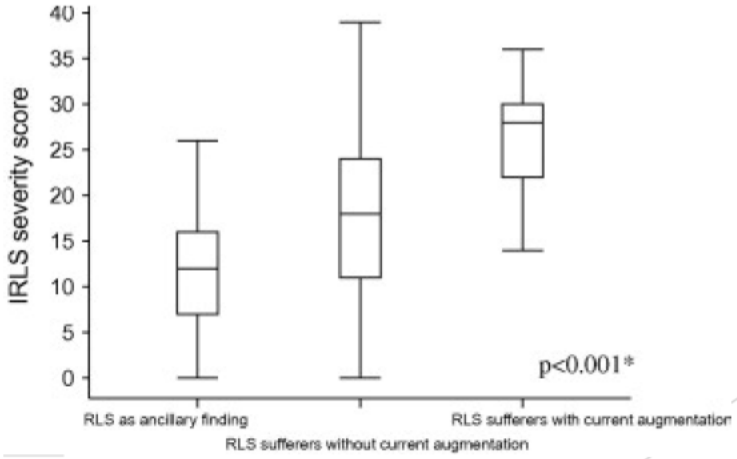


Silver N, Allen RP, Senerth J, Earley CJ. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med 2011; 12:440.

Risk Factors for Augmentation

- Higher daily doses
- Longer duration of use
- Family history of RLS (Ondo 2004)
- No evidence of neuropathy on electromyography or nerve conduction studies (Ondo 2004)
- Lower ferritin levels (Frauscher 2009)





Frauscher B, Gschliesser V, Brandauer E, et al. The severity range of restless legs syndrome (RLS) and augmentation in a prospective patient cohort: association with ferritin levels. Sleep Med 2009; 10:611.

Differential Diagnosis of Augmentation

	Augmentation	End-of-dose rebound	Tolerance	Natural progression	Exacerbating factors
Worse than before treatment	Yes	Yes in early morning	No	Yes	Yes
Earlier onset	Yes	Yes in early morning	No	Yes	Yes
Spread to arms	Yes	No	No	Yes	Yes
Breakthrough at night	Yes	Yes in early morning	Yes	Yes	Yes
Worse with increased dose	Yes but not immediately	No	No	No	No
Improved with decreased dose	Yes but not always	No	No	No	No

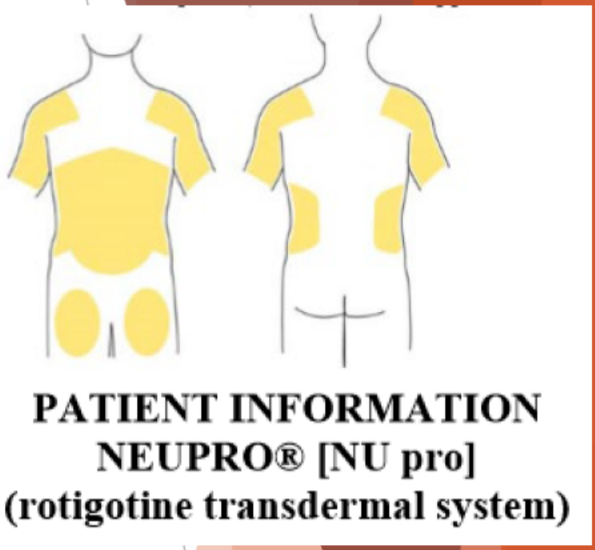
Adapted from Garcia-Borreguero D, Silber MH, Winkelman JW, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: A combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med 2016; 21:1.

How to Manage Augmentation

- Reassess iron stores
- Ask about new lifestyle changes / medications
- Mild augmentation - dose of a dopamine agonist can be split
  - If ineffective, dose can be modestly increased
- Severe augmentation - a couple of options…
  - Switch to Rotigotine
  - Replace with alpha-2-delta calcium channel ligands
- Avoid abrupt withdrawal - Dopamine withdrawal syndrome
  - Anxiety, panic attacks, depression, nausea, diaphoresis, pain, fatigue, and dizziness

Rotigotine

- Once daily patch – typically started at 1 mg / 24 hours
- Titrated upward to maximum dose of 3 mg/24 hours
- Cannot cut patches
- Most common side effect is application site reactions
  - To help…
    - Rotate application sites - clean, dry, and healthy skin
    - Avoid direct sun exposure if reaction - may change skin color
    - Remove patch before MRI or cardioversion - may cause a burn
- Contains sulfite
- Otherwise similar side effects to oral dopamine agonists



Rotigotine

- Meta-analysis of 5 randomized controlled trials of 644 pts on 1-4.5 mg (Aurora 2012)
  - Average improvement in the IRLS score over placebo was 7 (95% CI 5.6-8.4)
- Long-term open label safety and efficacy trials
  - 12 months - Improvement by 17.4 ± 9.9 on IRLS score with good or very good tolerability being reported in 80.3% of 220 pts (Oertel 2008)
    - Most common side effect: application site reaction in 40%
  - 24 months - Improvement by 17.2 ± 9.2 on IRLS score for the 190 pts that completed (Hogl 2010)

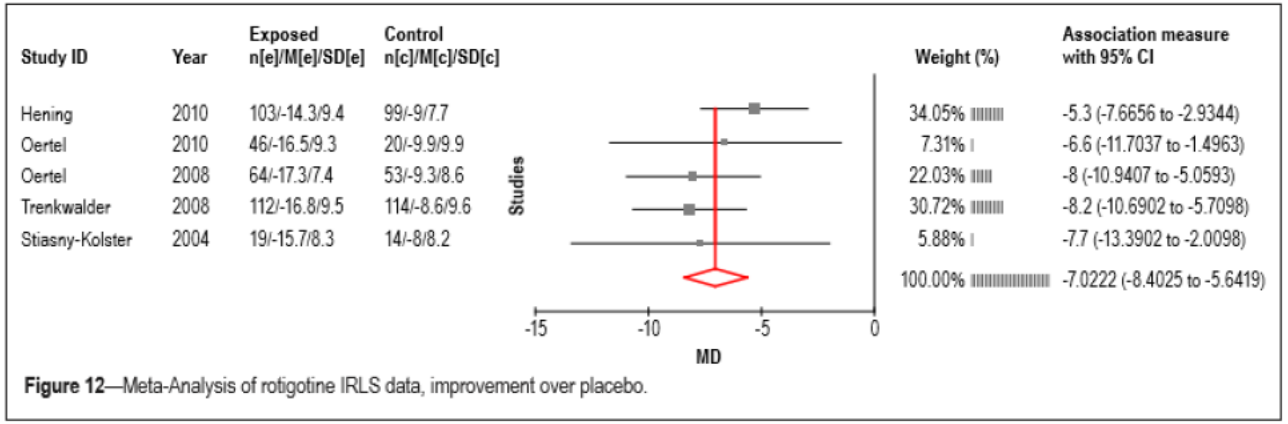


Figure 12—Meta-Analysis of rotigotine IRLS data, improvement over placebo.

Augmentation and Rotigotine

- 2.7% Clinically significant augmentation in a 1-year open-label study (Inoue 2013)

- 38% of patients using rotigotine for five years had augmentation (only clinically significant in 5% taking 1-3 mg/24 hours) (Oertel 2011)

- 2.9% had clinically relevant augmentation on an open label study over a 1.5 year period (Benes 2012)

Alpha-2-Delta Calcium Channel Ligands

- Gabapentin, pregabalin, and gabapentin enacarbil
- NO AUGMENTATION
- Consider for treatment of RLS in association with Parkinson disease
  - Often already on dopaminergic therapy
- May be considered as add-on in those on dopaminergic agents
- Monitor - worsening depression and suicidality
- Renal excretion

Gabapentin Enacarbil

- Pro-drug to Gabapentin - Long-acting
- For mod-severe RLS
- Recommended dose is 600mg
- Common side effects – somnolence and dizziness, generally mild to moderate
  - 52 wk open-label study – 2/3 reported mild to moderate side effects with 10% discontinuing (Ellenbogen 2011)

- 1200 mg found to reduce WASO (adjusted mean difference : -26.0 min; P < .0001) and PLMAi (adjusted mean difference: -3.1; P = .002) compared with placebo (Winkelman 2011)

Gabapentin Enacarbil

Meta-analysis of three randomized placebo-controlled trails with 468 pts looking at 1200 mg/d gabapentin enacarbil

- Average improvement in IRLS rating scale of 4.5 point over placebo (95% CI 2.5-6.5)

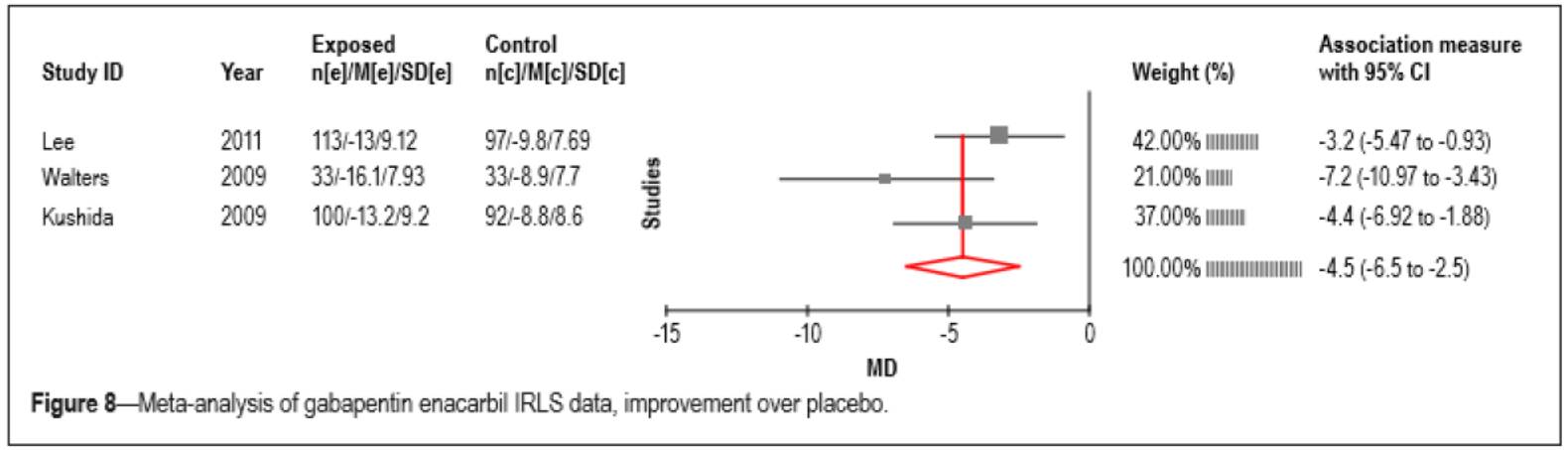
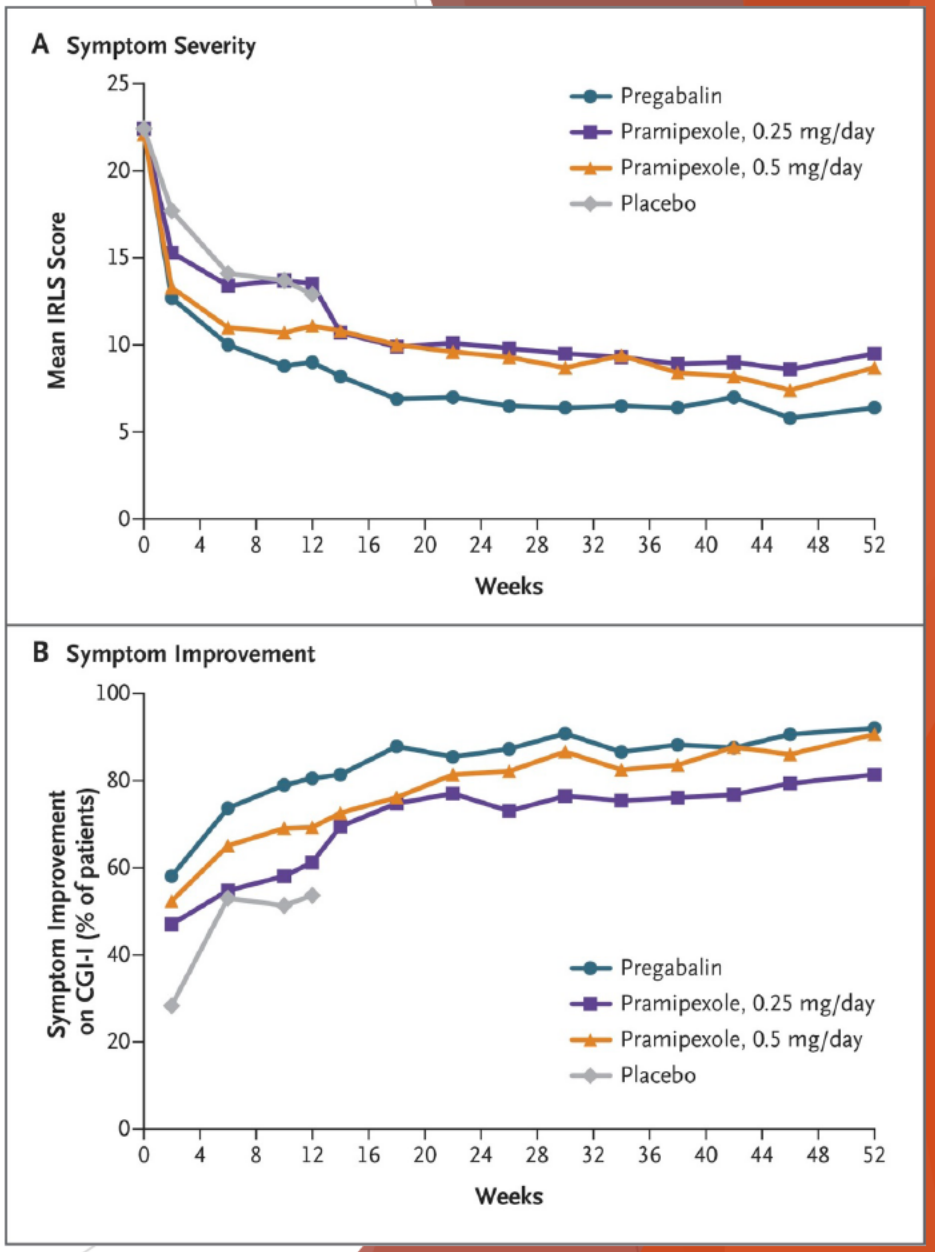


Figure 8—Meta-analysis of gabapentin enacarbil IRLS data, improvement over placebo.

Aurora RN, Kristo DA, Bista SR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults--an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep 2012; 35:1039.

Pregabalin

- Starting dose - 50-75 mg; Usual effective dose - 150-450 mg
- Common side effects: dizziness, somnolence, fatigue, and headaches - usually mild (Allen 2014)
- 52-wk randomized double-blind study of 719 pts assessed on pregabalin 300mg, pramipexole 0.25 and 0.50 mg, and placebo
  - At 12 wks, improvement in mean IRLS scale was 4.5 points greater among pregabalin than placebo (P<0.001)
  - At 12 wks, pts with symptoms that were "very much improved" / "much improved" was greater with pregabalin than placebo (71.4% vs. 46.8%, P<0.001).
  - Augmentation rate over 40 - 52 wks was significantly lower with pregabalin than pramipexole 0.5 mg (2.1% vs. 7.7%, P=0.001) but not at 0.25 mg (2.1% vs. 5.3%, P=0.08).
  - Pregabalin had a higher rate of discontinuation due to side effects (28% vs. 19 and 24% for pramipexole 0.25 mg and 0.5 mg)

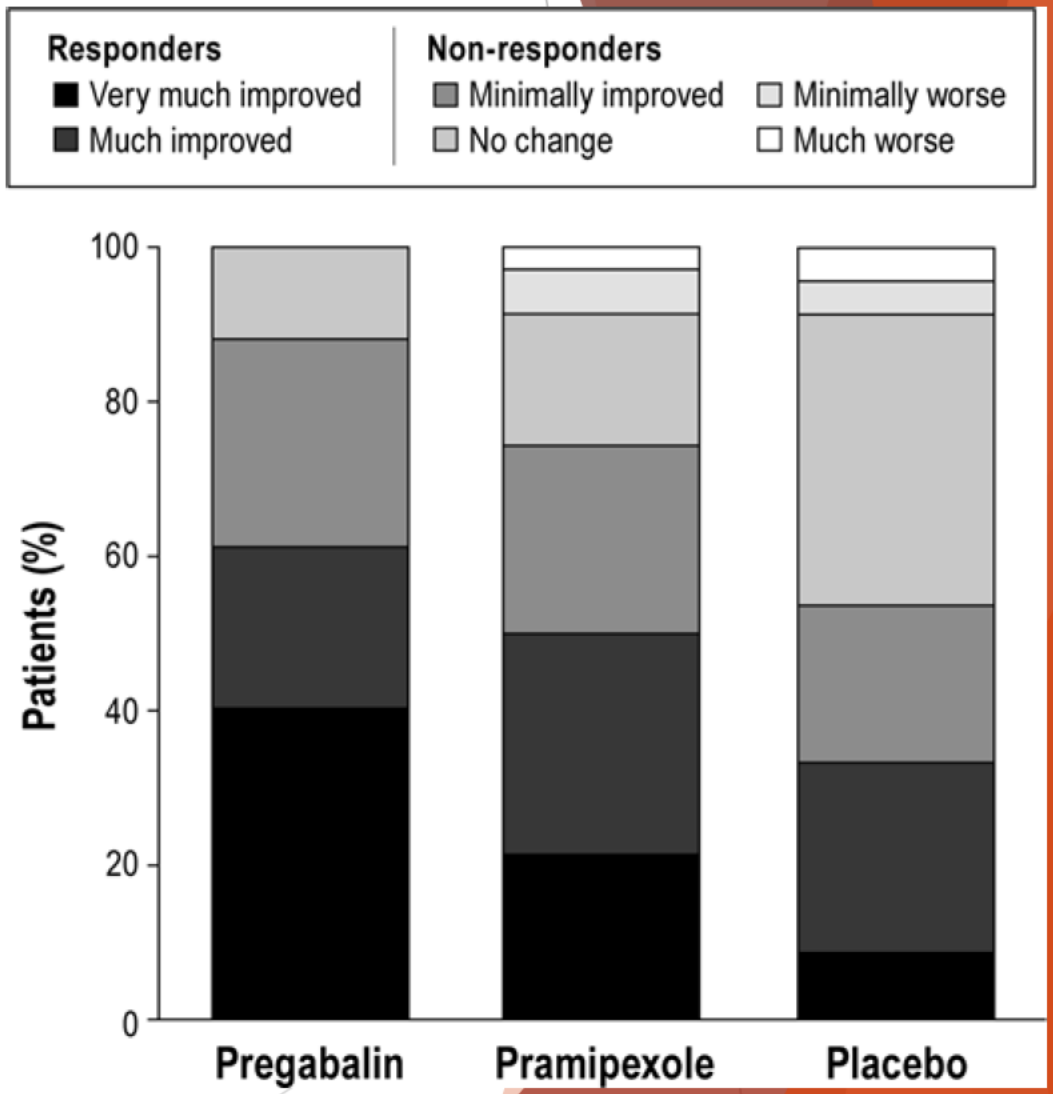


Allen RP, Chen C, Garcia-Borreguero D, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. N Engl J Med 2014; 370:621.

Pregabalin

Randomized, double-blind crossover study of 85 pts - 300mg pregabalin improves sleep measures on PSG (Garcia-Borreguero 2014)

- Reduce WASO (-27.1 min vs placebo [P<0.0001]; -26.9 vs pramipexole 0.5 mg)
- Reduce Awakenings after sleep onset (-2.7 vs placebo; -7.9 vs pramipexole 0.5 mg [P<0.0001])
- Reduce PLMAi (-3.7 PLMA/h vs placebo [P<0.0001], similar to pramipexole 0.5 mg)
- Pts symptoms that were "very much improved" / "much improved" was greater with pregabalin than placebo (61.2% vs 33.3%)



Garcia-Borreguero D, Patrick J, DuBrava S, et al. Pregabalin versus pramipexole: effects on sleep disturbance in restless legs syndrome. Sleep 2014; 37:635.

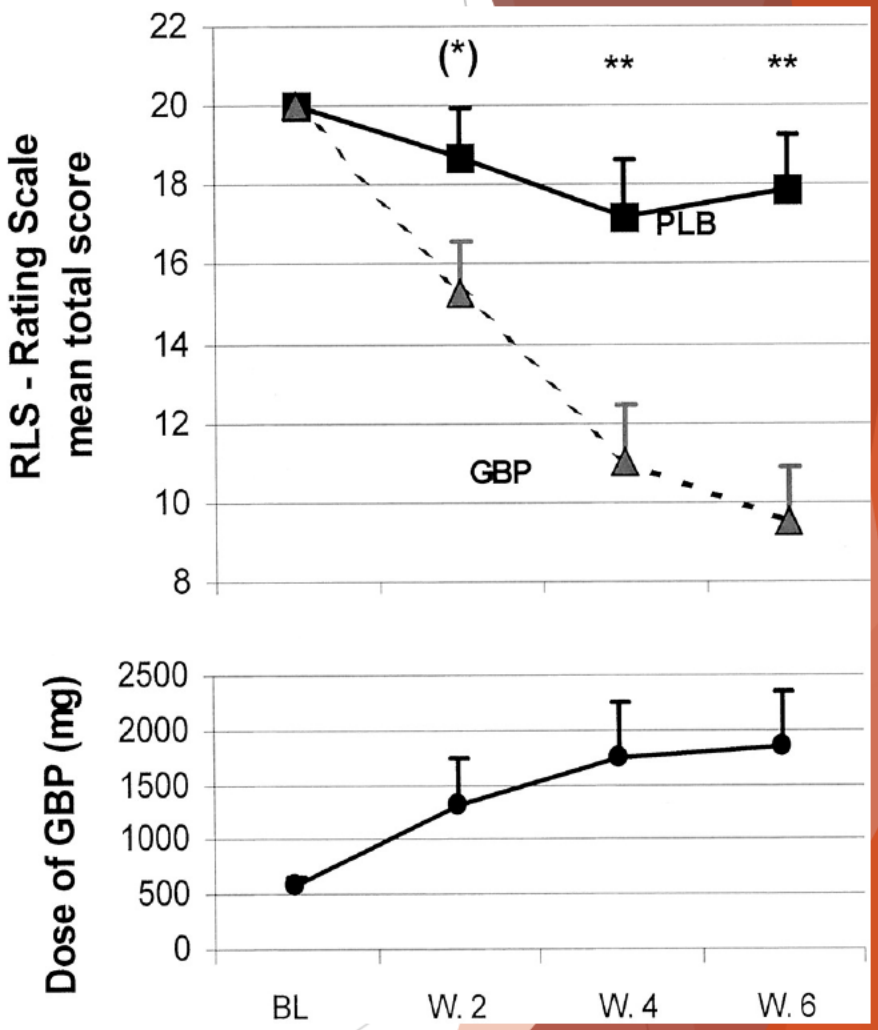
Gabapentin

- More limited data
- Dosing – suggest starting at 100-300 mg
  - Mean dose - 533 ± 328 mg (300 to 900 mg) - open-label study of 8 pts at 6-10 mths (Happe 2001)
  - Mean dose – 1,855 mg (±105.6) - randomized, placebo-controlled trial of 24 pts at 6 wks (Garcia-Borreguero 2002)
  - Hemodialysis pts – 200-300 mg gabapentin after each hemodialysis session was effective – 12 wk, double-blind crossover study (Thorp 2001)
- Side effects: malaise, dyspepsia, numbness, dizziness, sleepiness, and headache (Happe 2001; Garcia-Borreguero 2002)
  - Elderly - Somnolence and gait unsteadiness

Gabapentin

Randomized, placebo-controlled trial of 24 pts at 6 wks with either gabapentin or placebo

- RLS Rating Scale mean score was lower with gabapentin than placebo (9.5 ± 1.35 vs 17.9 ± 1.35; $p < 0.0005$)
- Clinical Global Impression of Change (1 = much better; 7 = much worse) showed a lower mean score after gabapentin than placebo (1.77 ± 0.26 vs 2.87 ± 0.26) ($p < 0.01$).
- PSQI had a reduction to 6.4 (±0.42) from mean baseline 9.7 with gabapentin, in contrast the mean score was 9.3 (±0.42) at the end of the placebo period ($p = 0.0001$)
- PLMI was lower with gabapentin than placebo (11.1 ± 3.3 vs 20.8 ± 3.3; $p = 0.05$)
- Patients with associated pain benefited most



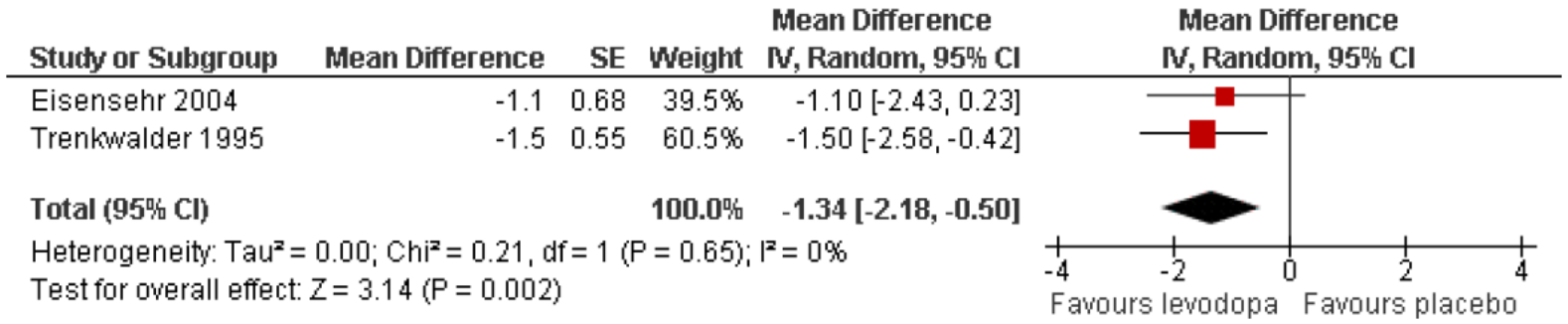
Garcia-Borreguero D, Larrosa O, de la Llave Y, et al. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology 2002; 59:1573.

Intermittent Symptoms

- Mild symptoms → Non-pharmacologic therapies
- Clinically significant symptoms → potential choices…
  - PRN carbidopa-levodopa or dopamine agonist
  - Other options →
    - low-potency opioid (codeine) or opioid agonists - tramadol
    - Benzodiazepine or benzodiazepine agonists, such as clonazepam, temazepam, zolpidem, zaleplon, or eszopiclone
- No adequate controlled trials of benzodiazepines for RLS
  - Likely treat insomnia associated with RLS
- Opinion is mixed on the use of benzodiazepine or benzodiazepine agonists
  - Side effects and tolerance
  - High frequency of sleepwalking / sleep-related eating disorder in RLS pts on Zolpidem - case series of 5 pts with sleep eating on zolpidem, all had RLS (Morgenthaler 2002)

Levodopa

- First to be formally studied in RLS, use has decreased given augmentation risk
  - May have rebound in the early morning / second half of the night
- Starting Dose - Carbidopa-Levodopa - 25 mg/100 mg, 0.5 - 1 tablet
  - Avoid Levodopa >200mg
- Short-term well tolerated
  - Side effects - nausea, dizziness, and somnolence - mild and improve with time
- Improves RLS symptom severity, PLMS, self-rated sleep quality, and quality of life
  - 2 studies with symptom severity on a 10-pt scale – improvement by a mean of 1.34 points compared to placebo

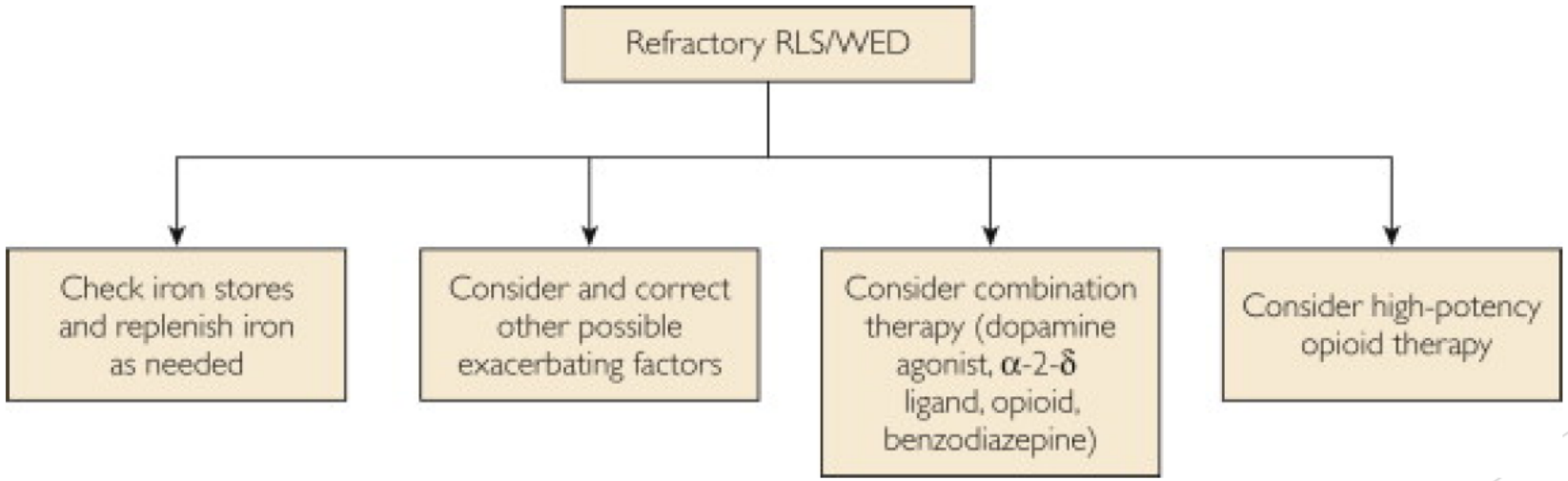


Scholz H, Trenkwalder C, Kohnen R, et al. Levodopa for restless legs syndrome. Cochrane Database Syst Rev 2011; :CD005504.

Refractory RLS

"Refractory RLS/WED is restless legs unresponsive to monotherapy with tolerable doses of first-line agents due to reduction in efficacy, augmentation, or adverse effects"

- ***Willis-Ekbom Disease Foundation revised consensus statement on the management of restless legs syndrome***



Silber MH, Becker PM, Earley C, et al. Willis-Ekbom Disease Foundation revised consensus statement on the management of restless legs syndrome. Mayo Clin Proc 2013; 88:977.

Opioids

- Effective in the treatment of chronic and refractory RLS
- Consider for those who have not responded to other therapies
- Choices
  - Low-potency opioids - Tramadol and Codeine
  - High-potency opioids - Oxycodone and Methadone (most require)
- Mechanism of action is unclear
  - Interaction between spinal opioid and dopamine receptors has been speculated (Trenkwalder 2017)
- Tolerance can develop with long-term use
  - Abuse potential appears to be low in patients with RLS in the absence of a history of substance abuse

Opioid Therapy

Restrict to severe symptoms which fail to respond to other therapies

Side effects: Constipation, nausea, fatigue, itchiness, depression, unsteadiness, and exacerbation of underlying sleep apnea

TABLE 2. Suggested Doses for Using Opioids in RLS

Drug	Starting total daily dose	Usual effective total daily dose
Tramadol (immediate or extended release)	50 mg (100 mg ER)	100-200 mg
Codeine	30 mg	60-180 mg
Morphine CR	7.5-15 mg	15-45 mg
Oxycodone (immediate or extended release)	5-10 mg	10-30 mg
Hydrocodone (immediate or extended release)	10-15 mg	20-45 mg
Methadone	2.5-5 mg	5-20 mg

CR = controlled release; ER = extended release; RLS = restless leg syndrome.

Silber MH, Becker PM, Buchfuhrer MJ, et al. The Appropriate Use of Opioids in the Treatment of Refractory Restless Legs Syndrome. Mayo Clin Proc 2018; 93:59.

MAYO CLINIC

CONSENSUS RECOMMENDATIONS

The Appropriate Use of Opioids in the Treatment of Refractory Restless Legs Syndrome

Michael H. Silber, MBChB; Philip M. Becker, MD; Mark J. Buchfuhrer, MD; Christopher J. Earley, MBBCh, PhD; William G. Ondo, MD; Arthur S. Walters, MD; and John W. Winkelman, MD, PhD; for the Scientific and Medical Advisory Board, Restless Legs Syndrome Foundation

1. Consider if not adequately controlled with first-line - poor response, adverse effects, or augmentation.
2. Consider low iron stores, agents that can exacerbate RLS, and OSA
3. Alternative approaches should be considered - combination therapy of non-opioid agents or a washout period in augmentation
4. Assess for risk of opioid use disorder - drug monitoring programs and a UDS
5. Inform about expectations of treatment and risks of opioids.
6. Use an opioid contract

MAYO CLINIC

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7. Regular follow-up – check drug monitoring programs regularly and UDS at least annually

8. Test initial response with short-acting drug - long-acting or ER/CR agents are preferred for night

- Per CDC - opioid-naïve pts should NOT be started on ER /long-acting opioids as initial therapy for chronic pain – only start if used >= 1 wk (Dowell 2016)
- Short acting - end-of-dose rebound / inadequate length of coverage

9. Start low dose, increase as needed / tolerated - risk-benefit ratio should be considered in high doses

10. Be familiar with dosing and differences between meds

11. Be careful if transitioning between different opioids - varying potencies and cross-tolerance

Efficacy of Opiate Therapy

Double-blind, randomized trial of 306 pts - CR oxycodone-naloxone versus placebo (Trenkwalder 2013)

Change in IRLS score after 12 wks was -16.5 (SD 11.3) in the oxycodone-naloxone group and -9.4 (SD 10.9) in placebo group (MD at 12 wks 8.15, 95% CI 5.46-10.85; p<0.0001)

Long-term retrospective study of 113 pts on opioid alone (36 pts) or with opioids added to other meds (77 pts) (Walters 2001)

- PSG on 7 pts performed after average 7 years and 1 month of opioid monotherapy (range, 1-15 years)
  - Decrease in PLMi, PLMAi, and PLMs while awake index
  - Increase in stage 3 and REM sleep, total sleep time, sleep efficiency, and decrease in sleep latency
- 2 of these 7 pts developed sleep apnea and a third had worsening of preexisting apnea
- Medication was discontinued in only 1 case because of addiction and tolerance

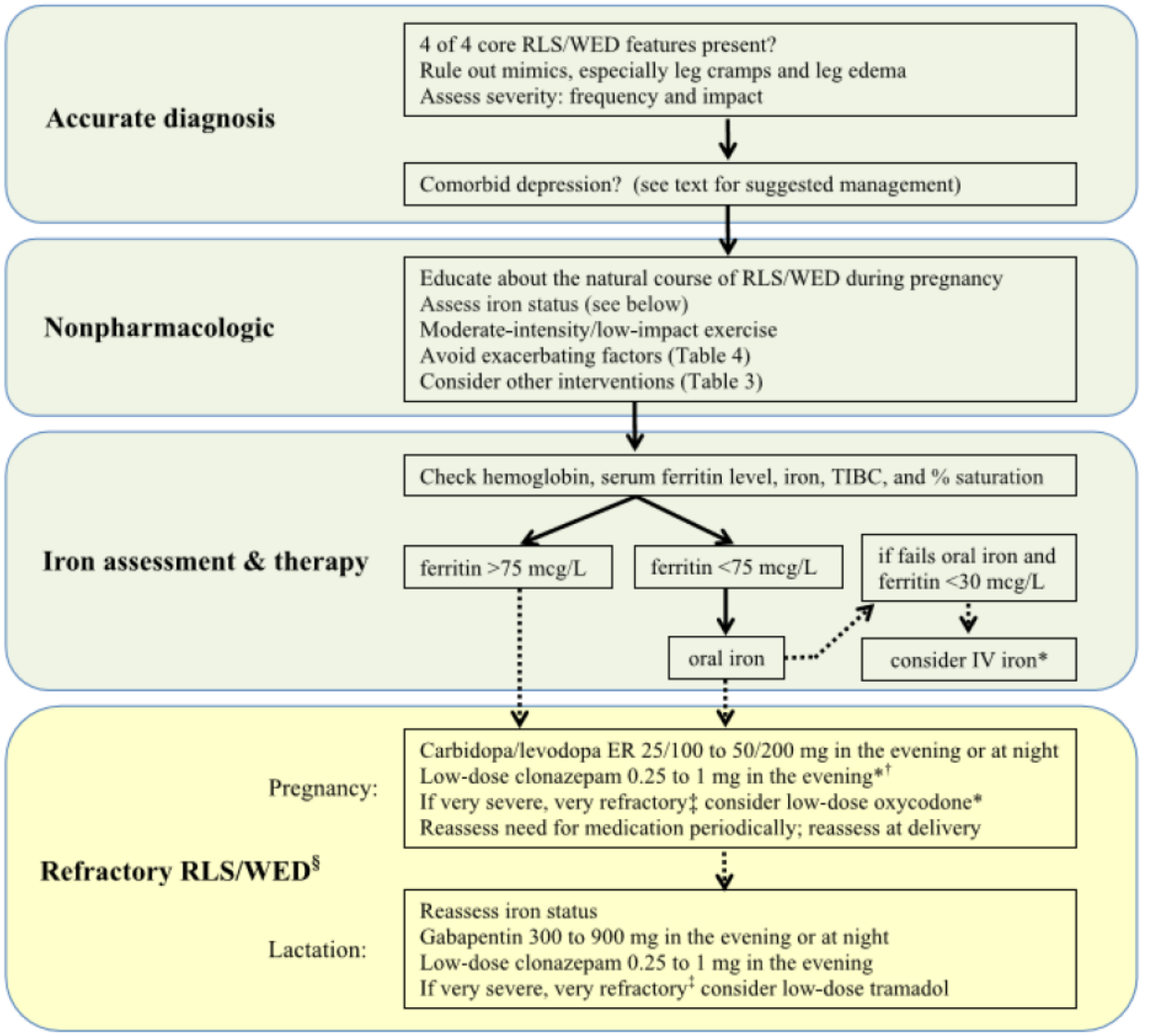
10-year, open-label study of methadone – 15% of 76 pts discontinued methadone treatment in the 1st year - remainder continued to use it with benefit (Silver 2011)

Pregnancy and Lactation

Consensus clinical practice guidelines for the diagnosis and treatment of restless legs syndrome/Willis-Ekbom disease during pregnancy and lactation

Daniel L. Picchietti [a,*], Jennifer G. Hensley [b], Jacquelyn L. Bainbridge [c], Kathryn A. Lee [d], Mauro Manconi [e], James A. McGregor [f], Robert M. Silver [g], Claudia Trenkwalder [h,i], Arthur S. Walters [j], On behalf of the International Restless Legs Syndrome Study Group (IRLSSG)

1) Common during pregnancy
2) Typically peaks in 3rd trimester; markedly improves after delivery
3) Non-medication treatments should be considered first
4) Assess iron status
5) Reserved meds for refractory cases – minimize duration and dose



Take Away Points

- Evaluate iron stores
- Mild / intermittent RLS - Non-pharmacologic therapy
- Chronic RLS – start with a non-ergot dopamine agonist or alpha-2-delta ligand

  Non-complex younger patient - consider alpha-2-delta ligand
- If first drug ineffective or not tolerated, switch classes
- Intermittent but disabling RLS - dopamine agonists or levodopa
- Refractory RLS - combination therapy and opioids
- Be mindful of augmentation!

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