Unrest at Rest: Innovations in Managing RLS

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18th Annual Sleep Medicine CME Course

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Learning Objectives

Upon completion of this activity, participants should be able to:

- Understand current recommendations for the use of IV iron in the management of RLS
- Select appropriate first and second-line agents for patients with chronic persistent RLS, including gabapentinoids, opioids, dopamine agonists and neuromodulation
- Develop competence in using low-dose opioids for refractory restless legs syndrome
- Learn how to balance the benefits and dangers of dopamine agonist therapy
- Recognize and manage restless legs augmentation from dopamine agonists

Criteria for the Diagnosis of RLS

- **Urge to move the legs**, usually but not always accompanied or caused by unpleasant leg sensations which are:

  A. Present during rest or inactivity
  B. Partially or completely relieved by movement such as stretching or walking
  C. Worst in evening and night

Diagnostic Difficulties

- Can RLS be painful? (Yes, but consider fibromyalgia , leg cramps and the paresthesias of neuropathies)
- Can RLS be asymmetric? (yes, may alternate between legs; occasionally consistently worse in one leg)
- Can RLS be felt in the trunk or arms? (yes, but almost always in addition to the legs)
- Is the urge to move essential? (Yes; unconscious jiggling of the legs while sitting is not RLS)
- Does relief by changing position support the diagnosis? (No, usually due to pressure on skin or soft tissue)
- Must symptoms be relieved by movement? (Yes, but recur on sitting again; relief by movement less evident in longstanding RLS)

General Issues

- Consider role of medications in exacerbating RLS

  Antidepressants – except bupropion

  Neuroleptic agents, incl. anti-emetics

  Sedating anti-histamines

- Consider role of OSA, insufficient sleep or sleep fragmentation in exacerbating RLS

- Be aware that RLS patients may have other causes of insomnia, such as depression or anxiety, which might need independent treatment

Iron should be considered as a first-line therapy for chronic persistent RLS *, with changing criteria for its administration

*RLS at least twice a week causing moderate to severe distress

Serum Ferritin may be Misleading as an Indicator of the Need for Iron in RLS

- **Serum ferritin is an acute phase reactant and may be falsely high in inflammation and malignancy**
- Values may be hard to interpret if it is uncertain which methodology is used
- Serum ferritin levels do not reflect CSF levels or iron levels in the basal ganglia
- Suggested cut-offs for IV iron therapy lack biologic justification

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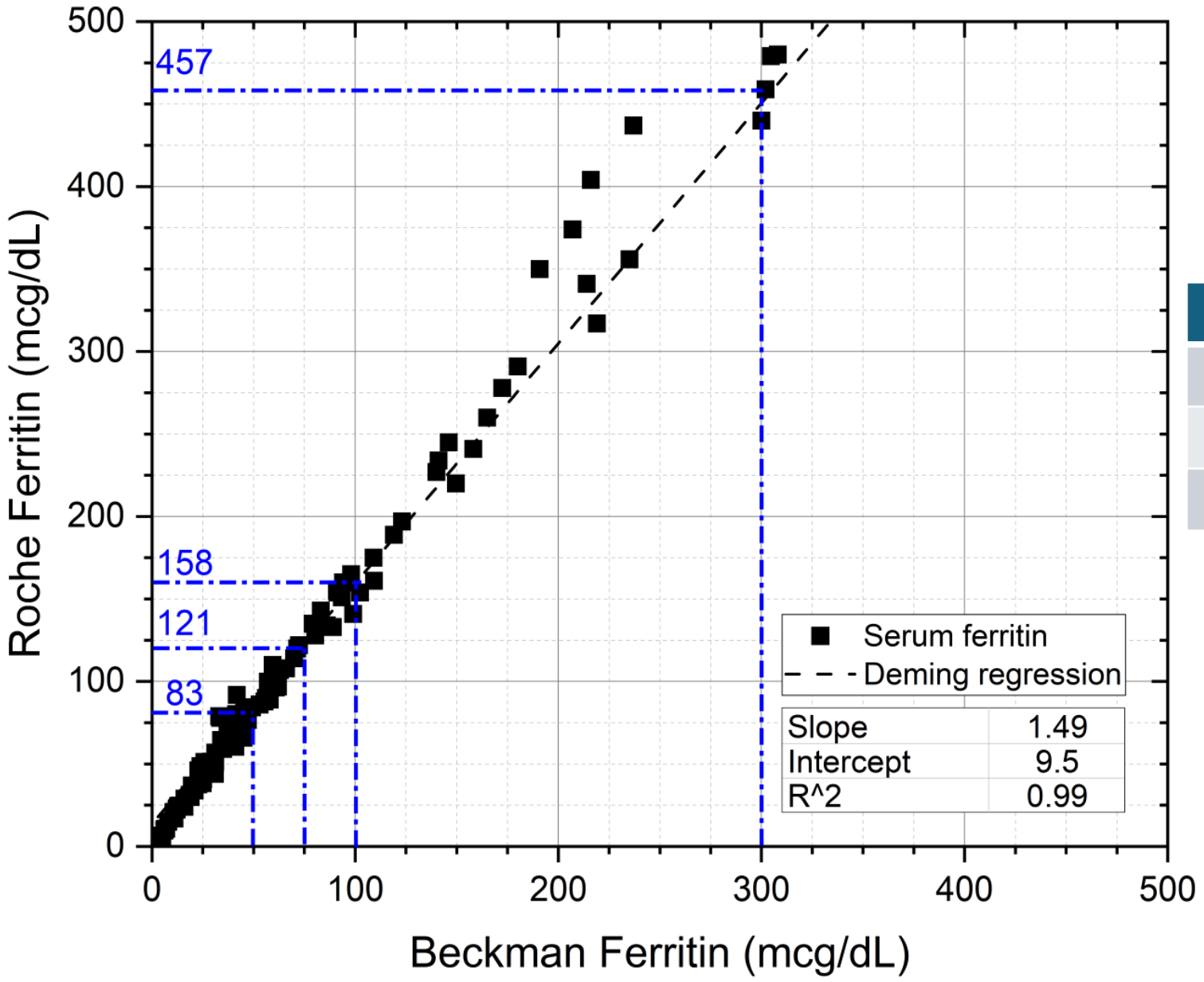

Beckman	Roche
75	120
100	160
300	450

Silber 2025

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Systemic and Brain Iron

- MRI and autopsy studies show reduced iron in basal ganglia in RLS patients

- CSF ferritin is lower in RLS patients even with normal serum ferritin

Earley 2000, Allen 2001, Connor 2003

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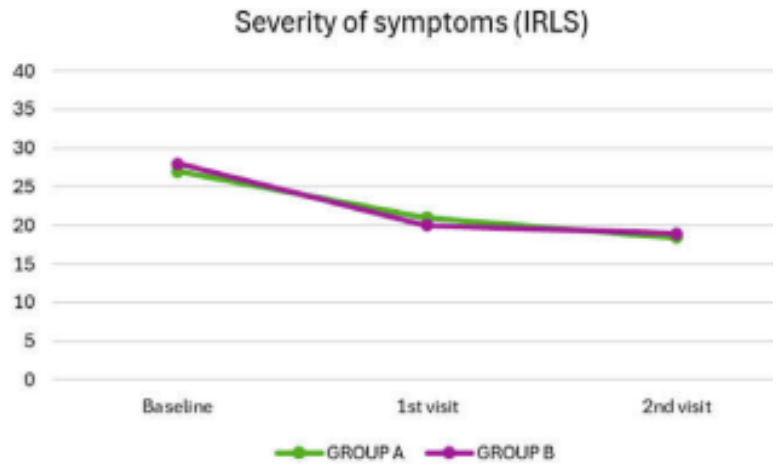
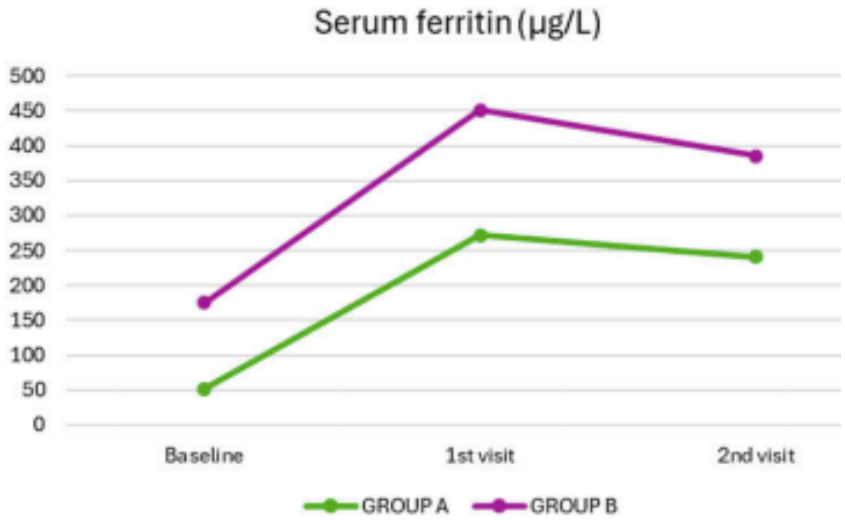
Is there an upper limit of serum ferritin for giving iron?

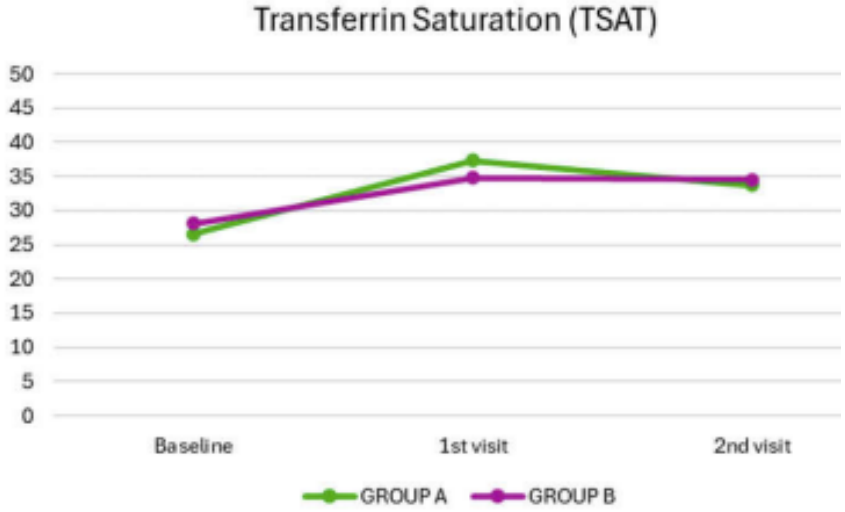
- The widely used cut-off of 100 µg/l in the 2018 practice guideline by the IRLSSG was determined empirically by the distribution of serum ferritin concentrations found in those participating in the major clinical trials rather than by biologic considerations

- Effectiveness of IV iron is no different for serum ferritin above or below 100 µg/l and there seems no increased risk of systemic iron overload with the higher levels

Allen 2018; Park 2020; Garcia-Malo 2025







2 patients had subsequent TSAT > 45%:

- One normalized by 15 months
- One was heterozygous for H63D
- **Neither showed any increase in transaminases**

Garcia-Malo 2025

Oral Iron Supplementation

- Use iron supplementation for serum ferritin levels below the lower limit of normal for age and sex (and investigate for a cause)
- Consider for serum ferritin < 75 µg/L (Oral iron poorly absorbed as ferritin level increases)
- Ferrous sulphate, ferrous fumarate or ferrous gluconate (65 mg elemental iron) once every other day before bed
- Vitamin C 100-200 mg with each dose
- Recheck ferritin after 3 months
- Goal serum ferritin ≥ 75 µg/l

Indications for Intravenous Iron Therapy

Moderate to severe chronic persistent RLS with
TSAT < 45%
AND

Serum ferritin concentration 75-300 µg/l **(Oral iron not absorbed if serum ferritin is > 75 µg/l)**	**Serum ferritin concentration <75 µg/l** **AND** **one or more of:** • **Inability to absorb oral iron due to GI disease or prior surgery** • **Inability to tolerate oral iron due to side effects** • **RLS has not improved after 3 month oral iron therapy** • **Due to severity of RLS, a rapid response is desired**

Use a slow-release formulation

	Administration	Advantages	Disadvantages
Ferric carboxymaltose	2 doses of 750 mg each one week apart or one dose of 1,000 mg over 15 min	Most supporting data from multiple clinical trials (Khan 2025)	Most expensive preparation • Results in hypophosphatemia in 40-74% of adults (18-20% children) • Generally not clinically significant unless repeated doses (total > 6 g) administered for anemia from chronic ongoing GI or uterine blood loss (then risk of osteomalacia with muscle weakness and microfractures)
Low molecular weight iron dextran	25 mg test dose and 975 mg in 1,000 ml normal saline over one hour	Cheapest preparation	Longer time of administration Only open label studies
Ferumoxytal	2 doses of 550 mg each one week apart or one dose of 1,200 mg over 15 min	Intermediate cost	May interfere with interpretation of MRI contrast studies for 3 months after administration Single study; equal to oral iron

- Risk of anaphylaxis 1/200,000 but administer in an area where resuscitation is possible
- 37-59% effective; response may be delayed 6 weeks
- Can repeat after 3 months if symptoms recur and TSAT < 45%, ferritin ≤ 300 µg/l

Gabapentinoids are the first-line drug therapy for chronic persistent RLS *, but have side effects and are not always effective

*RLS at least twice a week causing moderate to severe distress

GABAPENTINOIDS	Starting dose		Usual effective daily dose	Maximum daily dose
	< 65 yrs	> 65 yrs		
Pregabalin *	75 mg	50 mg	300 mg	600 mg#
Gabapentin *^	300 mg	100 mg	900-1,800 mg (divided doses)	3,600 mg
Gabapentin enacarbil *	600 mg	300 mg	600 mg	1,800 mg#

* Renal excretion; Adjust for renal dysfunction; ^ non-linear kinetics over 600 mg; # off-label dose

Controlled trials suggest 60-70% effective

Adverse Effects of Gabapentinoids

- Daytime drowsiness
- Dizziness and unsteadiness
- Mental fogging
- Weight gain (20% of users)
- Worsening of depression, esp. if suicidal ideation
- Respiratory depression in the setting of respiratory failure
- Abuse potential if prior history of opioid use disorder

Unlike dopamine agonists, NOT augmentation or impulse control disorders

Reasons for Second Line Agents

- Iron therapy ineffective or not indicated
- Gabapentinoids are ineffective at tolerable doses
- Patient experiences intolerable side effects with gabapentinoids
- By joint decision making, provider and patient have decided that gabapentinoids should not be used

Second Line Agents

- Opioids
- Dopamine agonists
- Peroneal nerve stimulation
- Dipyridamole

Which agents to use should be decided by joint decision making between provider and patient

Low-dose opioids are appropriate, frequently effective and generally well-tolerated for the management of refractory RLS

Supported by 12-week controlled trial of oxycodone and 10-year follow-up study of methadone

Trenkwalder 2013; Silver 2011

National RLS Opioid Registry: 5 Year Follow-up

- 410 patients (75% college educated)
- Median MME 37.5 mg, increase of 7.5 mg from baseline (66% dose unchanged)
- Larger increases (3.5%) associated with predictable factors:
  - Opioid use for non-RLS pain
  - Change to methadone
  - Addition of a dopamine agonist
  - Family history of prescription substance abuse
- RLS severity did not increase over 5 years, suggesting ongoing control

Winkelman 2026

Opioid Adverse Effects

- Constipation
- Nausea and vomiting
- Itch
- Cognitive effects and sleepiness
- Gait unsteadiness and falls
- Sweating and sexual dysfunction (due to low testosterone)
- OSA, CSA
- Risk of overdose or opioid use disorder

- (Methadone: Long acting; Delayed respiratory depression; QT prolongation in higher doses)

(Tramadol may cause augmentation-like symptoms; prefer not to use)

Which Opioid to Use?

Suggested Approach:

- Start with IR oxycodone once or twice a night
- If longer duration opioid needed, use morphine CR or buprenorphine
- If ineffective, change to methadone

	Starting dose	Usual effective daily dose	MME Ratio
Oxycodone IR or ER	5-10 mg	10-30 mg	1.5:1
Morphine CR	10-15 mg	15-45 mg	1:1
Hydrocodone IR /ER	10-15 mg	15-45 mg	1:1
Methadone	2.5-5 mg	5-20 mg	4.7:1 (up to 20 mg)

Buprenorphine

- Partial agonist at mu receptors; antagonist at kappa receptors
- Not well absorbed through GI tract
- Hepatic metabolism; fecal excretion
- Half-life 20 hours (in practice duration of action may be shorter)
- Less tolerance, euphoria, abuse or resp depression compared to traditional opioids
- Displaces opioids from the mu receptor and can precipitate acute withdrawal
- Special urine test needed

Buprenorphine

- Belbuca©

  Buccal film

  75 – 900 mcg
- Suboxone© (buprenorphine/naloxone)

  Sublingual film

  2 mg lowest dose (can be cut in half, a quarter or an eighth)

- Stop opioids 12-24 hours before
- Start at 150 mcg (Belbuca) if opioid naïve; start at 500 mcg (Suboxone) if on prior opioids
- Increase every 1-2 days; usual effective dose 0.5-4 mg (sometimes 6 mg may be needed)
- No food or drink 15 min before administration; brush teeth after film dissolves

Conditions for Use of Low Dose Opioids

- Educate patients about potential side effects, the risks of dependence and the need to secure medications
- Patients must sign an opioid use contract as determined by local requirements
- Patients and providers must understand other regulatory requirements, such as the need for follow-up visits, urine drug screens and assessment of state pharmacy data bases
- Doses should be adjusted to provide effective control of RLS but should rarely exceed recommended limits

Dopamine agonists remain an option for patients with moderate to severe chronic persistent RLS with adequate iron stores and failure of gabapentinoids, in keeping with the recent AASM practice guideline*

*In adults with RLS, the AASM suggests against the standard use of pramipexole (conditional recommendation, moderate certainty of evidence).

Remarks: pramipexole may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation)

Winkelman 2025

Problems with Dopamine Agonists

Risk of Augmentation

Development of worsening RLS with dopaminergic medication

- Earlier onset symptoms (2-4 hours+)
- Spread to arms or trunk
- Shorter duration of response to medication
- Paradoxical worsening of symptoms as dose is increased

Augmentation

- 42-70% of patients get augmentation after 8 to 10 years use

Allen 2011; Silver 2011; Oertel 2011; Lipford 2012

- Thus at least 30% do not augment and follow a more benign course

BUT

It is not possible to identify those patients in advance

- Once augmentation is established, it can be extremely difficult to manage and result in considerable patient distress

Problems with Dopamine Agonists

Risk of Impulse Control Disorders

- 6-17% of patients on dopamine get impulse control disorders (pathologic gambling, compulsive shopping, hypersexual behaviors)

Cornelius 2010

- Thus at least 83% do not

BUT

If they are not identified early, the psychological, financial, and legal consequences can be severe

- If identified and the dopamine agonists is stopped, the impulse control disorders almost always rapidly resolve

Conditions for the Use of Dopamine Agonists

- Patients must be educated about augmentation and ICD, must agree never to increase the dose themselves, and to report immediately if these conditions develop

- Dose must be kept as low as possible, never exceeding maximum daily limits (pramipexole 0.5 mg, ropinirole 2 mg, rotigotine 3 mg)

- Return visits with questioning about side effects are essential, at least every 6 months

- If even early augmentation develops, the drug must be appropriately weaned and if possible discontinued with substitution of other appropriate agents

Bilateral Peroneal Nerve Stimulation

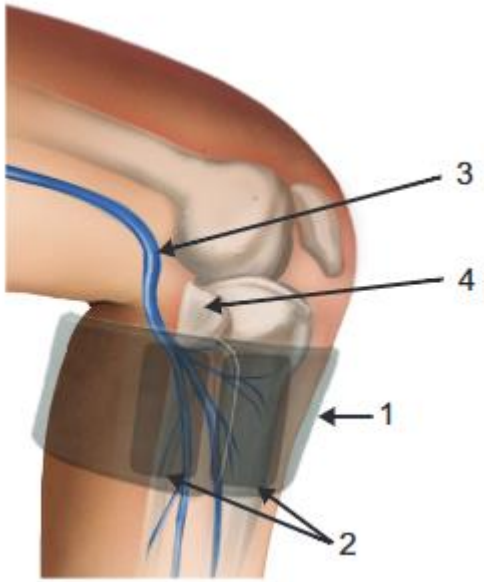
- 61% response rate at 8 weeks in controlled trial of 133 participants who had failed at least one drug (73% after 24 week open-label extension)
- 90% remained on an RLS medication during the trial

Bogan 2023; Roy 2023

- Apply 30 min at a time up to four times a day
- Few side-effects (skin abrasions from adhesive)

- Currently FDA approved for RLS with failure of a single medication
- Real-world experience suggest may be useful as adjunctive therapy to drugs
- May allow reduction in opioid dose required for RLS

Buchfuhrer 2023



Dipyridamole

- Increases adenosine
- Small controlled 2-week trial of 28 participants showed positive results (Garcia-Borreguero 2021)
- 100-300 mg in the evening
- Concern about use with other anti-platelet agents or anticoagulants
- Limited clinical experience suggest some patients may benefit but effect often wears off after a few months
- Use limited by side-effects, esp. dizziness (caution with antihypertensives) and abdominal discomfort
- Off-label use

Augmentation must be managed by careful reduction and, whenever possible, elimination of dopamine agonists

- Do not increase the dose, even with mild augmentation
- Do not substitute long-acting dopamine agonists such as rotigotine
- Do not use drug holidays and reintroduce agonists

Management of Augmentation

- Replenish iron stores
- Introduce a gabapentinoid or a low-dose opioid titrating up to a therapeutic dose
- Wean the dopamine agonist in downward steps of 0.25 mg for pramipexole, 1 mg for ropinirole and I mg for rotigotine
- Rate of reduction depends on patient preference and tolerance (range of one step every 3 days – once a month)
- Anticipate temporary rebound of RLS with each downward step; can increase the dose of the alternative agent if needed
- Some patients need to stay on a minimal agonist dose (success rate at complete discontinuation 68% in large series Yeung Lawah 2022)

Pregnancy

- Use non-pharmacologic techniques
- Replenish iron stores (IV iron safe in 2nd and 3rd trimesters)

- Use of medications in 2nd and 3rd trimesters based on joint decision making, keeping doses low

  (gabapentinoids, opioids and intermittent levodopa)

- Lactation: IV iron safe; gabapentin safe; can use opioids but monitor the infant for sedation or resp depression. No dopaminergics (suppress lactation)

Perioperative Management

- Whenever possible, continue oral RLS meds
- If on oral dopaminergics and oral intake not possible, convert to rotigotine
- Keep sleep deprivation, immobilization and restraints to the minimum
- Address blood loss by transfusions or IV iron
- Avoid antihistamines, dopamine antagonist anti-emetics (ondansetron acceptable)and neuroleptics
- If opioid naïve, use opioids in lowest dose and shortest duration compatible with pain control
- If on methadone or buprenorphine, continue and supplement with short-acting opioids for pain if needed; if on oxycodone or morphine, increase the dose for pain control

Cannabis

- No controlled trials
- Some anecdotal experience and single center case series suggests some possible benefit with short-lived relief after inhalation

  Megelin 2017, Ghorayeb 2019, 2020
- Formulations, dose, and mode of administration uncertain
- Drug interactions (dopamine agonists, gabapentinoids and benzodiazepines), adverse effects and legal constraints limit use

The Future?

- Spinal cord stimulation
- Transcranial magnetic stimulation
- Other anti-seizure medications
- Dual action orexin antagonists
- CGRP monoclonal antibodies
- CBT-I

Pagani-Estevez 2023; Winkelman; 2024; Suzuki 2025; Song 2020

Take Home Messages

- Consider iron therapy for all with chronic persistent RLS, including in patients with normal measures of systemic iron status
- Gabapentinoids are first-line drug therapy for chronic persistent RLS
- Select 2nd line drug therapy (opioids and dopaminergics) by joint decision making
- Low-dose opioids are very effective and should not be withheld from appropriate patients
- When dopamine agonists are used, keep the dose low, assess frequently for augmentation and wean the drug if it occurs
- Consider peroneal nerve stimulation therapy as augmentative therapy
- If augmentation present, withdraw dopamine agonists carefully, first covering with alternative medications