



# Medications for RLS



2019 Webinar  
Series

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# Objectives

Understand the use of medications to treat RLS:

- Iron
- Dopamine agonists
- Alpha-2-delta ligands
- Opioids

# Intermittent RLS

## Definition

RLS that is troublesome enough to require treatment but occurs on an average less than twice weekly

# ***Intermittent RLS***

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graph TD; A["Intermittent RLS"] --> B["Non-pharmacological therapy"]; A --> C["Intermittent medications"]; C --> D["Benzodiazepines"]; C --> E["Low-potency opioids"]; C --> F["Levodopa"];
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A flowchart illustrating treatment options for Intermittent RLS. The root node is 'Intermittent RLS', which branches into 'Non-pharmacological therapy' and 'Intermittent medications'. 'Intermittent medications' further branches into 'Benzodiazepines', 'Low-potency opioids', and 'Levodopa'.

**Non-pharmacological therapy**

**Intermittent medications**

Benzodiazepines

Levodopa

Low-potency  
opioids

# Behavioral Therapies

- Walking, stationary bicycling, rubbing or soaking limbs
- Mental alerting techniques
- Regular moderate physical activity
- Reduction in caffeine
- Consider withdrawal of antidepressants, anti-nausea meds, antihistamines
- Possibly leg vibration devices

# Chronic Persistent RLS

## Definition

RLS which is frequent and troublesome enough to require daily therapy, usually at least twice a week causing moderate or severe distress

(prevalence 1.5-2.7%)

# Iron



- In some patients with RLS, iron stores are reduced in the body (blood loss, frequent blood donations)
- MRI and autopsy studies show reduced iron in areas of the brain in RLS patients
- The problem may be problems transporting iron into the brain
- Iron is needed for the dopamine receptor
- Serum ferritin measures iron stores in the body, not the brain

# Oral Iron

- Do not take unless levels are low
- Consider oral iron replacement for serum ferritin < 50-75 mcg/l
- Once or twice daily between meals
- Vitamin C 100 mg with each dose
- Vitron C has iron and vitamin C combined



# Oral Iron

- Can cause indigestion, constipation and black stools
- Recheck ferritin every 3-6 months
- Goal serum ferritin >50-75 mcg/l

# Intravenous Iron

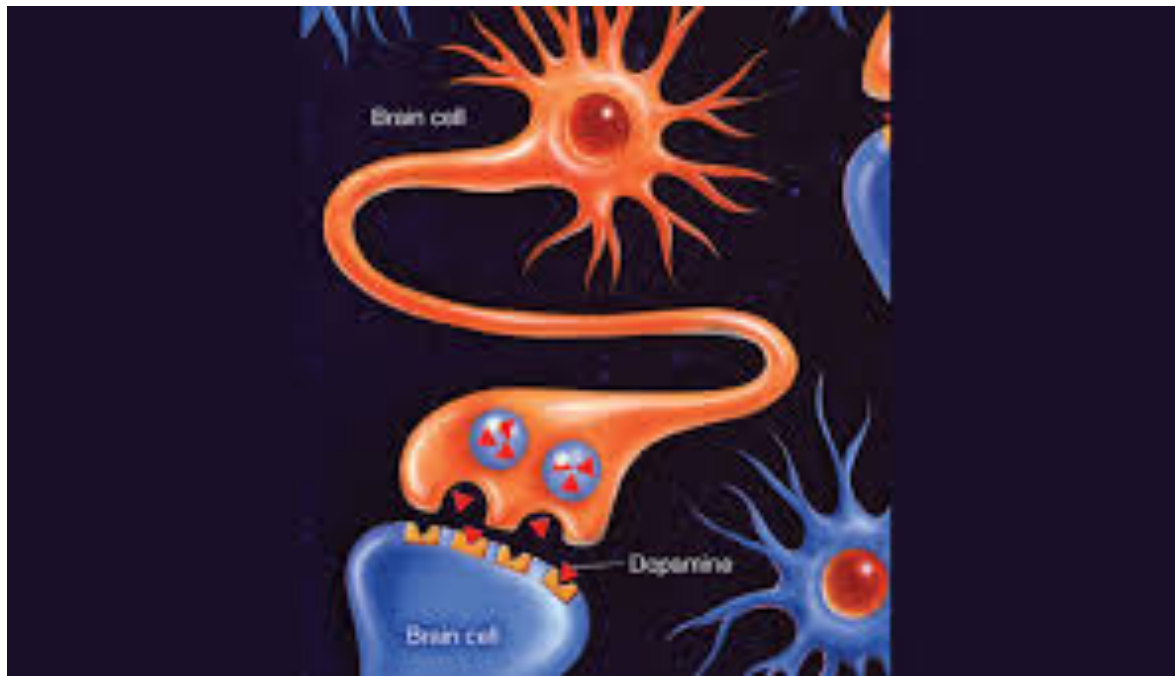
- Indications:
  1. cannot absorb iron by mouth
  2. cannot tolerate iron by mouth
  3. very severe symptoms needing a rapid response
- Consider for ferritin < 100 mcg/l if symptoms severe (and transferrin saturation < 45%)

# Intravenous Iron

- Low molecular weight iron dextran (INFed)
- One dose (1,000 mg) infused over 1 hour
- Give 25 mg test dose first
- Ferric carboxymaltose
- One dose (1,000 mg) Injected over 20 minutes
- 60% success rate
- May take more than 6 weeks to be effective
- Can repeat after 12 or more weeks if first dose successful

# Dopamine

- Dopamine is a neurotransmitter in the brain associated with movement, arousal, and the reward system
- Drugs enhancing dopamine work for RLS
- The problem may be reduced dopamine receptors (the proteins which bind dopamine)



# Dopamine Agonists

## Pramipexole and Ropinirole

- Bind to dopamine receptors
- Approved by the FDA for treatment of RLS
- Trials demonstrate efficacy (>1,000 patients)
- Generics available
- Limit maximum daily dose (much less than for Parkinson disease)  
(pramipexole 0.75 mg; ropinirole 4 mg)

# Dopamine Agonists

## Rotigotine Transdermal Patch

- Apply once a day
- Trials demonstrate efficacy (>1,000 patients)
- Approved by FDA for RLS/WED treatment
- Skin reactions common
- 1-3 mg daily

# How successful are the dopamine agonists?

Much or very much improved:

- Pramipexole: 59-75%
- Ropinirole: 53-68%
- Rotigotine: 50-75%

Oertel 2007, 2008; Winkelman 2006; Trenkwalder 2004, 2008;  
Walters 2004; Ferini-Strambi 2008; Giorgi 2013; Inoue 2013

# Long Term Follow Up

	<b>Pramipexole</b>	<b>Pramipexole</b>	<b>Rotigotine</b>
Patients	50	164	295
% on drug after 5 years	90	58	43
% on drug after 10 years	82	25	-
	Lipford 2012	Silver 2011	Oertel 2011



# Dopamine Agonists

## Mild Side Effects

- Lightheadedness
- Nausea or indigestion
- Nasal congestion
- Leg swelling
- Sleepiness

# Dopamine Agonists

## Serious Side Effects

- Augmentation
- Impulse control disorders

# Augmentation

Development of worsening RLS with increasing doses of dopaminergic medication

- Earlier onset symptoms (2-4 hours+)
- Spread to arms or trunk
- Shorter duration of response to medication

- A 55 year old woman had RLS from age 19 years, experienced only in bed before sleep at night.
- 8 years before presentation pramipexole was prescribed, initially as 0.5 mg an hour before bed with good results.
- Over the years, symptoms worsened and the dose was increased to 0.5 mg on waking, at 2 pm and at 5 pm, with 2 mg before bed (total daily dose 3.5 mg).
- RLS is now experienced whenever she sits down from 9 a.m. onwards and results in only 3-4 hours sleep a night.

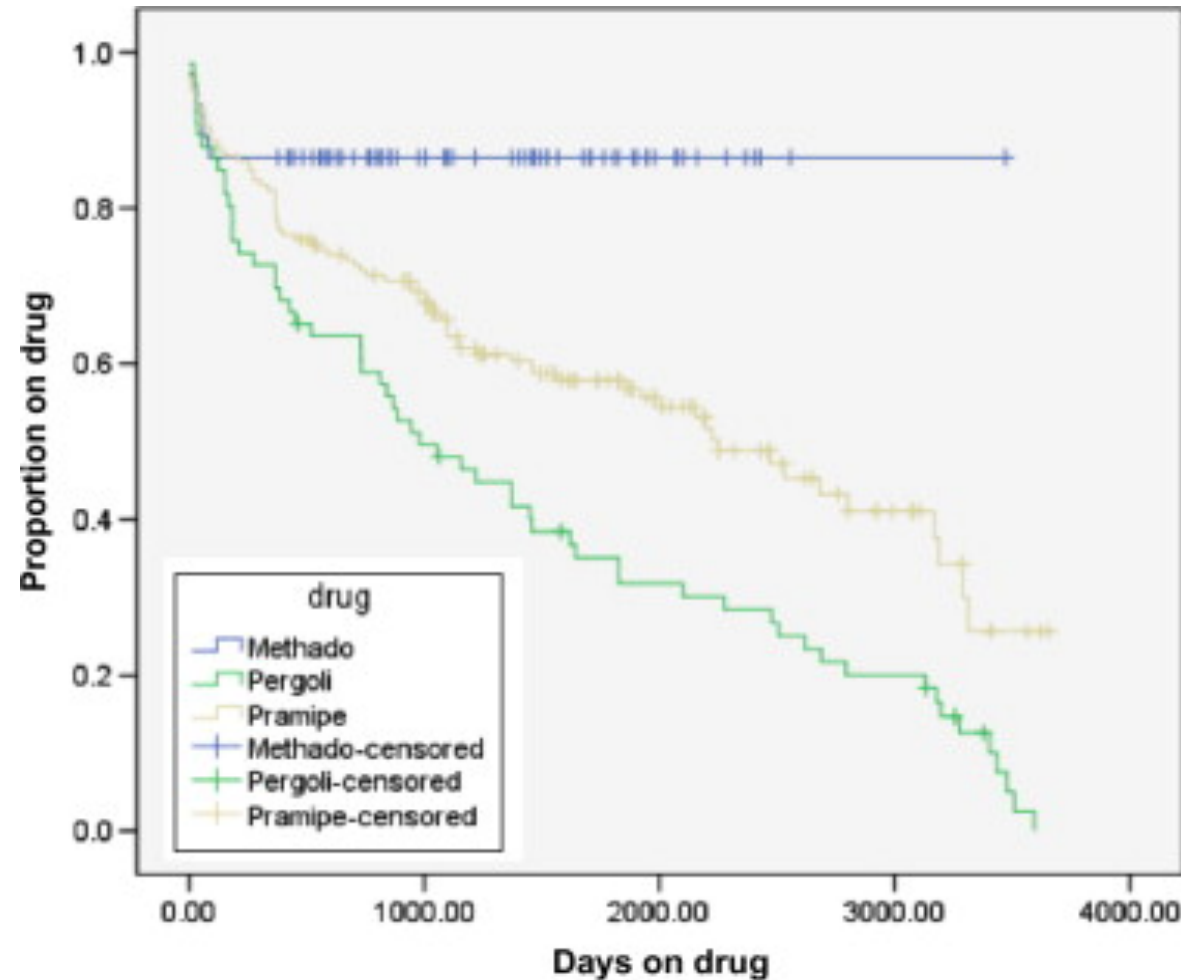
# Augmentation (10 year studies)

164 patients on pramipexole

10 years follow-up

Discontinuation rate  
due to augmentation:  
7% per year

Silver 2011



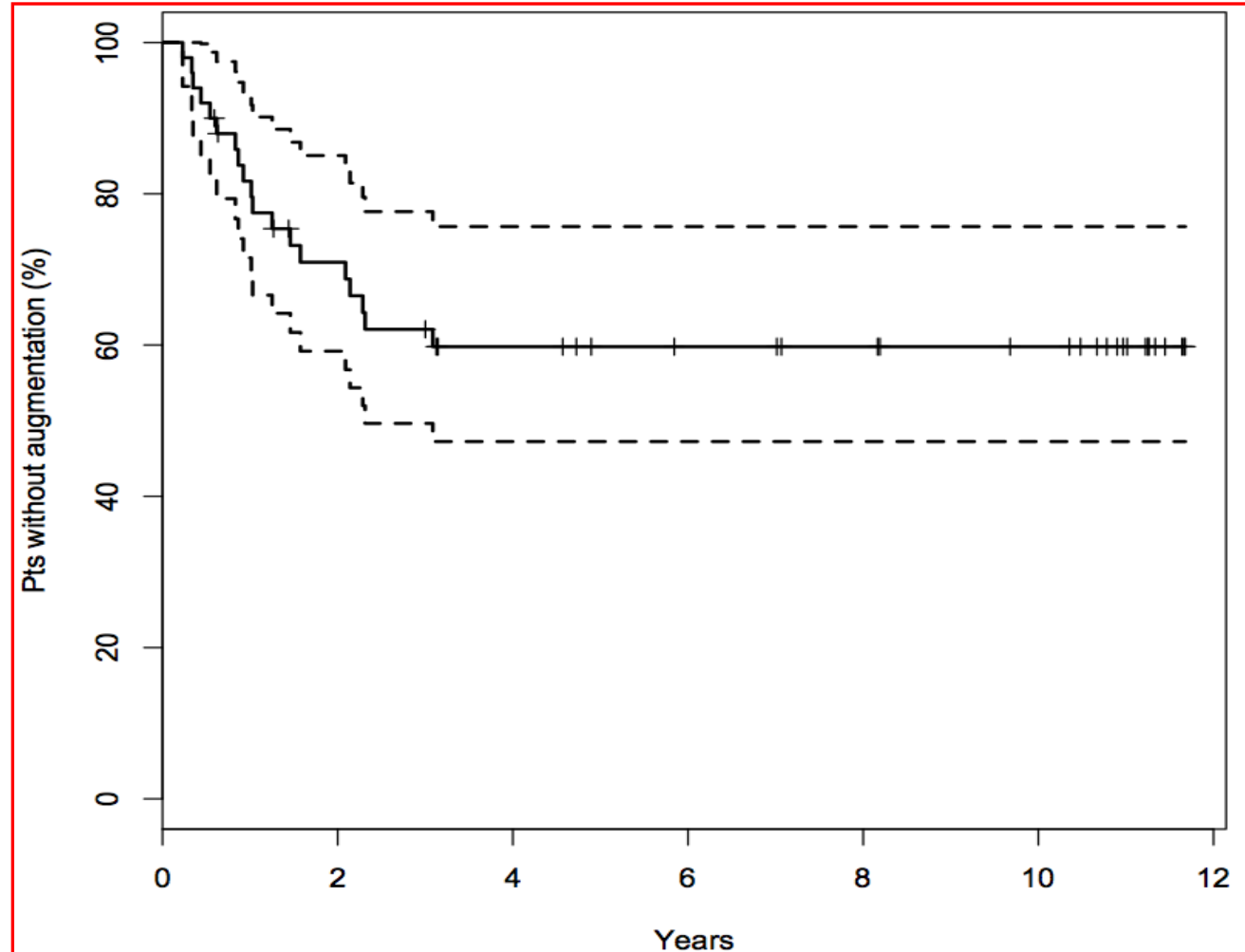
# Augmentation (10 Year Studies)

50 patients on pramipexole

Median follow-up  
9.7 yrs

Augmentation  
rate 42%

Lipford 2012



# Risk Factors for Augmentation

- High agonist dose
- Increasing duration of symptoms and treatment
- Lower iron stores
- Greater severity of symptoms pre-treatment
- Risk greater for levodopa than agonists and possibly more for intermediate compared to long-acting agonists

# Augmentation Rotigotine

- 5 year study
- 295 patients
- Augmentation rate 36%
- Discontinuation rate due to augmentation 4%

Oertel 2011



# Impulse Control Disorders

- Any ICD 17% (control 6%)
- Pathologic gambling 9% (control 0.4%)
- Compulsive shopping 5% (control 0.7%)
- Hypersexuality 3% (control 0.4%)
- Mean time of onset after starting therapy: 9 months
- Other studies: 6-12% frequency

# Calcium Channel ( $\alpha$ -2- $\delta$ ) Ligands

- Gabapentin
- Gabapentin Enacarbil (slow release; once a day)
- Pregabalin

**Side-Effects:** sleepiness, dizziness, unsteadiness, weight gain, leg swelling, mental fog, depression

# Gabapentin

- Least evidence, but cheapest
- Variable absorption into body
- Wide range of dosing possible (900-2,400 mg)
- One small trial (24 patients)

# Gabapentin Enacarbil

- Pro-drug of gabapentin; converted to gabapentin after absorption
- 65-78 % responders on 3 DB trials (>1,000 subjects)
- 600-(1,200) mg once daily (5 p.m.)
- FDA approved for RLS

# Pregabalin

- Large European study (719 subjects) showed pregabalin as effective as pramipexole, but more side effects
- No augmentation
- Better absorption into body
- Dose 150-400 mg

# Prevention of Augmentation

- Consider alternative medications to dopamine agonists
- Use intermittent therapy if RLS is infrequent
- Keep dopamine agonist doses as low as possible
- Monitor for early detection, especially as duration of treatment increases.
- Keep iron stores replete (serum ferritin > 50-75 µg/l)

# Chronic Persistent RLS

Dopamine Agonist **OR**  $\alpha$ -2- $\delta$  Ligand

Dopamine Agonists	Alpha-2-delta Ligands
Very severe RLS	Comorbid pain
Comorbid depression	Comorbid anxiety
Obesity/metabolic syndrome	Comorbid insomnia
	Prior impulse control disorder or addiction

**If none of the above, consider an  $\alpha$ -2- $\delta$  ligand for initial therapy**

# Treatment of Augmentation

- Check iron stores
- Split agonist dose, cautiously increase total dose watching for progressive augmentation and not exceeding recommended total daily dose
- Change to rotigotine
- Change to an alpha-2-delta ligand



# Refractory RLS

## Definition

RLS unresponsive to monotherapy with tolerable doses of 1<sup>st</sup> line agents due to reduced efficacy, augmentation or side effects

# Refractory RLS

- Reassess iron stores. Consider IV iron therapy.
- Consider other exacerbating factors (drugs; sleep apnea)
- Use combination therapy: Reduce the dose of the first line agent and add one or more alternative agents (e.g. alpha-2-delta ligand to agonist)
- Substitute a medium or high potency opioid

# Opioids

- Very effective for refractory RLS with persistent benefit up to 10 years
- 2% serious side-effects (vomiting, severe constipation)
- Doses are very low compared to chronic pain
- Tolerance or dependence rate far lower than with high dose therapy
- Prescribed drugs include oxycodone (10-30 mg), methadone (2.5-10 mg), morphine and others

# Opioid Side Effects

- Itch
- Constipation
- Nausea and vomiting
- Cognitive effects
- Gait unsteadiness and falls
- Sleep apnea
- Overdose
- Addiction

# Assess Risk of Addiction

- Young white males
- FH of alcohol or drug abuse
- Personal history of alcohol or drug abuse
- Psychiatric co-morbidities
- Use Opioid Risk Tool

# Issues with Opioids in RLS

Confusion of RLS and chronic pain together with widespread opioid addiction, leading to:

- Insurance reimbursement issues
- Providers' fear of professional consequences
- Threatened restrictive administrative rules and legislation

Work with the RLSF to educate providers, insurance and legislators

# Responsible Opioid Use

- Opioid contract
- No early refills
- No replacements for lost prescriptions or drugs
- No changes in regime without discussion with provider
- Opioids from only one provider
- Random urine drug screens
- Use of state prescription monitoring programs
- Frequent reassessment of response and side effects (usually 3-6 monthly visits)



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## **QUESTION AND ANSWER**