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SLEEP MEDICINE UPDATE 2023

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RESTLESS LEGS SYNDROME

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INDUSTRY

- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Gabapentin, pregabalin, opioids for the treatment of RLS

LEARNING OBJECTIVES

- Understand initiation of therapy for a newly diagnosed patient with RLS
- Describe the indications for iron therapy in RLS
- Discuss therapeutic approaches for a patient with refractory restless legs, including use of opioids

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Part One

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

Prevalence

1.5-2.7%

for RLS

- at least 2 days a week
- causing at least moderate distress

Allen 2010, 2011

Common Differential Diagnoses

- Nocturnal leg cramps
- Pressure discomfort relieved by change in position
- Habitual leg jiggling
- Paresthesias due to peripheral neuropathy
- Fibromyalgia
- Periodic limb movements

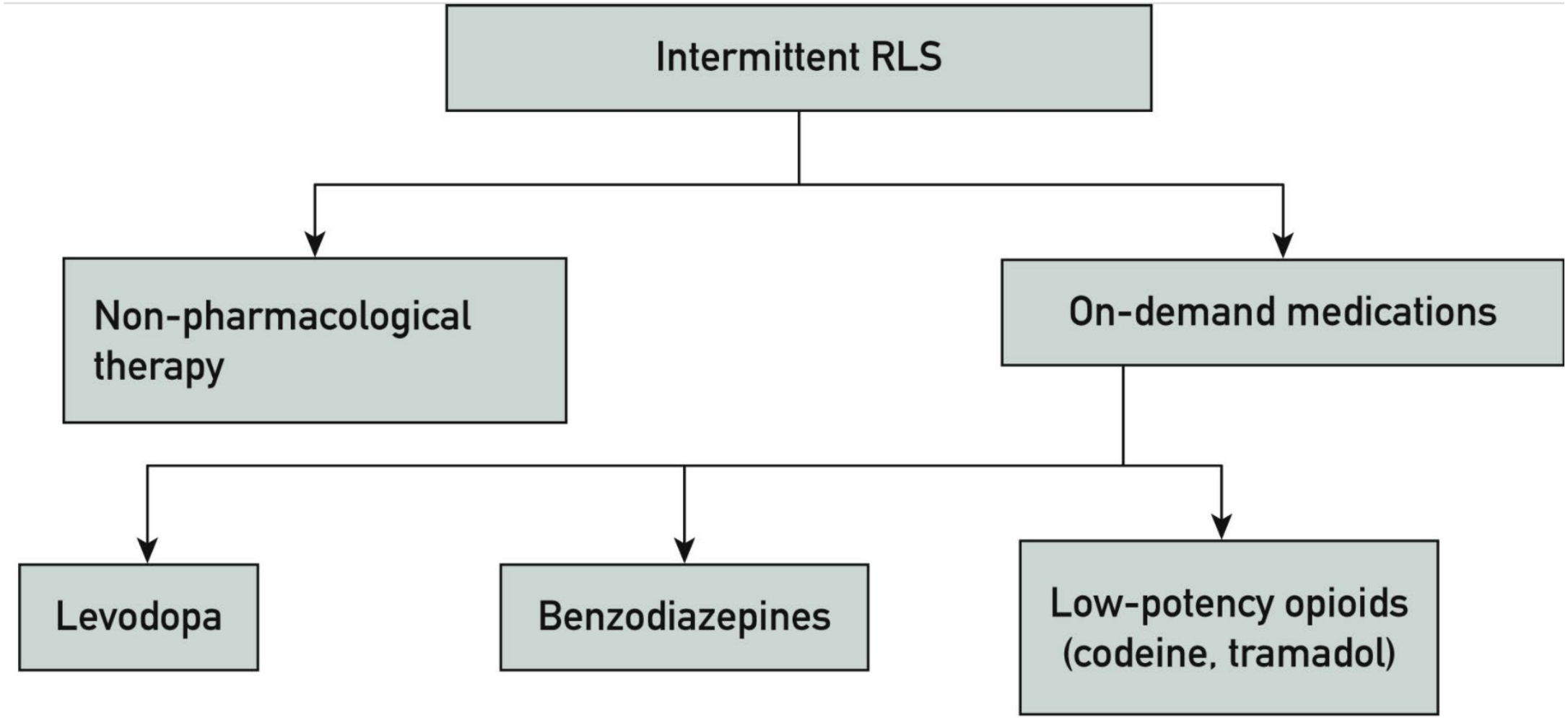
Mayo Clinic Proceedings
Volume 96, Issue 7, July 2021, Pages 1921-1937

Review

The Management of Restless Legs Syndrome: An Updated Algorithm

Michael H. Silber MBChB [a], Mark J. Buchfuhrer MD [b], Christopher J. Earley MBBCh, PhD [c], Brian B. Koo MD [d], Mauro Manconi MD [e, f], John W. Winkelman MD, PhD [g, h]

Scientific and Medical Advisory Board of the Restless Legs Syndrome Foundation


Intermittent RLS
Non-pharmacological therapy
On-demand medications
Levodopa
Benzodiazepines
Low-potency opioids (codeine, tramadol)

Non-Pharmacologic Therapies

- Walking, stationary bicycling , rubbing or soaking limbs
- Mental alerting techniques (e.g. video games, crossword puzzles)
- Regular moderate physical activity
- Consider a trial of reducing caffeine and alcohol

Other General Issues

- Consider role of meds in exacerbating RLS (antidepressants - except bupropion - , neuroleptics, sedating antihistamines)
- 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

Case One

- A 42-year-old woman presents with untreated typical restless legs syndrome. Symptoms started 5 years before but have increased in severity, now delaying sleep onset by 1 to 2 hours each night and waking her at 2:00 a.m. 3 nights a week. She does not have symptoms during the day.
- She does not have menorrhagia and does not donate blood.
- No significant past medical history
- Her mother also has RLS.
- Neurologic examination is normal. BMI 22.5
- Serum ferritin is 198 µg/l

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Case One
Which of the following is the most appropriate first step in management?

✓ 1 A. Pregabalin

0%

2 B. Pramipexole

0%

3 C. Oxycodone

0%

4 D. Intravenous ferric carboxymaltose



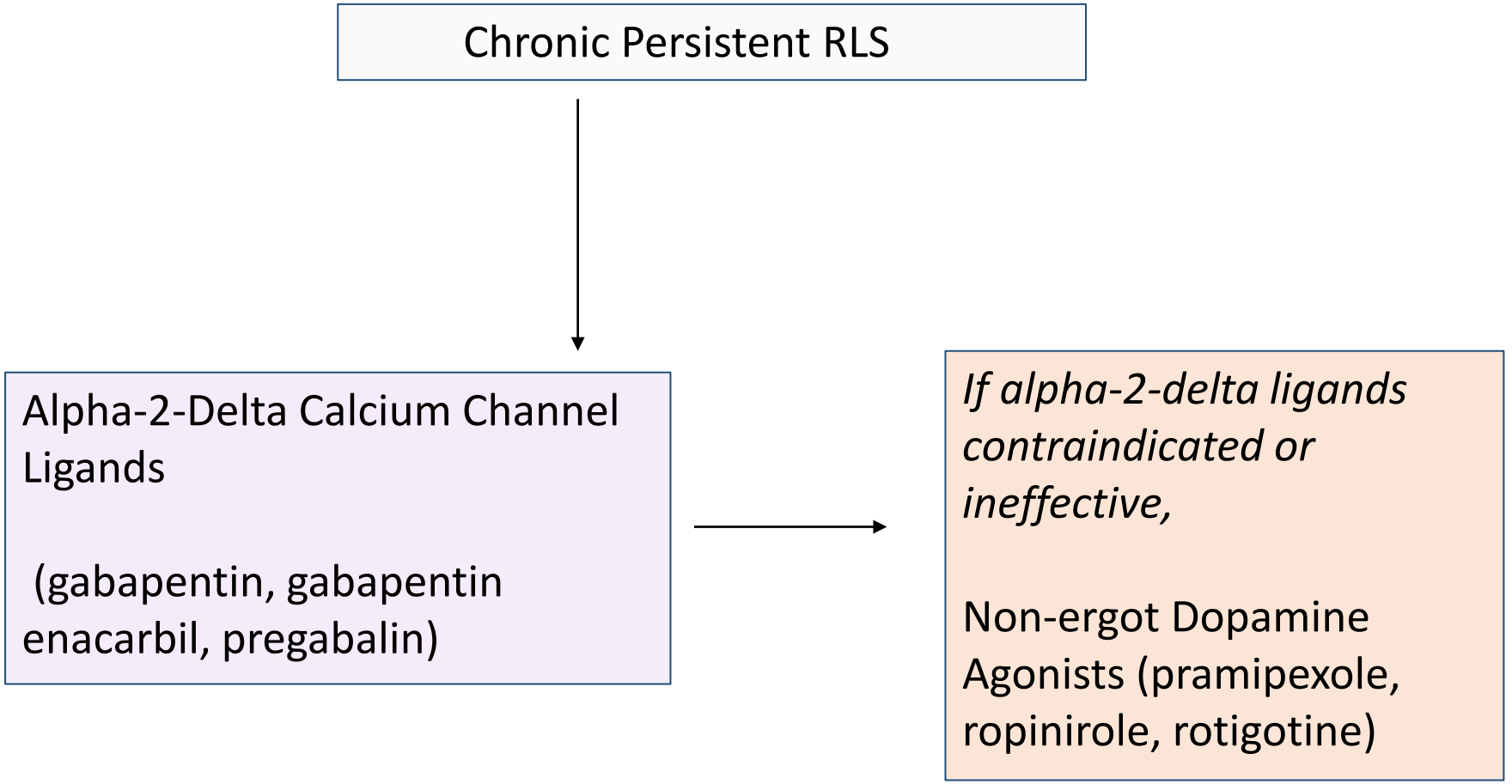
100%

Sample Results

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



Modified from Silber et al. The Management of Restless Legs Syndrome: An Updated Algorithm Mayo Clin Proc 2021;96:1921-37

National Use of DMN Agonists for RLS

- 670,404 RLS patients in U.S. National Prescription Audit database
- 59% on DMN agonists
- 19% > FDA recommended maximum doses

Winkelman Sleep 2022

Why not Start with Dopamine Agonists?
Risk of 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
- Paradoxical worsening of symptoms as dose is increased

42-70% risk with oral dopamine agonists over 10 years

Silver 2011; Lipford 2012

Why not Start with Dopamine Agonists? Risk of Impulse Control Disorders

- Any ICD 17% (control 6%)

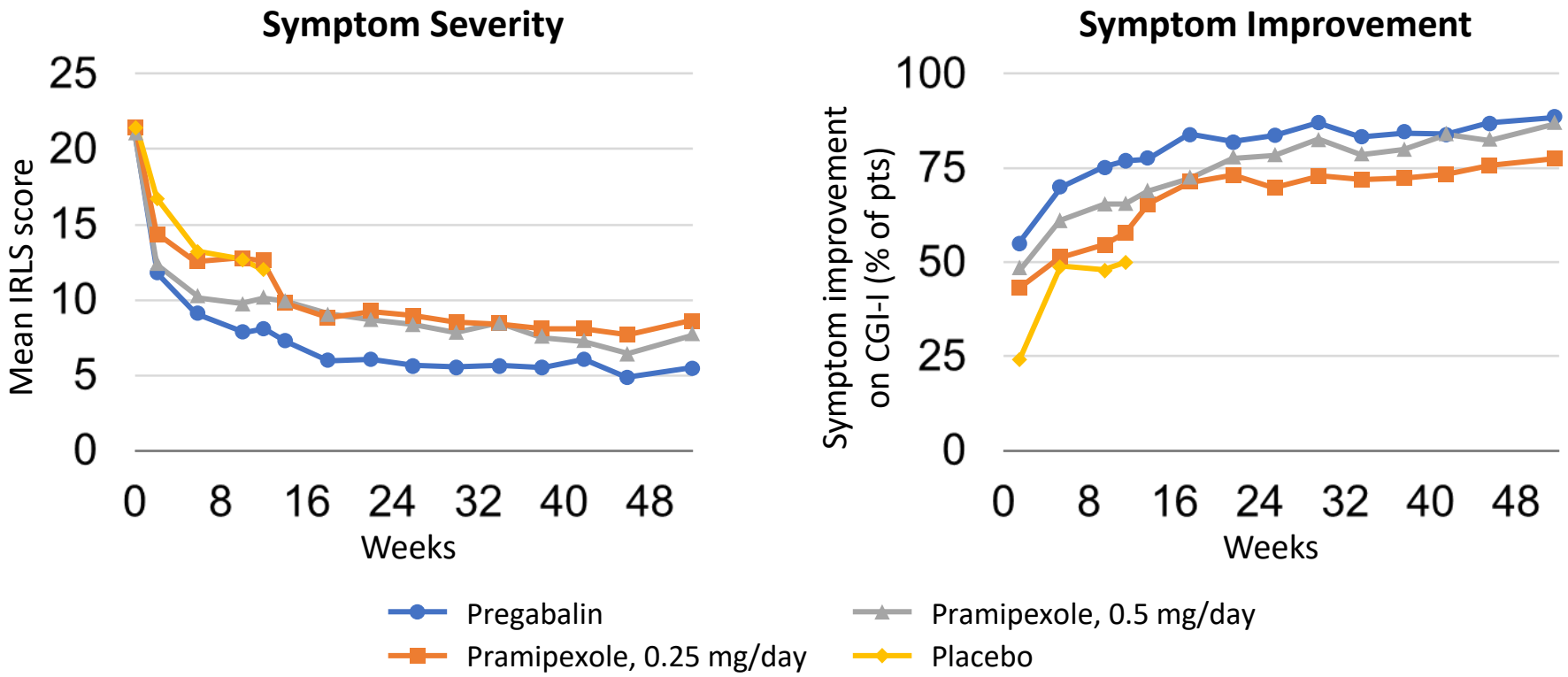
- Pathologic gambling 9% (control 0.4%)
- Compulsive shopping 5% (control 0.7%)
- Hypersexuality 3% (control 0.4%)

Cornelius 2010

Other open label studies: 6%

Pregabalin

719 subjects with moderate to severe RLS



Redrawn from: Allen RP et al. N Engl J Med 2014;370:621-631

α2δ ligands	Starting dose		Usual effective daily dose	Maximum daily dose
	< 65 yrs	> 65 yrs		
Pregabalin *	75 mg	50 mg	300 mg	450 mg
Gabapentin *^	300 mg	100 mg	900-1,200 mg	3,600 mg
Gabapentin enacarbil *	600 mg	300 mg	600 mg	1,200 mg

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

Adverse Effects of Alpha-2-Delta Ligands

- Daytime drowsiness
- Dizziness and unsteadiness
- Mental fogging
- Weight gain
- Depression, including suicidal ideation
- Respiratory depression
- Abuse potential

NOT augmentation or impulse control disorders

Contraindications to Starting with an Alpha-2-Delta Ligand

- Obesity and its complications
- Moderate or severe depression
- Gait instability
- Respiratory failure
- History of substance use disorder

	Pramipexole	Ropinirole	Rotigotine Patch
Starting Dose	0.125 mg	0.25-0.5 mg	1 mg
Maximum Dose	0.5 mg	2-4 mg	3 mg
Metabolism and Excretion	Renal excretion	Hepatic metabolism	Hepatic metabolism

Dopamine Agonists: Other Side Effects

- Lightheadedness
- Nausea or dyspepsia
- Nasal congestion
- Leg edema
- Nightmares
- Hypersomnia
- Application site reactions (rotigotine) (30-60%)

Case One

- With 300 mg pregabalin an hour before sleep, restless legs symptoms were reduced to only a few times a month.

- No side effects were noted.

Case Two

- A 54-year-old man presented with severe RLS resulting in an estimated 3 to 4 hours sleep a night.
- Pramipexole caused serious gambling behavior and had been discontinued. Gabapentin in a dose of 600 mg daily caused dizziness, unsteadiness and a sense of mental fogging.
- He was not on medications known to worsen RLS.
- Serum ferritin was 51 µg/l, percentage transferrin saturation 28%

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Case Two
Which of the following is the most appropriate next step in management?

1 A. Pregabalin

0%

2 B. Rotigotine patch

0%

3 C. Oxycodone



100%

✓ 4 D. Intravenous ferric carboxymaltose

0%

Sample Results

Oral Iron Supplementation

- Consider for serum ferritin < 50-75 mcg/l

  (Do not use oral iron if ferritin greater than 75 as transporters saturated)
- If chronic inflammation or malignancy, also check transferrin saturation (low <20%)
- Ferrous sulphate, ferrous fumarate or ferrous gluconate (65 mg elemental iron) once daily or every other day before bed
- Vitamin C 100-200 mg with each dose
- Recheck ferritin every 3-6 months
- Goal serum ferritin ≥75 mcg/l

Intravenous Iron

- Indications:

1. Iron malabsorption states
2. Oral iron intolerance
3. Severe symptoms needing rapid relief
4. No improvement after 3 months oral iron

- Serum ferritin < 100 mcg/l and transferrin saturation < 45%

- Positive 28 day, 46 patient controlled trial with ferric carboxymaltose (baseline ferritin 20-100)

Allen 2018

Intravenous Iron

Ferric carboxymaltose

- 1,000 mg over 20 min IV
- Hypophosphatemia (50-75%) (risk of osteomalacia with repeated doses for chronic iron deficiency anemia)

Low molecular weight iron dextran 1 gram (20 ml) in 250 normal saline over 1 hour (single dose)

- Give 25 mg test dose first

- 37-59% effective; response may be delayed 6 weeks
- Can repeat after 3-6 months if symptoms recur (ferritin <300; % sat<45)

Case Two

- He received 1 gram IV low molecular weight iron dextran.
- This resulted in marked improvement in RLS after a week.
- The effect lasted 6 months after which another infusion was administered.

Part Two

Case Three

- A 64-year-old woman with a history of RLS for 40 years experienced increasing symptoms from 12 noon through the rest of the day and night with spread to her arms concomitant to an increase in her dose of pramipexole to 2 mg spread through the 24 hours.
- The rotigotine patch (3 mg daily) was substituted with worsening symptoms and was changed back to pramipexole after 2 weeks
- Serum ferritin was 199 µg/l

Case Three

- Pregabalin was introduced with the dose increasing to 300 mg an hour before bed and pramipexole was then weaned over 7 days

- RLS worsened as the dose of pramipexole was reduced despite increase in pregabalin to 450 mg.

- Seven days after discontinuing pramipexole, she was obtaining at most 2 hours sleep a night. Suicidal ideation became prevalent

Case Three
Which of the following was NOT an error in her management?

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1 A. Pramipexole dose was too high



60%

2 B. Rotigotine dose was too low



20%

3 C. Pramipexole was weaned too fast



20%

✓ 4 D. Intravenous iron was not given

0%

Sample Results

Refractory RLS

Definition

RLS unresponsive to monotherapy with tolerable doses of dopamine agonists or alpha-2-delta ligands due to reduced efficacy, augmentation or side effects

Mild Augmentation

- Symptoms manifest predominantly as a temporal shift of symptoms to earlier in the day
- Dopaminergic monotherapy is at a total daily dose at or below maximum recommended levels
- Consider splitting the DA dose; possibly a single increase in total dose if not maximum, watching for further augmentation

Severe Augmentation

- Replenish iron stores (ferritin< 100; % saturation < 45%)
- Substitute a long-acting dopamine agonist (rotigotine patch)
- Cross-titrate gabapentin or pregabalin and slowly wean the DA
- Substitute an opioid and slowly wean the DA

Severe Augmentation

Substitute a long-acting dopamine agonist (rotigotine patch)

- The shorter acting dopamine agonist can be discontinued and the equivalent dose of the long-acting agent substituted IF total dose of pramipexole is ≤ 0.5 mg or ropinirole ≤ 2 mg
- If higher doses, use combined therapy initially and slowly wean the short-acting DA

Silber 2021, Laiwah 2022

Equivalent Doses	Rotigotine	
Pramipexole		
0.25 mg	2 mg	
0.50 mg or higher	3 mg	
Ropinirole		
0.5-1.0 mg 2 mg or higher	2 mg 3 mg	

Severe Augmentation

Cross-titrate gabapentin or pregabalin and slowly wean the DA

- First titrate up gabapentin to 900 mg or pregabalin to 300 mg before reducing the DA dose
- Reduce DA dose very slowly, depending on initial dose, patient wishes, and severity of withdrawal symptoms
- Suggested rate about 0.25 mg pramipexole per month if daily dose ≤ 1 mg and 0.5 mg per month if > 1 mg (some patients can tolerate faster withdrawal)
- Be aware that many patients will need to remain on a low residual DA dose

Dopamine Agonist Withdrawal Syndrome

- Anxiety
- Depression, including suicidal ideation
- Irritability, agitation and panic attacks
- Profound insomnia
- Drug craving
- Diaphoresis and flushing
- Nausea and vomiting
- Orthostasis

Dopamine Agonist Withdrawal Syndrome

- 15-19% of PD patients withdrawing from dopamine agonists

Yu, Fernandez 2017

- Recovery: (13 patients)

  < 6 months 61%; > 1 years 23%, needed to restart DA 15%

Pondal 2013

- Reported in RLS

Darfman 2013, Shimo 2015, Launois 2013

Effect of Rapid Withdrawal

- 24 subjects withdrawn from DMN agonists in preparation for a research study

- Mean pramipexole equivalent dose 0.69 mg
- Withdrawn at rate of 0.25 mg every 3 nights

- Mean total sleep time night one after end of withdrawal = 2.75 hours
- Mean total sleep time night 8 after end of withdrawal = 5.1 hours

Wang 2018

Severe Augmentation

Substitute an opioid and slowly wean the DA

- If other measures fail, introduce a low dose opioid
- In appropriate patients, low dose opioids have been shown to be effective and well tolerated

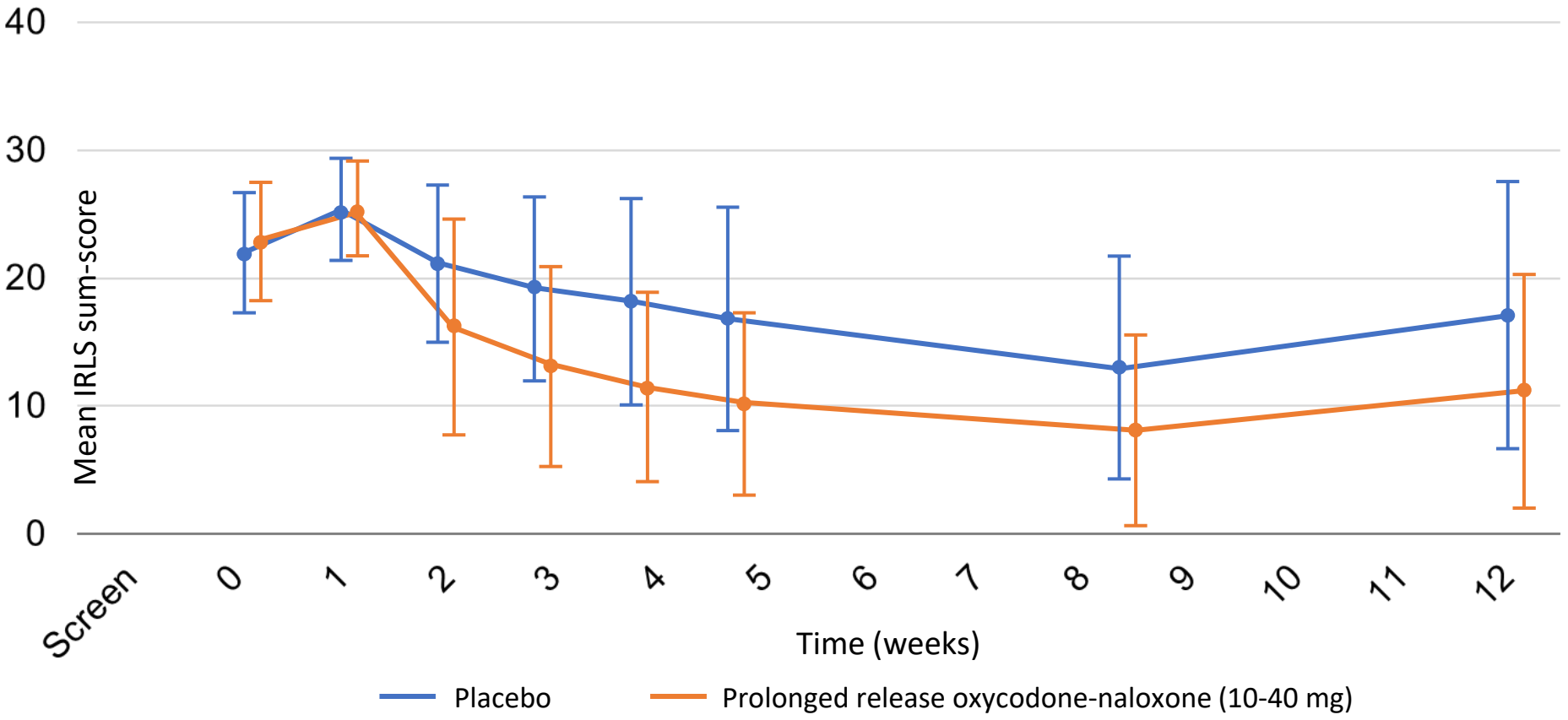
Silber 2018

Oxycodone-Naloxone Study

- Oxycodone-naloxone effective for RLS v. placebo at 12 weeks, sustained over 52 weeks
- Improved QOL with drug v. placebo
- 43% remitters at 52 weeks (22% symptom free)
- Mean daily dose 20 mg
- No augmentation, 8% constipation (one ileus) despite naloxone; 1% drug withdrawal symptoms after 52 weeks

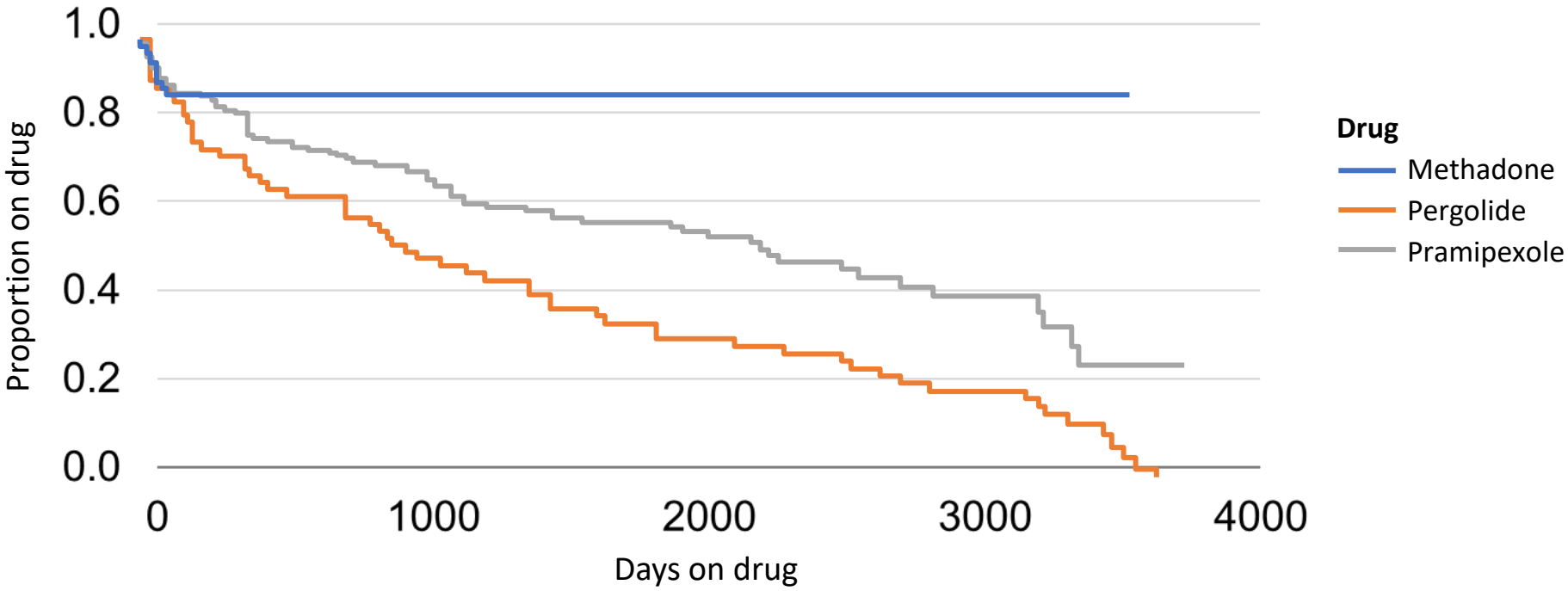
Trenkwalder 2013

276 subjects with moderate to severe RLS who failed other treatments



Redrawn from: Trenkwalder C et al Lancet Neurol 2013;12:1141-50

Opioid versus DA Use in RLS



Discontinuation rate due to augmentation: 7% per year

Redrawn from: Silver 2011

	Starting dose	Usual effective daily dose	MME Ratio
Tramadol	50-100 mg	100-200 mg	0.1:1
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 or ER	10-15 mg	20-45 mg	1:1
Methadone	2.5-5 mg	5-20 mg	4:1 (up to 20 mg)

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
- Overdose
- Addiction

- (Tramadol may cause augmentation)

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

Opioid Rules

- Sign 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

National RLS Opioid Registry

- 500 patients (95% retention after 2 years)
- Mean MME 30 mg
- One year follow up: 31% dose increase (mean 10 MME); 16% dose decrease
- Increase associated with predictable factors:
    - Opioid use for non-RLS pain
    - < 1 year use
    - Change to methadone
    - Discontinuation of non-opioid drug

National RLS Opioid Registry

Side Effects

- Constipation 52%
- Drowsiness 24%

  BUT

  43% had decreased drowsiness
- Itch 19%
- Sweating 1%

Winkelman Sleep 2021, Neurology 2023

Real World Management of Augmentation

- Single center study
- 63 patients with augmentation (98% temporal; 57% spatial)

- Mean use of DMN agonists 11 years
- Mean dose 1.23 mg PPX equivalents
- Mean follow-up 28 months

- 75% responders (CGI ≤ 2)
- 41% of responders could not completely discontinue DMN agonists

- **Mean rate of weaning DMN agonist 0.35 mg PPX equivalent /month (median 0.12 mg)**

	α2δ agents	Opioids
% Used	90%	48%
Successful D/C of DMN Agonists	40%	68%
Mean Dose of Successful Group	1,115mg gabapentin equivalents	39 mg MME

From data in Laiwah Sleep 2022

Case Three

- Pregabalin was discontinued
- ER oxycodone was introduced, 10 mg at noon and 10 mg before bed, increasing to 20 mg before bed (total daily dose 30 mg)
- This resulted in dramatic relief of symptoms with short lived RLS recurring once a night and total sleep time increasing to 6-7 hrs.
- No side effects, increased daytime alertness.
- Sustained response for a year.

Pregnancy

- Use non-pharmacologic techniques
- Replenish iron stores

- Clonazepam
- Carbidopa-levodopa
- Opioids

Cannabis

- No controlled trials
- Some anecdotal experience and single center case series suggests some possible benefit

  Megelin 2017, Ghorayeb 2019
- Formulations, dose, and mode of administration uncertain
- Drug interactions (dopamine agonists, alpha-2-0delta ligands and benzodiazepines), adverse effects and legal constraints limit use

Possible Future Therapies

Mechanical or Electrical Devices

- No evidence for efficacy of leg vibration or pneumatic device
- Transcutaneous spinal cord stimulation may be worth exploring

Dipyridamole

- Inhibitor of adenosine transporters resulting in increased extracellular adenosine
- Small positive DB placebo-controlled trial

Garcia-Borreguero 2021

Placebo (and Nocebo) Effects

- IRLS Scale (0-40)

  6.6 points (based on 84 RCTs)

- Global Impression of Change

  46% of clinicians and 40% of patients report much or very much improved (based on 24 RCTs)

- Nocebo Effect:

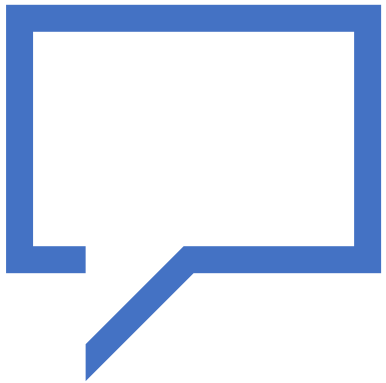
  45% of patients have adverse effects with placebo

Silva 2017

Take Home Messages

- Assess all RLS patients for iron status and correct orally or intravenously as indicated
- Unless contraindications, alpha-2-delta ligands are first-line therapy for chronic persistent RLS
- When dopamine agonists are used, keep the dose low and assess frequently for augmentation
- Withdraw dopamine agonists slowly, first covering with alternative medications
- Low-dose opioids are highly effective in refractory restless legs and should not be withheld from appropriate patients
- Current therapies are only moderately successful and ongoing research for new approaches is essential

QUESTIONS
& DISCUSSION



QUESTIONS
& DISCUSSION

