Fighting the URGE: Optimizing the Treatment of Restless Leg Syndrome

pmiCME Updates
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Faculty:

David B. Rye, MD, PhD

Ana Krieger, MD, MPH

Educational Partner
The Institute for Continuing Healthcare Education
Session 6: Fighting the URGE:
Optimizing the Treatment of Restless Leg Syndrome

Learning Objectives
1. Evaluate the underlying etiology and pathophysiology of RLS and determine how these may impact diagnosis and treatment.
2. Apply current guidelines for the treatment of RLS into practice, thereby improving rates of appropriate diagnosis.
3. Analyze current guidelines for the management of RLS and employ in clinical practice those that may improve patient outcomes.
4. Assess the efficacy and side effect profiles of pharmacologic treatments for RLS, and utilize those that minimize patient symptoms and maximize quality of life.

Faculty
David B. Rye, MD, PhD
Professor of Neurology
Emory University School of Medicine
Atlanta, Georgia

David Rye, MD, PhD, is a professor of neurology at Emory University’s School of Medicine and the director of research for Emory Healthcare’s program in sleep medicine. He is an internationally recognized expert in narcolepsy and related disorders of excessive daytime sleepiness and movement disorders in sleep, particularly RLS.

Dr Rye is the former chair of the RLS medical advisory board and is on the medical advisory board of the Narcolepsy Network. He is a past recipient of the American Academy of Neurology’s Sleep Science Award (2008) and the Sleep Research Society’s Outstanding Scientific Achievement Award (2009). He also is the recipient of numerous grant awards from the National Institutes of Health.

Ana Krieger, MD, MPH
Medical Director
Weill Cornell Center for Sleep Medicine
New York, New York

Ana C. Krieger, MD, MPH, is an associate professor of clinical medicine in the departments of medicine, neurology, and neuroscience. She is a board certified specialist in sleep medicine by the American Academy of Sleep Medicine and the medical director of the Weill Cornell Center for Sleep Medicine.

Over the past 14 years, Dr Krieger has been actively involved in patient care, training of sleep specialists, and sleep disorders education and research. Besides her clinical activities, Dr Krieger is a clinician scientist, the principal investigator on National Institutes of Health-sponsored translational research projects investigating the mechanisms of cardiovascular disease and thrombosis in sleep apnea, and is involved in multiple other collaborative multidisciplinary research projects in sleep medicine.

Faculty Financial Disclosure Statements
The presenting faculty reports the following:

David B. Rye, MD, PhD, is a consultant and on the advisory board for UCB; is on the external data monitoring committee for Merck; and is on the advisory board for Impax Laboratories and Jazz Pharmaceuticals.

Ana C. Krieger, MD, MPH, has no financial relationships to disclose.

Education Partner Financial Disclosure Statement
The content collaborators at the Institute for Continuing Healthcare Education have reported the following:
Cathy Pagano, CCMEP, President; Allison A. Muller, PharmD, D.ABAT, Medical Director; Scott Kober, MBA, CCMEP, Director, Content Development; April Reynolds, MS, ELS, Content Editor; Sandra Davidson, Director, Project Management; and Tina Chiu, MED, Project Manager, have no financial relationships to disclose.
**Suggested Reading List**


Session 6
3:30 PM – 4:45 PM

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Speakers:
David B. Rye, MD, PhD
Ana Krieger, MD, MPH

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Off-Label/Investigational Discussion
In accordance with pmICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Pharmacologics Within This Presentation

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
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<tbody>
<tr>
<td>Pramipexole</td>
<td>Mirapex</td>
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<tr>
<td>Pergolide</td>
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<td>Cabergoline</td>
<td>Dostinex</td>
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<td>Pregabalin</td>
<td>Lyrica</td>
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<tr>
<td>Gabapentin enacarbil</td>
<td>Horizant</td>
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<tr>
<td>Rotigotine</td>
<td>Neupro</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Niravam, Xanax</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Respar</td>
</tr>
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<td>Iron dextran</td>
<td>Deferox, Iferrox, IRFeD</td>
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<td>Iron sucrose</td>
<td>Venofer</td>
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<td>Ferric gluconate</td>
<td>Ferinject, Nulecit</td>
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<td>Ferric carboxymaltose</td>
<td>Ferinject</td>
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<td>Levodopa</td>
<td>Dopar, Larodopa</td>
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<td>Gabapentin</td>
<td>Fanatrex, Gabaron, Neogab, Gralise, Neurontin, Nupentin</td>
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<td>Clonazepam</td>
<td>Caberclon, Klonopin, Klonopin Wafer</td>
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<td>Citalopram</td>
<td>Cialera</td>
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<td>Etipiram</td>
<td>Ambien, Ambien CR, Edluar, Intermusco, Stilnox, Sublinox, Edipamist</td>
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Learning Objectives

• Evaluate the underlying etiology and pathophysiology of restless legs syndrome (RLS) and determine how these may impact diagnosis and treatment

• Apply current guidelines for the treatment of RLS into practice, thereby improving rates of appropriate diagnosis

• Analyze current guidelines for the management of RLS and employ into clinical practice those that may improve patient outcomes

• Assess the efficacy and side effect profiles of pharmacologic treatments for RLS, and utilize those that minimize patient symptoms and maximize quality of life

Please indicate the number of patients you see each week with RLS

1. 0-5
2. 6-10
3. 11-15
4. 16-20
5. 21-25
6. 26-30
7. >30

Activity Pre-Test
In which of the following patients would you suspect a greater than average possibility of the presence of RLS (choose all that apply)?

1. UT, a 32-year-old female complaining of frequent migraines
2. PA, a 57-year-old male with renal failure
3. JK, a 45-year-old male with a recent knee replacement
4. TY, a 75-year-old female with multiple sclerosis
5. SS, a 24-year-old HIV-positive male

For a pregnant 29-year-old patient in her third trimester who presents with severe RLS-related symptoms, which of the following agents would best combine safety and efficacy?

1. Pramipexole
2. Folic acid supplementation
3. Pregabalin
4. Gabapentin enacarbil
5. Ropinerole
6. Rotigotine

Which of the following might lead you to conclude that your RLS patient is suffering from augmentation?

1. Symptoms occurring only between the hours of 2-5 a.m.
2. Significant worsening of symptoms with decrease in medication dosage
3. Spread of symptoms to previously unaffected areas
4. Significant improvement in symptoms with increase in medication dosage

In an RLS patient being treated with rotigotine, which of the following potential side effects would you be most concerned about?

1. Fluid retention
2. Sleepiness
3. Morning drug hangover
4. Skin irritation/infection

What We’ll Cover

- Defining RLS
- Epidemiology of RLS: comorbidities and factors influencing trait expressivity
- Tools and clinical pearls to help recognize RLS
- Pathophysiology of RLS
  1) Iron
  2) Spinal sensorimotor systems
  3) Molecular genetics

Epidemiology and Diagnostic Considerations

David Rye, MD, PhD
Professor of Neurology
Emory University
Atlanta, GA
The Burden of RLS is Significant

- 5-10 million Americans clinically significantly affected
- Quality of life is negatively impacted to a degree comparable to other common, complex, chronic diseases
- Higher cross-sectional rates of mood disorders
  - Major depressive disorder (odds ratio [OR]=4.7, range: 1.6-14.5)
  - Panic disorder (OR=12.9, range: 3.6-46.0)
- Higher cross-sectional rates of cardiovascular problems
  - Hypertension (OR=1.5, range: 0.9-2.4)
  - Heart disease (OR=2.5, range: 1.4-4.3)

A Multitude of Descriptors are Chosen by Patients to Describe Their Sensory RLS Experience
(N=360 respondents)

- “Creepy, crawling”: 43.6%
- “Aching”: 39.4%
- “Tingling”: 28.3%
- “Electric”: 27.8%
- “Painful”: 24.2%
- “Indescribable”: 23.9%
- “Like worms”: 20.0%

<20%: “pins & needles”; “pulling”; “tugging”; “ache”; “numbness”; “itching”; “burning”

“Do You Experience Your Sensory Symptoms as ‘Painful’?”

- Percentage who answered in the affirmative
  - 35% of a population-based sample of Icelanders (N=951)
  - 35%-56% of smaller RLS cohorts reported by others

Supportive Features

- Family History = 30%-65%
- Symptom amelioration with dopaminergics (80%-90%)
- Periodic limb movements of sleep (~90%)

IRLSSG/NIH Essential Diagnostic Criteria for RLS

- An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations
- Onset or worsening of symptoms at rest or inactivity, such as when lying or sitting
- Relief with movement—partial or total relief from discomfort by activities such as walking or stretching
- Worsening of symptoms in the evening and at night

RLS prevalence is high and influenced by ethnicity
PLMS = Periodic Limb Movement Index

**Renal Iron Condition Prevalence of**

- Schöls deficiency failure/hemodialysis 50%
- Donation 25%
- Parkinson's Multiple Limb RLS Myelopathy ~40% (without anemia) ~40%
- Movement Conditions
- LM Trotti et al. *Sleep* 2009;10:668

**Iron Impacts RLS Symptomatology, But it is NOT a Sine Qua Non**

- RLS occurs in ~40% of subjects with iron deficiency (ie, iron deficiency by itself is insufficient to cause RLS)
- In vivo and in vitro iron depletion occurs in *some patients* in dopamine-rich brain regions of RLS patients
- Iron deficiency adversely affects dopamine signaling
- Intravenous iron can ameliorate RLS symptoms, although recent controlled studies demonstrate less consistent and less dramatic clinical responses

**RLS Expressivity is Also Affected by the ‘Environment’ (ie, Other Medical Conditions)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence of RLS</th>
</tr>
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<tbody>
<tr>
<td>Red blood donation</td>
<td>25% (women)</td>
</tr>
<tr>
<td></td>
<td>15% (men)</td>
</tr>
<tr>
<td>Iron deficiency (without anemia)</td>
<td>~40%</td>
</tr>
<tr>
<td>Pregnancy (esp. 3rd trimester)</td>
<td>26%</td>
</tr>
<tr>
<td>Renal failure/hemodialysis</td>
<td>50% (African Americans) 70% (Caucasians)</td>
</tr>
</tbody>
</table>

**RLS Occurs at Greater Frequency Than Expected by Chance in Many Conditions**

- Rheumatologic disorders
- Diabetes
- Pulmonary hypertension
- Chronic obstructive pulmonary disease (COPD)
- Chronic liver disease
- Crohn’s disease
- Celiac disease
- Gastric bypass surgery
- Irritable bowel syndrome
- Migraine

**Neurological Conditions in Which RLS Occurs at High Frequencies**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence of RLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson's disease</td>
<td>11%-24%</td>
</tr>
<tr>
<td>Spinocerebellar ataxia ICA-3</td>
<td>45%</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>33%</td>
</tr>
<tr>
<td>Myasthenia</td>
<td>~40%</td>
</tr>
</tbody>
</table>

**Periodic Lim Movement (PLM) and RLS Are Often, But Not Always, Overlapping Conditions**

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Iron Deficiency is Not Necessary for RLS Diagnosis
(Iron measures in a clinic-based RLS sample)

- % RLS patients ferritin <20 ug/dL = 22%
  - Of whom only 1 in 3 are anemic
- % RLS patients ferritin 21-40 ug/dL = 20%
  - Of whom only 1 in 6 are anemic

RLS Has a Significant Genetic Component

- 30%-65% of RLS patients have a first-degree relative with the disorder
- High (54%-83%) concordance in identical twins
- Most pedigrees described exhibit an autosomal dominant inheritance pattern
- “Anticipation” in some families
- Genetic linkage studies have been largely uninformative

Case Study #1

Our Patient — CC

- 27-year-old male presenting for the evaluation of restless legs and intermittent insomnia
- Recently married, no children
- Past history of depression (associated with the death of his father and brother) and anxiety, stable off medications for 4 years
- Patient reports nail biting and skin picking
- Patient is a writer, drinks 1 cup of coffee in the morning
- No other medical problems are present

CC’s RLS-Related History

- Childhood history of “growing pains” in both legs, mostly at night, described as a uncomfortable, “tingling-like” sensation associated with an urge to move them
- As a teenager, leg discomfort started to interfere with sleep onset
- Recently married; leg movements at bedtime keep his wife awake
- Current complaints are leg discomfort at night that delay onset of sleep by at least 30 minutes and interfere with his wife’s sleep
- Has not been previously diagnosed or treated for RLS

Your Call

What would you recommend at this point?
1. Prescribe hypnotics at bedtime
2. Iron supplementation
3. Recommend melatonin at bedtime
4. Initiate dopaminergic agents
5. No treatment
Your Call

Would you order a ferritin level in this patient?

1. Yes
2. No

Your Call

Would you order an overnight sleep study in this patient?

1. Yes
2. No

Panel Discussion

• Should we check ferritin levels in every patient?
• At which point should we recommend iron supplementation?
• When should we order a sleep study?

Case Study #2

Our Patient — JD

- 62-year-old female
- Small-business owner
- History of anxiety and arthritis
- Exercises regularly, does not smoke
- Drinks 1 cup of coffee each morning
- Medications include daily multivitamin, ibuprofen as needed, and alprazolam as needed during the day for anxiety (average use = twice a week)

JD’s RLS-Related History

- 2003: Husband noticed her legs were restless while laying quietly in bed prior to going to sleep. Despite feeling somewhat uncomfortable in the legs, patient did not consider it a problem
- 2009-2010: Leg discomfort increased, causing difficulty falling asleep. Patient started walking around the room to get some relief, worsening her anxiety
JD's RLS-Related Treatment History

- **June 2011**: Started on ropinirole 0.5 mg at 9 p.m. daily with adequate clinical response
- **October 2011**: Seen for follow-up with primary care physician. Patient described earlier onset of symptoms, occurring in the late afternoon. Dosage was increased to 1 mg and timing changed to 5 p.m. with adequate response
- **December 2011**: Break-through bedtime leg discomfort. Dosage increased to 1.5 mg at 5 p.m. with partial improvement
- **January 2012**: Early afternoon tingling sensation occurring in the arms, not improved after increasing dosage to 2 then 3 mg at 5 p.m. Leg discomfort at night feels worse than baseline symptoms

Your Call

Which of the following would you choose as the next step in the management of this patient?

1. Continue to increase ropinirole dosage
2. Change the time of the medication to lunchtime
3. Add a second dose of ropinirole at noon
4. Switch to long-acting ropinirole
5. Continue ropinirole and add another medication
6. Decrease the dosage of ropinirole

Panel Discussion

- What may be the reason for this patient's worsening symptoms?
- With which signs of augmentation did she present?
- Would you have treated her RLS differently during the initial 8 months?
- Would you have considered checking ferritin levels?
- What would be your next treatment option(s)?

Treatment Considerations for RLS

Ana C. Krieger, MD, MPH, FCCP, FAASM
Associate Professor
Weill Cornell Medical College
Cornell University

When to Consider Treatment

- When symptoms are severe enough based on:
  - Subjective sensation
  - Sleep disruption
  - Impact on social or professional performance
  - Changes in quality of life

What to Consider in RLS Treatment

- Primary vs. secondary RLS
- Concurrent medical problems/medications
- Presence of overlapping PLMs in sleep
- Severity, duration, and timing of symptoms
  - Circadian rhythmicity of symptoms
Approaches to Treatment

- Consider the need for further testing
  - Polysomnography (REM sleep behavior disorder, PLMs)
  - Blood draw (hemoglobin, transferrin saturation and ferritin, vitamins B12, D, and folate)
  - Neurological assessment
- Treat underlying conditions
  - Sleep apnea, hypoventilation
  - Diabetes mellitus, renal failure, electrolyte imbalance


Focused RLS Treatment Approach

- Supportive
- Pharmacological

GOALS
- Reduce symptoms (based on IRLS score)
- Improve Clinical Global Impression (CGI) scores
- Improve quality of life
- Improve sleep (if altered)

Supportive Treatment for RLS

- Iron supplementation — if ferritin <45 ng/mL
- Exercise, yoga
- Also suggested:
  - Vitamin supplementation: C, D, E
  - Leg compression
  - Cold/warm packs
- No clear evidence that melatonin helps


Iron Supplementation

- May be used in conjunction with other treatments, including pharmacotherapy
- Route:
  - Oral
    - Several weeks (low rate of transport across the intestinal wall)
    - GI-related side effects (constipation)
  - IV
    - One or two doses
    - Potential side effects (anaphylactic/anaphylactoid reactions)


IV Iron Treatment

- Iron dextran:
  - Low molecular weight – fewer side effects
  - High molecular weight – effective, low cost, more side effects
- Iron sucrose
- Ferric gluconate
- Ferric carboxymaltose

Side effects if high molecular weight avoided <1:200,000 include dyspnea, hypotension, nausea, flushing, pruritus, anaphylaxis


IV Iron Treatment

- Ferric carboxymaltose: 1 dose, 500 mg IV
- N=20, ferritin <45 ng/mL
- 12/20 responders after 7 days
- IRLS ↓10 points in responder group

**IV Iron Treatment**

- Randomized, placebo controlled
- N=46, off RLS therapy
- IV ferric carboxymaltose: 1 dose 1000 mg = 500 mg IV 5 days apart
- 45% responded, 29% remitted (IRLS ≤10)
- 25% free of other RLS treatments at 24 weeks
- IRLS ↓8.9 points vs. ↓4 placebo

<table>
<thead>
<tr>
<th>Time</th>
<th>FCM 2 doses 500 mg (n=24)</th>
<th>Placebo (n=10)</th>
<th>p (Student’s t test)</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>25.0±3.84</td>
<td>24.2±3.90</td>
<td></td>
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<tr>
<td>Day 5</td>
<td>-6.1±6.1</td>
<td>-5.2±6.3</td>
<td>0.014</td>
</tr>
<tr>
<td>Day 14</td>
<td>-7.7±7.2</td>
<td>-6.2±8.9</td>
<td>0.106</td>
</tr>
<tr>
<td>Day 21</td>
<td>-8.9±8.5</td>
<td>-4.0±6.1</td>
<td>0.008</td>
</tr>
</tbody>
</table>


**Pharmacotherapy**

- Not recommended in pregnancy
- Medications can be given intermittently or daily
- FDA-approved drugs:
  - Dopamine agonists (oral)
    - Pramipexole (D2/D3 receptor agonist)
    - Ropinirole
  - Dopamine agonists (skin patch)
    - Rotigotine
  - α₂δ agonists
    - Gabapentin enacarbil

**Recommended Medications**

<table>
<thead>
<tr>
<th>Practice Parameter with High Body of Evidence</th>
<th>Harm/Burden Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicians should treat patients with RLS with pramipexole or ropinirole</td>
<td>Benefits clearly outweigh harms FDA Approved for RLS</td>
</tr>
<tr>
<td>Clinicians can treat patients with RLS with gabapentin enacarbil or rotigotine</td>
<td>Uncertainty in balance between benefits and harms FDA Approved for RLS</td>
</tr>
<tr>
<td>Clinicians can treat RLS patients with levodopa with dopa decarboxylase inhibitor</td>
<td>Benefits closely balanced with harms. This is particularly true for those with intermittent RLS who use this medication sporadically Off-label use</td>
</tr>
<tr>
<td>Clinicians can treat RLS patients with cabergoline only if other recommended agents have been tried first and failed, and close clinical follow-up is provided</td>
<td>Benefits closely associated with harms Off-label use</td>
</tr>
</tbody>
</table>

**Pramipexole in RLS*”**

- Double-blind, randomized, placebo-controlled
- N=234, 26 weeks follow-up
- IRLS scale ≥15, ferritin >30 ng/mL
- Dosage: 0.125-0.75 mg/day
- Efficacy:
  - IRLS score ↓13.7 vs. 11.1 (p<0.008)
  - IRLS score ≤50% baseline in 59% vs. 43% (p<0.004)
- Augmentation: 9% vs. 6% placebo
- Side effects: nausea (15%), spasms (6%), arthralgia (5%)
- Only trial over 12 weeks in duration


**Pramipexole in RLS**

Adjusted mean change in IRLS scores (N=321)

* p<0.001  b p<0.01

**Ropinirole in RLS**
- Randomized, single/double-blinded, placebo-controlled
- Single-blind enrollment phase: N=202, Primary RLS, IRLS score ≥15 for 24 weeks
  - Mean IRLS score ↓12.8
- Dosage: 0.25–4 mg (mean=2 mg/d)
- Efficacy in double-blind phase (N=92, 12 weeks):
  - IRLS score compared to single-blind pre-enrollment: ↓8.7
  - CGI much/very much improved in 69% vs. 47% (p=0.03)
  - Side effects: nausea (18%), headache (11%), upper respiratory tract infection (2%)

**Rotigotine in RLS**
- Moderate to severe RLS, N=295, age 58±10 years
- 2-year, open-label, follow-up study: mean daily dose=3 mg
- Efficacy:
  - 95% much/very much improved CGI
  - 17±9 improvement on IRLS score
- Safety: 1% nausea (29%), 2.3% fatigue
- Local reaction: 16% (52%)
- Augmentation: 2.4% (2.7%)

**Gabapentin Enacarbil in RLS**
- Randomized, double-blind, placebo-controlled, 12 weeks
- Primary RLS, off treatment, ferritin ≥20 mg/mL
- n=115 (600 mg), n=113 (1200 mg) and n=97 (placebo)
- Efficacy
  - 600 mg dose – IRLS ↓14, CGI 73%
  - 1200 mg dose – IRLS ↓13, CGI 78%
  - Placebo – IRLS ↓10, CGI 45%
- Compliance: >94%
- Responders: 64% (600 mg), 58% (1200 mg), 40% (placebo)
- Side effects: somnolence (22% 600 mg; 18% 1200 mg), dizziness (10% 600 mg; 24% 1200 mg)

**Gabapentin in RLS**
- Randomized, crossover, double-blind study (n=24)
- Dose: 600 mg to 2400 mg
- Baseline:
  - 56% patients with pain
  - Excluded ferritin <20 ng/mL
- Gabapentin side effects:
  - 26% malaise
  - 9% somnolence

**Pregabalin in RLS**
- Double-blind, placebo-controlled, randomized study
- 12 weeks, N=98
  - Excluded if ferritin <10 ng/mL
  - IRLS ↓12 pregabalin vs. ↓10 in placebo (p<0.005)
  - Mean dose: 322 mg
- Side effects: unsteadiness (50%), daytime sleepiness (43%), headache (13%)
### Medications Dosages

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose Range</th>
<th>Half-Life</th>
<th>Titration Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ropinirole</td>
<td>1–3 mg</td>
<td>5–7 h</td>
<td>7 d</td>
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<tr>
<td>Rotigotine enacarbil</td>
<td>600 or 1200 mg</td>
<td>7–9 h</td>
<td>5–10 d</td>
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<tr>
<td>Gabapentin enacarbil</td>
<td>300–2700 mg</td>
<td>5–7 h</td>
<td>3–6 d</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>25–300 mg</td>
<td>10 h</td>
<td>3–6 d</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5–2 mg</td>
<td>30–40 h</td>
<td>1–3 d</td>
</tr>
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### Potential Side Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ropinirole</td>
<td>Nausea, low blood pressure, diziness, headache, nasal congestion</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>Nausea, low blood pressure, diziness, headache, nasal congestion, heart failure (possible association)</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>Skin irritation, nausea, low blood pressure, diziness, headache, nasal congestion</td>
</tr>
<tr>
<td>Gabapentin enacarbil</td>
<td>Dizziness, somnolence, fatigue</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Sleepiness, diziness, fluid retention</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Sleepiness, diziness, headache, fluid retention</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Sleepiness, diziness, morning drug hangover</td>
</tr>
</tbody>
</table>

### Monitoring Therapy

- **Symptoms improvement/resolution**
  - **Day 1**
    - Period of day
    - Onset
    - Mild
    - Moderate
    - Severe
    - No symptoms

### Augmentation

- **Earlier onset of symptoms (≥2 hours)** OR 2 of the following:
  1. Intensity increase with increasing dose
  2. Decreased intensity with decreasing dose
  3. Shorter rest time to provoke symptoms than before treatment
  4. RLS symptoms occur in previously unaffected limbs or body parts
  5. Shorter duration of treatment benefit than with initial treatment
  6. PLMS or PLM while awake (PLMW) occur for the first time or are worse than either before treatment of after initial treatment

- **Associated with low ferritin**
  1. Problem with dopaminergic agents
    - Levodopa = 60% (up to 80% if >300 mg)
    - Pramipexole = 9%–24%
    - Rotigotine = 13%
    - Ropinirole = 3%–4%; may accumulate yearly up to 20%
Managing Augmentation

• Differential diagnosis:
  – Progression of disease
  – Early AM rebound
  – Tolerance

• Prevention: keep dopamine doses as low as possible

• Treatment: if clinically relevant
  – Reduce or discontinue use of dopamine agents
  – Change to other drug category
  – Use longer-acting drugs
  – Treat low ferritin

Placebo Effect in RLS Treatment

• Approximately 40% in many studies

• Consider other symptoms and problems prior to selecting therapy

When to Refer to a Specialist

• Patient requires maximal recommended dose for symptom control (any meds)

• Symptoms refractory to treatment
  – Not improved after 1 dopa and 1 non-dopa drug

• Intolerable/unusual side effects/augmentation

• Children or elderly patients (>75 years)

Summary

• Treatment is symptomatic and considered on an individual basis according to:
  – Severity of disease
  – Underlying medications
  – Co-morbidities

• In pregnant patients, only iron and folic acid supplementation are considered safe

Summary II

• Medications should be carefully monitored to:
  – Keep the lowest effective dosage
  – Avoid (or quickly detect) augmentation

• With the exception of rotigotine, medications should be taken just prior to patients’ usual onset of symptoms

Important Final Consideration

• Impulse control disorders with dopamine agonists:
  – Compulsive behavior (sexual, gambling, eating, shopping)
  – Associated with higher doses

• In Parkinson’s disease:
  – Dopamine agonist withdrawal syndrome (DAWS):
    • Risk factor: impulse control disorder
    • Symptoms similar to drug addiction withdrawal
      – Depression, fatigue, anxiety, insomnia, irritability, panic, diaphoresis
    • Prevention: slow weaning of high doses
    • Recovery: 60% in 6 months, additional 23% in 12 months
  – About 15% unable to discontinue dopamine agonists

Further Information
European RLS Study Group: www.eurlssg.org
- RLS information
- Symptom diary
- Diagnostic algorithm (online)
- Latest references
- Links

Our Patient — TJ
- 63-year-old female
- RLS symptoms first emerged at age 27 during third trimester of pregnancy
  - Resolved after delivery but re-emerged sporadically for the next 3 decades
- Exacerbation at age 59, resulting in initiation of pramipexole
- Son, maternal uncle, and cousin have all been diagnosed with RLS
- Relevant medical history
  - Disc herniation and right L5-radiculopathy treated surgically in 1978
  - C5-C6 herniated disc repair in 1999
  - Hysterectomy as a result of uterine cancer in 2008

TJ’s Initial Presentation
- Current medications
  - Pramipexole 0.25 mg daily for RLS
  - Citalopram 20 mg daily for panic attacks and anxiety
  - Zolpidem 5 mg PRN for psychophysiological insomnia
  - Lansoprazole 15 mg daily for gastroesophageal reflux
- Clinical exam
  - Patient demonstrates tolerance to pramipexole and symptom augmentation
  - Flexor withdrawal-like, non-volitional movements in her right toe and ankle
  - 3+ tendon reflexes throughout
  - No pathological spread
- Laboratory results
  - Iron= 56 µg/dL, ferritin=22 ng/mL, transferrin saturation=17%

Your Call
What would you recommend for TJ at this point?
1. Decrease the dosage of pramipexole to 0.125 mg daily
2. Stop the pramipexole and initiate treatment with ropinirole 1 mg daily
3. Consider adding new medication class (eg, gabapentinoid or opioid)
4. Introduce iron supplementation and split or increase the pramipexole dose (eg, to 0.125 mg twice a day or 0.25 mg twice a day)

Six Years Later...
Patient has tried and failed multiple treatment regimens:
- Ropinerole 1 mg daily
- Ropinirole 1 mg daily + carbidopa-levodopa 25/100 PRN + oral iron supplementation
- Ropinirole 3 mg daily + carbidopa-levodopa 25/100 PRN + oral iron supplementation
- Pramipexole 0.125 mg twice daily + oral iron supplementation
- Pramipexole 0.25 mg three times daily + oral iron supplementation
- Pramipexole 0.25 mg twice daily + gabapentin enacarbil 600 mg daily + oral iron supplementation
Today's Clinical Presentation

• IRLS Group Rating Scale = 21 (out of 40)
• Augmentation has largely resolved but patient sometimes has early day symptoms when she “forgets” to take her early doses of pramipexole
• Patient experiences additional “breakthrough” RLS in the middle of the day even when remembering to take her medication
• Patient notes improvements in sleep quality and overall RLS symptoms
• Clinical exam
  • PLM while awake is less obvious than upon initial presentation
  • Diffuse hyper-reflexia remains
• Laboratory results
  • Iron=109 ug/dL, ferritin=78 ng/mL, transferrin saturation=39%

Your Call

What would you recommend for TJ at this point?

1. Continue with the current treatment regimen until symptoms significantly worsen
2. Consider initiation of rotigotine transdermal patch to simplify medication regimen (discontinuing other RLS medications) and avoid variability in symptoms
3. Further increase dosage of pramipexole to 1.0-1.25 mg
4. Add an additional medication class, such as an opioid

Activity Post-Test

In which of the following patients would you suspect a greater than average possibility of the presence of RLS (choose all that apply)?

1. UT, a 32-year-old female complaining of frequent migraines
2. PA, a 57-year-old male with renal failure
3. JK, a 45-year-old male with a recent knee replacement
4. TY, a 75-year-old female with multiple sclerosis
5. SS, a 24-year-old HIV positive male

For a pregnant 29-year-old patient in her third trimester who presents with severe RLS-related symptoms, which of the following agents would best combine safety and efficacy?

1. Pramipexole
2. Folic acid supplementation
3. Pregabalin
4. Gabapentin enacarbil
5. Ropinerole
6. Rotigotine

Which of the following might lead you to conclude that your RLS patient is suffering from augmentation?

1. Symptoms occurring only between the hours of 2-5 a.m.
2. Significant worsening of symptoms with decrease in medication dosage
3. Spread of symptoms to previously unaffected areas
4. Significant improvement in symptoms with increase in medication dosage
In an RLS patient being treated with rotigotine, which of the following potential side effects would you be most concerned about?

1. Fluid retention
2. Sleepiness
3. Morning drug hangover
4. Skin irritation/infection