Restless Legs Syndrome and Periodic Limb Movement Disorder

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Objectives:
- Define RLS
- Compare and contrast RLS and PLMD
- Identify risk factors for RLS
- Describe appropriate treatment for RLS
Restless Legs Syndrome and Periodic Limb Movement Disorder

Tom V. Cloward, M.D., FACCPS
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Faculty Disclosures

• No current disclosures
• Former speaker for B-I (manufacturer of Mirapex)
• I will speak regarding off-label use of a few medications for RLS
Which of the following is a primary diagnostic criterion for Restless Legs Syndrome (RLS)?

- history of RLS in a first-degree relative.
- periodic limb movements noted on nocturnal polysomnography.
- positive Suggested Immobilization Test (SIT).
- circadian variation in symptoms.
Which of the following diagnostic tests is most important to obtain in the patient being evaluated for possible Restless Legs Syndrome?

- nocturnal polysomnography
- serum ferritin
- cerebrospinal dopamine level
- glycosylated hemoglobin
Overview

• Clinical presentation and diagnosis
• Pathophysiology and genetics
• Primary and secondary RLS
• Epidemiology and consequences
• Treatment
Essential Criteria for RLS

Distressing need/urge to move the legs, usually accompanied by an uncomfortable, deep-seated sensation in the legs that is:

Brought on by rest
Relieved with moving or walking
Worse in the night or evening (circadian)
RLS: Core Symptoms

“URGE”

_Urge_ to move limbs, usually accompanied or caused by uncomfortable and unpleasant feelings in the limbs

Rest or inactivity precipitates or worsens symptoms

Getting up or moving improves the sensation

Evening or nighttime appearance or worsening of symptoms


Acronym courtesy of Philip M. Becker, MD.
Supportive Features of RLS

Family history
- 3-5 x increased prevalence in 1st degree relatives

Response to dopaminergic therapy
- Most respond, at least initially

Periodic limb movements
- 85% of those with RLS have PLM’s
- PLM’s are very common and nonspecific
  - Prevalence increases with aging and with medications
PLMI in 100 Matched Patients
n= 20 each, M=F, 47 yrs

<table>
<thead>
<tr>
<th>Group</th>
<th>PLMS index</th>
<th>PLMI&gt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>6.9±6.9</td>
<td>55%</td>
</tr>
<tr>
<td>Insomniacs</td>
<td>4.9±7.4</td>
<td>40%</td>
</tr>
<tr>
<td>Hypersomniacs</td>
<td>5.1±7.3</td>
<td>30%</td>
</tr>
<tr>
<td>Narcoleptics</td>
<td>18.6±16.0</td>
<td>80%</td>
</tr>
<tr>
<td>RLS patients</td>
<td>34.1±33.7</td>
<td>85%</td>
</tr>
</tbody>
</table>

Prevalence of PLMS in Normal Subjects (Index > 5 / hour)

Age 50 years: 5 %

Age 50-65 years: 30 %

Age > 65 years: 45 %

Ancoli-Israel S, Sleep 1991
PLMD Defined (ICSD 2, 2005): Diagnostic Criteria

A. Polysomography demonstrates repetitive, highly stereotyped, limb movements that are:
   1. 0.5 to 5 seconds
   2. Of amplitude $>25\%$ of toe dorsiflexion during calibration
   3. In a sequence of four or more movements
   4. Separated by an interval of more than five seconds (from limb-movement onset) and less than 90 seconds (typically an interval of 20-40 seconds)

B. The PLMS Index exceeds 5 per hour in children and 15 per hour in most adult cases
PLMD Defined (ICSD 2, 2005): Diagnostic Criteria

C. There is clinical sleep disturbance or a complaint of daytime fatigue

B. The PLM’s are not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or a substance use disorder.

Note: If PLMS are present without clinical sleep disturbance, the PLMS can be noted as a polysomnographic finding, but criteria are not met for a diagnosis of PLMD.
What IS a PLM?
(AASM Scoring manual, 2007)

The minimum duration is 0.5 seconds
The maximum duration is 10 seconds
The minimum amplitude is an 8 microvolt increase in EMG voltage above resting EMG
The onset is the point at which there is an 8 microvolt increase in EMG voltage above resting EMG
The ending is the start of a 0.5 sec period during which the EMG is not at least 2 microvolts above resting EMG
PLM Series
(AASM Scoring Manual, 2007)

The minimum number needed to define a PLM series is 4
The minimum length between movements in a series is 5 seconds
The maximum period length between them is 90 seconds
Movements of 2 different legs separated by less than 5 seconds are counted as one.
NOTE!!! (AASM Scoring Manual 2007)

- A leg movement should not be scored if it occurs within 0.5 seconds before or after an apnea/hypopnea
- An arousal and PLM are associated if they occur within 0.5 seconds of each other
- Separate channels for the legs are preferred
- Leg movements on 2 different legs separated by less than 5 seconds between movement onsets are counted as a single leg movement
10 Minute Sample Epoch
Relationship between RLS and PLMS
Conditions Associated with RLS

ADHD (Walters AS, JCSM 2008; Zak R, Perecept Mot Skills 2009)
COPD (Lo Coco D, Sleep Med 2008)
Depression and Panic Disorder (Lee HB, J Neuropsychiatry Clin Neurosci. 2008)
Fibromyalgia (Stehlik R, Eur Neurol. 2009)
Migraine (Rhode AM, Cephalgia, 2007)
Medication Use (Pearson VE, Eur J Neurol. 2008)
Multiple Sclerosis (Deriu M Mov Disord, 2008; Manconi M, Sleep 2008)
Neuropathy (Hattan E, Neurology 2009)
Parkinson’s Disease Treatment (Lee JE, Mov Disord 2008)
Pulmonary Hypertension (Minai OA, J Heart Lung Transplant. 2008)
Shift Work (Sharifian A, J Circadian Rhythms 2009)
Celiac Disease (Weinstock LB Dig Dig Sci 2009)
Neuroticism (Kalaydjian A, Sleep Med 2009)
RLS: Assessment

History: Essential method of diagnosis. Ask about the 4 core diagnostic features, e.g. URGE

Neurologic examination: normal if idiopathic

Lab testing: CBC, serum ferritin, percent iron saturation, folate, chemistries (BUN, creatinine), glucose, glycosylated HGB
RLS: Assessment

Consider referral to neurologist for EMG/NCV if you suspect peripheral neuropathy

Consider referral to sleep center for polysomnography

- In children
- If you suspect coexisting OSA or narcolepsy
Overview

• Clinical presentation and diagnosis
• Pathophysiology and genetics
• Primary and secondary RLS
• Epidemiology and consequences
• Treatment
Iron-DA Model of RLS

Brain Iron Insufficiency

CNS Dopamine Abnormalities (Brain & Spinal Cord)

RLS
Cerebrospinal Fluid (CSF): DA Circadian Pattern

- **RLS**
- **Healthy subjects**

Dopaminergic function

night  night
The Iron ↔ DA Connection

How does iron fit into the DA hypothesis?

Brain
Fe^{+3} ↔ DA
The Iron ↔ DA Connection

Iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme for DA synthesis. Iron deficiency may decrease the number of DA – D2 receptor binding sites.
Iron Deficiency: Secondary Causes of RLS

Pregnancy: May be associated with iron deficiency (also folate and other factors)
- Pregnant women with RLS have higher estradiol

Gastric surgery: probably related to impaired iron absorption

Iron deficiency anemia: Iron replacement improves RLS and RLS severity correlate with ferritin levels

End Stage Renal Disease: Iron and erythropoietin replacement or transplantation improves RLS
Brain Iron Insufficiency: CSF Evidence

30 subjects with idiopathic (primary) RLS and 22 age- and sex-matched controls

Nighttime CSF ferritin levels

Women with early-onset RLS had the lowest CSF ferritin levels

Strong correlation between age of RLS-symptom onset and CSF ferritin values ($r = 0.64$)
RLS/PLM Genetics

• RLS “runs in families:” 40-60% of cases
  – Twins with high concordance rates
• RLS with PLMS is strongly linked to at least 3 single-nucleotide polymorphisms (SNP’s) on chromosome 6p (Stefansson NEJM 2007)
• Despite linkage studies, no specific gene identified
• Genes involved with neurodegeneration, iron regulation, and DA metabolism have been investigated
Overview

• Clinical presentation and diagnosis
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• Primary and secondary RLS
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Primary vs Secondary RLS

• Primary (idiopathic) accounts for most cases
  – Onset earlier in life
  – Stronger family history
• Secondary causes of RLS
  – Iron deficiency
  – Anemia
  – Pregnancy (~25% of women)
  – ESRD on dialysis (~60%)

• Other potential secondary causes of RLS
  – Medications
    • TCA’s
    • SSRI’s
    • Older generation antihistamines
  – OSA
  – Neuropathy
  – Spinal disease
  – Anything that makes you sleepy
Lifestyle and RLS

RLS symptoms are increased in smokers (OR 2.06, CI 1.27-3.36)
RLS symptoms are increased in obesity (OR 1.31, CI 1.11-1.53 for every 5 kg/m²)
RLS symptoms are higher in those who exercise less than 3 hours/month (OR 3.32, CI 1.67-6.3)

Phillips B et al, Arch Int Med 2000
RLS and Pregnancy

RLS is extremely common in pregnancy
- Estimates range from 11%-50%
- Severity increases in third trimester

Etiology is uncertain
- Anemia
- Abdominal distention
- Inactivity

No increase in fetal risk documented
Parity increases risk in mothers in dose-dependent way (Berger, Arch Intern Med, 2004)

Pregnancy may account for all of the gender difference in prevalence (Pantaleo NP Sleep Med 2010)
Things That Mimic RLS

- Volitional movements
- Akathisia
- Nocturnal leg cramps (Charley Horse)
- Positional discomfort
- Leg pain
- Physiologic leg movements during sleep
- Claudication
Overview

Clinical presentation
Diagnosis
Pathophysiology
Primary and secondary RLS
Epidemiology and consequences
Treatment
My 5 Worst You Bunkers
RLS: Epidemiology

Overall prevalence: 3%–15%\textsuperscript{1-5}

- Up to 25% of primary care patients have RLS symptoms\textsuperscript{6,7}
- Mean age of onset, 34 ± 20 years\textsuperscript{8}
  - Age of onset is often in childhood/young adulthood\textsuperscript{9}

Gradually progressive\textsuperscript{3,10}

- Diagnosis is often in mid-life
RLS by Age, Gender, and Risk Factor (Berger, Arch Intern Med 2004, n= 4310)
Summary of the REST General Population Questionnaire

Table 1. Summary of the REST General Population Questionnaire

<table>
<thead>
<tr>
<th>Questionnaire Parts</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Introductory questions</td>
<td>No. of times consulted PCP, specialist in past 3 mo</td>
</tr>
<tr>
<td>(2) Screening questions</td>
<td>Symptoms currently experienced (from a list of 22)</td>
</tr>
<tr>
<td></td>
<td>Diagnostic questions</td>
</tr>
<tr>
<td></td>
<td>Do you have, or have you sometimes experienced, recurrent, uncomfortable feelings or sensations in your legs while sitting or lying down?</td>
</tr>
<tr>
<td></td>
<td>Do you have, or have you sometimes experienced, a recurrent need or urge to move your legs while sitting or lying down?</td>
</tr>
<tr>
<td></td>
<td>Do these uncomfortable feelings or sensations in your legs, or the need or urge to move, disappear/improve when you are active or moving around?</td>
</tr>
<tr>
<td></td>
<td>Are these uncomfortable feelings, or this urge to move, worse in the evening or at night compared with the morning?</td>
</tr>
<tr>
<td></td>
<td>Frequency of symptoms</td>
</tr>
<tr>
<td></td>
<td>Degree of distress</td>
</tr>
</tbody>
</table>
Prevalence of RLS in the REST Study

RLS Patients (n=416)
- All
- Men
- Women

Prevalence, %

Age Groups
- 20-29
- 30-39
- 40-49
- 50-59
- 60-69
- 70-79
- ≥80
# Prevalence of RLS Symptoms by Country and Degree of Severity

## Table 2. Prevalence of RLS Symptoms by Country and Degree of Severity

<table>
<thead>
<tr>
<th>Country</th>
<th>Questionnaires Distributed, No.</th>
<th>Fully Completed Questionnaires, No. (%)</th>
<th>Any Frequency</th>
<th>≥ Once/wk</th>
<th>≥ Twice/wk</th>
<th>≥ Twice/wk and of Moderate or Extreme Distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>2010</td>
<td>1884 (93.7)</td>
<td>203/1884 (10.8)</td>
<td>125/1884 (6.6)</td>
<td>103/1884 (5.5)</td>
<td>79/1884 (4.2)</td>
</tr>
<tr>
<td>Germany</td>
<td>2040</td>
<td>1929 (94.6)</td>
<td>79/1929 (4.1)</td>
<td>53/1929 (2.7)</td>
<td>38/1929 (2.0)</td>
<td>25/1929 (1.3)</td>
</tr>
<tr>
<td>Italy</td>
<td>2036</td>
<td>1768 (86.8)</td>
<td>119/1768 (6.7)</td>
<td>74/1768 (4.2)</td>
<td>55/1768 (3.1)</td>
<td>43/1768 (2.4)</td>
</tr>
<tr>
<td>Spain</td>
<td>2020</td>
<td>1896 (93.9)</td>
<td>92/1896 (4.9)</td>
<td>66/1896 (3.5)</td>
<td>58/1896 (3.1)</td>
<td>37/1896 (2.0)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>2082</td>
<td>1950 (93.7)</td>
<td>167/1950 (8.5)</td>
<td>109/1950 (5.6)</td>
<td>95/1950 (4.9)</td>
<td>45/1950 (2.3)</td>
</tr>
<tr>
<td>United States</td>
<td>6014</td>
<td>5964 (99.2)</td>
<td>454/5964 (7.6)</td>
<td>346/5964 (5.8)</td>
<td>289/5964 (4.8)</td>
<td>197/5964 (3.1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16 202</strong></td>
<td><strong>15 391</strong></td>
<td><strong>1114/15 391 (7.2)</strong></td>
<td><strong>773/15 391 (5.0)</strong></td>
<td><strong>638/15 391 (4.1)</strong></td>
<td><strong>416/15 391 (2.7)</strong></td>
</tr>
</tbody>
</table>

Abbreviation: RLS, restless legs syndrome.

*Excludes those from respondents younger than 18 years.
†Prevalence indicates respondents who met all 4 diagnostic criteria for RLS.
RLS Patients and SF 36

The chart compares the mean scores of different health domains for RLS patients (n = 158) and other patient groups.

- **Physical Functioning**
- **Role Physical**
- **Bodily Pain**
- **General Health**
- **Energy/Vitality**
- **Social Functioning**
- **Role Emotional**
- **Mental Health**

Each group is color-coded and includes:
- RLS Patients (n = 158)
- Patients in the US General Population With Type 2 Diabetes Mellitus (n = 541)
- Osteoarthritis With Hypertension (n = 175)
- Depression (n = 502)
## Daytime Consequences: Excessive Daytime Sleepiness

N=2,821 participants from the Wisconsin Sleep Cohort with RLS symptoms

<table>
<thead>
<tr>
<th>RLS Symptoms</th>
<th>Frequent (1-6/wk) OR (95% CI)</th>
<th>Daily OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS &gt;10:</td>
<td>2.48 (1.75, 3.53)</td>
<td>3.22 (2.20, 4.71)</td>
</tr>
<tr>
<td>EDS &gt;5 times/mo:</td>
<td>2.53 (1.70, 3.78)</td>
<td>3.28 (2.15, 5.00)</td>
</tr>
</tbody>
</table>
Overview

Clinical presentation
Diagnosis
Pathophysiology
Primary and secondary RLS
Epidemiology and consequences

Treatment
RLS Treatment Considerations

Clinical history
Age of patient
Identification of potential aggravators
Frequency, severity, and timing of symptoms
Presence of comorbid conditions
Treatment Strategies

Remove potential aggravators

- Alcohol
- Exercise (too much vs too little)
- Caffeine
- Smoking

Consider discontinuing medications that can worsen RLS

- SSRIs (eg, paroxetine, fluoxetine, sertraline)
- Tricyclics (eg, amitriptyline, nortriptyline)
- Dopamine antagonists (eg, clozapine, risperidone)

Treat secondary causes

- Iron deficiency
- Renal disease
SSRIs and RLS

In a population based study of 18,980 individuals, the use of SSRIs was demonstrated to be a risk factor for RLS (OR 3.11; 95% CI 1.66-5.79)\(^1\)

A prospective study of 271 patients showed that about 9% developed or had worsening RLS after starting “modern” SSRIs, worse with mirtazapine.\(^2\)

- Antidepressant use may be more strongly associated with RLS in men than in women (Baughman KR, Mov Disord 2009).

Several studies have found an increase in PLM with the use of SSRIs\(^3\)
Antidepressants and PLM’s
(Yang C 2005 Biol Psychiatry)
Nonpharmacological Treatment

Moderate daytime and reduced nighttime exercise\(^1, 2\)
Relaxation techniques

- Warm baths/thermal biofeedback
- Leg vibration/massage
- Acupuncture\(^2\)
- Enhanced external counter pulsation (EECP)\(^3\)

Pharmacologic Management of RLS
<table>
<thead>
<tr>
<th>-drug</th>
<th>Initial daily dose</th>
<th>Minimum interval to assess effect before increasing dose</th>
<th>Usual effective daily dose range*</th>
<th>Metabolism and clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine agonists</strong></td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pramipexole (IR)</td>
<td>0.125 mg 2 to 3 hours before bedtime</td>
<td>2 to 3 days</td>
<td>0.25 to 0.5 mg (occasionally up to 1 mg has been used)</td>
<td>▪ &gt;90% renally excreted as unchanged drug&lt;br&gt;▪ Use longer titration interval (ie, 14 days) in moderate to severe renal impairment and in older adults</td>
</tr>
<tr>
<td>Ropinirole (IR)</td>
<td>0.25 mg 1 to 3 hours before bedtime</td>
<td>2 to 3 days</td>
<td>2 to 4 mg</td>
<td>▪ ~90% metabolized, primarily by CYP1A2&lt;br&gt;▪ Not studied in moderate to severe hepatic impairment; increased levels are likely&lt;br&gt;▪ Use with caution in severe renal impairment (maximum 3 mg daily in dialysis-dependent patients)</td>
</tr>
<tr>
<td>Rotigotine transdermal patch</td>
<td>1 mg per 24 hour patch</td>
<td>5 to 7 days</td>
<td>2 to 3 mg per 24 hour patch</td>
<td>▪ Hepatic metabolism (multiple substrates) and glucuronidation&lt;br&gt;▪ No dose adjustments recommended in renal or hepatic impairment for the dose ranges provided</td>
</tr>
<tr>
<td><strong>Alpha-2-delta calcium channel ligands</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin (IR)</td>
<td>100 to 300 mg 2 hours before bedtime</td>
<td>5 to 7 days</td>
<td>900 to 2400 mg in two divided doses (late afternoon and 2 hours before bedtime)</td>
<td>▪ &gt;95% renally excreted as unchanged drug&lt;br&gt;▪ Dose adjustment is needed in renal impairment*</td>
</tr>
<tr>
<td>Gabapentin enacarbil (ER)</td>
<td>300 to 600 mg in early evening (eg, ~5 PM)</td>
<td>No titration (doses 2000 mg per day provided no added benefit)</td>
<td>600 mg</td>
<td>▪ &gt;95% renally excreted as unchanged drug&lt;br&gt;▪ Dose adjustment is needed in renal impairment*</td>
</tr>
<tr>
<td>Pregabalin (IR)</td>
<td>50 to 75 mg 1 to 3 hours before bedtime</td>
<td>5 to 7 days</td>
<td>150 to 450 mg</td>
<td>▪ &gt;95% renally excreted as unchanged drug&lt;br&gt;▪ Dose adjustment is needed in renal impairment*</td>
</tr>
</tbody>
</table>

**IR**: immediate release; **ER**: extended release; **US FDA**: US Food and Drug Administration.

* Upper doses may exceed recommendation in US FDA-approved prescribing information. Refer to UpToDate topic review.

† Specific dose adjustment recommendations for patients with impaired kidney function are provided in the Lexi-comp drug specific monographs included within UpToDate.
# Pharmacologic Treatment

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopaminergics</td>
<td>carbidopa/levodopa</td>
<td>Can be used prn</td>
<td>80% develop augmentation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Useful for intermittent RLS</td>
<td>Insomnia, sleepiness, GI problems</td>
</tr>
<tr>
<td></td>
<td>pramipexole*</td>
<td>Useful in moderate-to-severe RLS</td>
<td>Sleepiness, Nausea, and disinhibition</td>
</tr>
<tr>
<td></td>
<td>ropinirole*</td>
<td>High efficacy</td>
<td></td>
</tr>
</tbody>
</table>

*FDA-approved
<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Codeine, hydrocodone, tramadol</td>
<td>Useful for intermittent and daily RLS</td>
<td>Constipation, sleepiness, cognitive changes, tolerance, dependence</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Clonazepam, temazepam</td>
<td>Helpful in some patients when other agents are not tolerated</td>
<td>Daytime sleepiness and cognitive impairment</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Gabapentin enacabril**</td>
<td>Consider when dopamine agonist fail</td>
<td>GI disturbance, nausea, sedation, dizziness</td>
</tr>
<tr>
<td>Iron</td>
<td>Ferrous sulfate, IV iron dextran</td>
<td>Use in patients serum ferritin&lt;50 mg/L</td>
<td></td>
</tr>
</tbody>
</table>
Levodopa for RLS

Efficacy and safety studied in many open-label and randomized controlled trials\(^1\)
Dosing: immediate or controlled release carbidopa/levodopa 25 mg/100 mg\(^2\)
Can give prn (eg, plane or car ride, theater)\(^3\)
Side effects: nausea, dizziness, sleepiness
Not FDA approved for RLS

Ropinirole for RLS

Efficacy and safety studied in many open-label and double-blind trials

Effective dose is 1.5–6 mg/d in single or divided doses, average is about 2 mg/d

Main side effects: nausea, vomiting, orthostasis, dizziness, sleepiness, insomnia, compulsive behavior

Hepatically metabolized
Pramipexole for RLS

Efficacy and safety studied in many open-label and double-blind trials

Doses of 0.125-0.75 mg/d in single or divided doses, average is 0.25 mg/d

Main side effects: nausea, vomiting, orthostasis, dizziness, sleepiness, insomnia, compulsive behavior

Renally excreted
Gabapentin Enacabril (Horizant) for RLS

Efficacy based on 2 12-week clinical trials in adults.
Dosing: 600 mg at 5 pm with food.
ER gabapentin yields different concentrations than intermediate-release gabapentin (Neurontin)
Side effects include drowsiness (should be advised not to drive at first) and dizziness.
All drugs used to treat epilepsy carry a suicide warning.
Diagnosis and management of RLS/WED during pregnancy and lactation

Accurate diagnosis

4 of 4 core RLS/WED features present?
Rule out mimics, especially leg cramps and leg edema
Assess severity: frequency and impact

Comorbid depression? (see text for suggested management)

Nonpharmacologic

Educate about the natural course of RLS/WED during pregnancy
Assess iron status (see below)
Moderate-intensity/low-impact exercise
Avoid exacerbating factors
Consider other interventions

Iron assessment and therapy

Check hemoglobin, serum ferritin level, iron, TIBC, and % saturation

Ferritin >75 mcg/L

Ferritin <75 mcg/L

If fails oral iron and ferritin <30 mcg/L

Oral iron

Consider IV iron

Pregnancy:
- Low-dose clonazepam 0.25 to 1 mg in the evening, or
- Carbidopa/levodopa ER 25/100 to 50/200 mg in the evening or at night.
- If very severe, very refractory consider low-dose oxycodone
- Reassess need for medication periodically: reassess at delivery

Refractory RLS/WED

Lactation:
- Reassess iron status
- Gabapentin 300 to 900 mg in the evening or at night, or
- Low-dose clonazepam 0.25 to 1 mg in the evening,
- If very severe, very refractory consider low-dose tramadol

Dotted arrows: Consider medication only after assessment of severity, risks, and benefits by provider and patient, in patients who have significant impact on quality of life.
My 5 Most Interesting Cases of RLS

1. 36 yo mom tainted current and all future daughter’s slumber parties by sleep-walking wearing only underpants
My 5 Most Interesting Cases of RLS

1. 36 yo mom tainted current and all future daughter’s slumber parties by sleep-walking wearing only underpants

2. 38 yo male with RLS sx and violent leg kicks, resistant to several therapies ➔ found to have Creutzfeldt-Jakob Dz
My 5 Most Interesting Cases of RLS

1. 36 yo mom tainted current and all future daughter’s slumber parties by sleep-walking wearing only underpants
2. 38 yo male with RLS sx and violent leg kicks, resistant to several therapies → found to have Creutzfeldt-Jakob Dz
3. 72 yo male with RLS, iron-deficiency, found early stage colon cancer → early cure
My 5 Most Interesting Cases of RLS

1. 36 yo mom tainted current and all future daughter’s slumber parties by sleep-walking wearing only underpants
2. 38 yo male with RLS sx and violent leg kicks, resistant to several therapies → found to have Creutzfeldt-Jakob Dz
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4. 65 yo female dragged (literally) into clinic by husband asleep. When she awakened, she vomited.
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5. 50 yo female with depression (on antidepressants and antipsychotics) resistant to therapy
Augmentation of RLS Symptoms

Characterized by worsening of symptoms:
- Onset earlier in day or
- Increased intensity or
- Spread of symptoms to arms

Risk and severity far less with newer dopamine agonists vs levodopa:
- One third to one half of patients vs ~70% with levodopa
- However, symptoms can still occur in the daytime

Managing Augmentation in Patients Taking Dopamine Agonists

Take dose earlier in day
Split existing dose into early evening and bedtime doses
Switch to longer-acting dopamine agonist (eg, from levodopa to pramipexole or ropinirole)
If augmentation continues to progress with earlier and/or more severe symptoms, switch to different class of medications
Compulsive Behaviors in Dopaminergic Treatment (Pourcher E J Neurol Sci 2009)

Questionnaire mailed to RLS patients
97/151 responded
12 developed new compulsions (12%)
- Eating
- Buying food or clothes
- Trichotillomania
- Gambling

Those who developed compulsive behavior had more stress, depression and sleep problems.
5 Most Common Mistakes in RLS Management

1. Pramipexole and ropinirole overdose - giving RLS patients the dose normally given for Parkinson’s Disease
2. Treating augmentation symptoms with higher and higher doses of DA’s
3. Not giving RLS meds at least 2 hours before bedtime
4. Not eliminating offending agents/conditions
5. Wrong diagnosis
Summary of Key Points- The Bottom Line

- RLS is prevalent, affecting 3-15%. Clinically significant (needing therapy) is 2-3%
- Women are at increased risk for RLS
- RLS is a genetic disorder, and has something to do with dopamine and iron
- The diagnosis of RLS is made by HISTORY, not PSG
- Most people with RLS have PLMS (~ 80%), but most people with PLMS do NOT have RLS (~ 20%)
Summary of Key Points - The Bottom Line

• Four FDA-approved medications are available: ropinirole, pramipexole, gabapentin enacarbil, and transdermal rotigotine
• Your job is to search for reversible exacerbating factors: iron deficiency, offending drugs, sleep apnea, renal disease, anemia
• Augmentation is a big issue with DA’s
• “Rescue” medications: benzodiazepines and opioids