Restless Legs Syndrome

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Restless Legs Syndrome

- First described by Thomas Willis in 1685.
- In 1945 Carl Ekbom described all of the clinical features and coined the name “Restless Legs Syndrome”.
- RLS is a common disorder affecting 2-3% of the population.
- Increased frequency with advancing age.
- More common in women than men.
Restless Legs Syndrome

- Can occur as a primary disorder or may arise as a secondary disorder of an underlying medical or neurological condition
  - Iron deficiency
  - Uremia
  - Pregnancy
Conditions with Increased Occurrence of Restless Legs Syndrome

- Iron deficiency
- Uremia
- Pregnancy

Medications (most frequently reported):
- serotonergic/norepinephrine agents
- dopamine receptor antagonists
- Antihistamines

Neurotherapeutics (2014) 11:177-187
Conditions with Increased Occurrence of Restless Legs Syndrome

- Neurological conditions:
  - spinocerebellar ataxia 1, 2, and 3
  - narcolepsy
  - multiple sclerosis
  - peripheral neuropathy
  - migraine
  - amyotrophic lateral sclerosis
  - Parkinson disease

Conditions with Increased Occurrence of Restless Legs Syndrome

- Medical conditions:
  - celiac disease
  - Crohn’s disease
  - rheumatoid arthritis
  - fibromyalgia
  - diabetes

- Psychiatric conditions
  - anxiety
  - depression

Neurotherapeutics (2014) 11:177-187
Restless Legs Syndrome

- Can result in delayed sleep onset, decreased sleep time, resultant excessive daytime sleepiness and decreased quality of life

- Evidence suggests that RLS is associated with low intracerebral iron stores, possibly due to defective iron transport mechanisms across the blood brain barrier, and down-regulation of striatal dopamine receptors
Restless Legs Syndrome

Question 1

Which of the following is part of the IRLSSG criteria for Restless Legs Syndrome?

- A. An urge to move the legs which is worse during daytime hours
- B. A periodic limb movement arousal index greater than 10 on polysomnographic testing
- C. The urge to move is relieved by rest and elevation of the legs
- D. In some cases the arms or other parts of the body are involved
- E. Improvement in symptoms are noted with institution of an SSRI.
Restless Legs Syndrome

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- E. Improvement in symptoms are noted with institution of an SSRI.
Diagnostic Criteria Established by the International Restless Leg Syndrome Study Group

**Essential Features**

- An urge to move the legs, usually accompanied by or caused by uncomfortable and unpleasant sensations in the legs. Sometimes the urge to move is present without the uncomfortable sensation, and sometimes the arms or other body parts are involved in addition to the legs.

- The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.

- The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.

- The urge to move or unpleasant sensations are worse in evening or night than during the day, or they only occur in the evening or night. When symptoms are very severe, the worsening at night might not be noticeable but must have been previously present.
Nonessential but Common Features

- Family history: The prevalence of RLS among first-degree relatives of people with RLS is three to five times greater than in people without RLS.

- Response to dopaminergic therapy

- Periodic leg movements during sleep (PLMS) or during wakefulness (PLMW).

- Natural clinical course: may begin at any age, but most severely affected patients are middle-aged or older. The course is usually progressive, but a static course or remission can occur.

- Sleep disturbance

- Medical evaluation and physical examination: No abnormalities in the primary form, but in the secondary form, signs of a peripheral neuropathy or radiculopathy may be present. Iron status should be evaluated because decreased iron stores are a significant potential risk factor that can be treated.

RLS, restless legs syndrome.
International Restless Legs Syndrome Study Group Rating Scale

1. Overall, how would you rate the RLS discomfort in your legs or arms?
   - Very severe, 4; Severe, 3; Moderate, 2; Mild, 1; None, 0

2. Overall, how would you rate the need to move around because of your RLS symptoms?
   - Very severe, 4; Severe, 3; Moderate, 2; Mild, 1; None, 0

3. Overall, how much relief of your RLS arm or leg discomfort do you get from moving around?
   - No relief, 4; Slight relief, 3; Moderate relief, 2; Complete or almost complete relief, 1; No RLS symptoms, 0

4. Overall, how severe is your sleep disturbance from your RLS symptoms?
   - Very severe, 4; Severe, 3; Moderate, 2; Mild, 1; None, 0

5. How severe is your tiredness or sleepiness from your RLS symptoms?
   - Very severe, 4; Severe, 3; Moderate, 2; Mild, 1; None, 0

6. Overall, how severe is your RLS as a whole?
   - Very severe, 4; Severe, 3; Moderate, 2; Mild, 1; None, 0

7. How often do you get RLS symptoms?
   - Very often, 4; Often, 3; Sometimes, 2; Occasionally, 1; Never, 0

8. When you have RLS symptoms, how severe are they on an average day?
   - Very severe, 4; Severe, 3; Moderate, 2; Mild, 1; None, 0

9. Overall, how severe is the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school or work life?
   - Very severe, 4; Severe, 3; Moderate, 2; Mild, 1; None, 0

10. How severe is your mood disturbance from your RLS symptoms—for example angry, depressed, sad, anxious or irritable?
    - Very severe, 4; Severe, 3; Moderate, 2; Mild, 1; None, 0

In the full version of the scale, each of the choices for question 7 has an operational definition.
The 2012 revised criteria adds:

- The above features are not solely accounted for by other medical or behavioral conditions such as myalgias, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping, and other sensory-motor disorders.
Uncomfortable sensations in the legs have been described as:

- Crawling
- Tingling
- Creeping
- Cramping
- Electric
- Burning
- Prickly
- Heebie Jeebies
- Elvis Legs
- Wriggling Maggots
- Shpilkes
## Restless Legs Syndrome: Differential Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leg cramps</strong></td>
<td>Complaint of a painful sensation in the leg with muscle hardness or tightness that causes awakenings from sleep because of painful leg sensations, often improved with massage, movement, or application of heat</td>
</tr>
<tr>
<td><strong>Peripheral neuropathy</strong></td>
<td>Pain in both feet and/or tingling that is usually present during the day time, but may be worse during the evening</td>
</tr>
<tr>
<td><strong>Radiculopathy</strong></td>
<td>Shooting pains down one leg, often present during the day and with activity</td>
</tr>
<tr>
<td><strong>Arthritis</strong></td>
<td>Pain localized to a joint that usually is associated with swelling of the joint; often worse with the use of the joint or weight-bearing</td>
</tr>
<tr>
<td><strong>Positional discomfort</strong></td>
<td>Discomfort that occurs with a particular position; a single movement can relieve the discomfort</td>
</tr>
<tr>
<td><strong>Frequent unconscious foot or leg movements (hypnic jerks, foot-tapping, leg-shaking, nervous movements)</strong></td>
<td>Not preceded by abnormal sensations or an urge to move the leg; often without conscious awareness of the movement</td>
</tr>
<tr>
<td><strong>Akathisia</strong></td>
<td>Generalized restlessness not localized to the legs and occurring without a circadian pattern; often associated with dopamine receptor antagonist or as a feature of Parkinson disease</td>
</tr>
</tbody>
</table>
Periodic limb movements of sleep

- Highly stereotyped movements typically involving extension of the great toe, with partial flexion of the ankle, knee, and sometimes the hip (triple flexion)

- Occasionally involves the upper extremities

- Present in 80%-90% of RLS patients

- Movements are usually bilateral but may predominate in one leg or alternate between legs
Periodic limb movements of sleep

- Movements are 0.5-5 second in duration and separated by an interval of 5-90 seconds, and reoccur at least four times.
- Can be associated with arousals and decreased quality of sleep for both the patient and bed partner.
- PLMS increase with age.
  - Occur at a rate of > 5/hr in 45% of people > 65 y.o.
  - PLMS index is also, on average greater for elderly men than women.
Periodic Limb Movements of Sleep

- Secondary causes
  - Multiple Sclerosis
  - Central Sleep Apneas
  - Obstructive Sleep Apnea
  - Spinal Cord Injury
  - Fibromyalgia
  - REM Behavior Disorder
  - Parkinson’s Disease
  - Narcolepsy

Restless Legs Syndrome
Restless Legs Syndrome

- Periodic Limb Movements of Sleep
  - Heart rate after each PLMS shows increases of 15% over 7 beats followed by transient decreases to slightly below baseline.

- Periodic Limb Movement Disorder
  - A sleep wake disturbance resulting from PLMS in excess for age and without any secondary causes.
  - Studies failing to find any relationship between PLMS and EDS raise doubts about the significance or even the existence of PLMD.
Treatment of Secondary RLS

- Iron Deficiency
  - The most reliable indicator of body stores of iron is serum ferritin, transferrin, and transferrin saturation
  - Current recommendation is that all RLS patients should be evaluated for iron deficiency.
  - A serum ferritin concentration <50mcg/L has been associated with an increased severity of RLS, and treatment of patients with ferritin levels < 75 mcg/L has been shown to improve symptoms.
  - Very low ferritin (<20mcg/ml) appears to increase the risk of augmentation

Iron Deficiency

Dosage

- 325 mg (65mg. elemental iron), 2-3 times/day
- Combine with 100-200mg Vit. C to enhance absorption
- Ideally should be taken on an empty stomach but can be taken with food
- Follow up ferritin level in 3-4 months, then every 3-6 months until ferritin level is > 75mcg/ml and Fe saturation is > 20%
- Serial follow-up levels q 1-2 years to ensure levels do not decrease or earlier if symptoms worsen
- Patients do not always respond to iron therapy

Restless Legs Syndrome
Iron Deficiency

Dosage

- Intravenous Iron

  - Can be effective in patients unable to tolerate oral iron
  
  - An open label study showed that 6 of 10 patients had complete resolution of their restless legs symptoms and remained free of any other RLS symptoms for 3-36 months after treatment with IV Iron Dextran.

Iron Deficiency

- Intravenous Iron

  - A randomized double blind study using two 500 mg doses of ferric carboxymaltose given 5 days apart showed significant improvement, even in previously refractory cases.

Iron Deficiency

- Intravenous Iron
  - There are no clear biological or clinical markers that predict who will respond to IV iron.

- Adverse effects
  - Anaphylaxis - Iron Dextran (0.6%-0.7%)
    - Less incidence with low molecular weight Fe Dextran, ferric carboxymaltose, iron sucrose, Ferric gluconate
  - Nausea, Cramps, Bloating, Headache - usually minor
Treatment of Secondary RLS

- **End Stage Renal Disease**
  - Occurs in 20%-60%
  - Definitive treatment is renal transplant
  - Uremic RLS may be associated with more rapid disease progression, greater subjective severity and a higher degree of sleep disturbance compared to idiopathic RLS

Treatment of Secondary RLS

- End Stage Renal Disease
  - Pharmacologic treatment is similar to treatment in non-renal failure patients with the exception of medications which are renally metabolized
  - Often benefit is suboptimal
  - In a prospective study of 100 dialysis patients, a higher severity of RLS was associated with a higher risk of new cardiovascular events and higher short term mortality.
Treatment of Secondary RLS

- Pregnancy
  - Affects 10%-34% of pregnant women
  - Factors associated with RLS in pregnancy include anemia (both Fe and folate deficiency), childhood growing pains, a family history of RLS and growing pains, older age, maternal weight (>79 kg), concomitant SDB, periodic limb movements in sleep, and smoking.
  - Estrogen has been implicated
  - Patients with pre existing RLS have worsening of symptoms in the third trimester and new onset patients experience transient symptoms during the third trimester which normally end within days of delivery.
Treatment of Secondary RLS: Pregnancy

Figure 138-2 Kryger pg. 1578

Restless Legs Syndrome

Pregnant woman with new or recurrent symptoms of excessive daytime sleepiness or sleep disturbances

- Assess and treat SDB as early as possible to prolong gestation, delay preclampsia onset and reduce IUGR severity
- Examine clinical and pregnancy history:
  1) Load snoring, excessive daytime sleepiness, witnessed apneas or choking sensation during sleep in especially women with excessive weight gain
  2) Chronic hypertension, gestational hypertension or pre-eclampsia in especially women with pre-pregnancy obesity and a large neck size
  3) Gestational diabetes and previous unexplained intrauterine growth restriction associated with snoring and obesity
  4) Worsening/recurrence of symptoms in women with preexisting RLS
- Overnight PSG to determine objective snoring, oxyhemoglobin desaturations, flow limitation events and RDI (AH1 and IFL)
- If one of them exists:
  1) An RDI of 5-30/hr with few/no SaO2 < 90% and clinical symptoms
  2) RDI > 30/hr
  3) Repeated SaO2 < 90%
  4) Chronic hypertension and objective evidence of snoring or flow limitation events
  5) Gestational hypertension or pre-eclampsia and objective evidence of snoring or flow limitation events
  6) Indication of insufficient treatment in preexisting OSA

- Clinical diagnosis based on the 4 main clinical criteria mentioned in the text:
  - PSG is not necessary.
  - Supportive diagnosis criteria:
    1) Positive family history
    2) Previous pregnancy with RLS
    3) Presence of PLM
- Treatment: auto-tiltering CPAP or recalibration of the CPAP pressure in pre-existing OSA or other modality e.g., BIPAP in women with pre-pregnancy obesity and SDB; main goal is to eliminate maternal hypoxemia, RDI ≥ 5 and clinical symptoms

Assess for parasomnias especially sleepwalking and terrors

Assess for nocturnal gastroesophageal reflux

Assess for clinical history: Current complaints and/or any prior history of dyspeptic or reflux-type symptoms

If available, sleep laboratory monitoring

1) Reduction of risk factors and maximization of the safety of bedroom e.g., night light, door alarm
2) Self-hypnosis and relaxation techniques at bedtime
3) In severe cases, low doses of benzodiazepines can be useful

1) Elevating the head of bed and sleeping on left side
2) Avoiding spicy, acidic or fried foods, instead eat small bland meals during the day
3) If these are inadequate, antacids or sucralfate are considered the first-line on-demand drug therapy
## Restless Legs Syndrome

### Table 138-2 pg 1581

Kryger

<table>
<thead>
<tr>
<th>Classification</th>
<th>Category B</th>
<th>Category C</th>
<th>Category D</th>
<th>Category X</th>
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<tbody>
<tr>
<td>Sedatives and Hypnotics (Benzodiazepines)</td>
<td>Zolpidem (1)</td>
<td>Zaleplon (1)</td>
<td>Alcohol (Ethanol) D/X (1)</td>
<td>Estazolam (1, 2)</td>
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<td></td>
<td>Diphenhydramine (1)</td>
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<td>Alprazolam (1)</td>
<td>Flurazepam (1, 2)</td>
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<td>Diazepam (1, 4)</td>
<td>Quazepam (1, 2)</td>
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<td>Lorazepam (1)</td>
<td>Temazepam (1, 2)</td>
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<td>Midazolam (1)</td>
<td>Triazolam (1, 2)</td>
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<td>Secobarbital (1)</td>
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<td>Central Analgesics</td>
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<td>Clonidine (2)</td>
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<td>Anticonvulsants</td>
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<td>Gabapentin (1, 2)</td>
<td>Clonazepam (2, 4)</td>
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<td>Carbamazepine (2, 4)</td>
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<td>Antiparkinsonian Agents (Dopaminergics)</td>
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<td>Bromocriptine (2)</td>
<td>Carbidopa (2)</td>
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<td>Cabergoline (2)</td>
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<td>Pramipexole (2)</td>
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<td>Ropinirole (2)</td>
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### Treatment of Secondary RLS: Pregnancy

#### Classification of Medications Used for Sleep Disorders

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</tr>
</thead>
<tbody>
<tr>
<td>Narcotic Agonist Analgesics (Opioids)</td>
<td>Meperidine-B/D (2)</td>
<td>Codeine-C/D (2)</td>
<td>Morphine-C/D (2)</td>
<td>Propoxyphene-C/D (2)</td>
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<td>Antidepressants and Depressants</td>
<td>Sodium oxybate (Xyrem) (4)</td>
<td>Amitriptyline (1, 2)</td>
<td>Doxepin (1, 2)</td>
<td>Fluoxetine (3)</td>
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<tr>
<td>Stimulants</td>
<td>Caffeine (3)</td>
<td>Dextroamphetamine (3)</td>
<td>Pemoline (3)</td>
<td>Mazindol (3)</td>
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</tbody>
</table>
Non Pharmacologic Treatment

- Cold and hot compresses
- Leg massage
- Accupressure
- Vibrational counterstimulation (Relaxis)
- Relaxation techniques
- Aerobic and resistance training exercises
- Walking or gentle stretching exercises before bedtime
Non Pharmacologic Treatment

- Avoiding alcohol, caffeine, nicotine
- Adequate sleep hygiene
- Avoidance of dopamine antagonists, SSRIs, antihistamines
- Weight management
- Mental alerting activities - video games, crossword puzzles
- Avoidance of SNRIs, SSRIs, and Dopamine antagonists (Haldol, Metaclopramide) if possible
Pharmacologic Treatment

- Dopamine Agonists (DA)
  - The most widely used class of meds for RLS
  - Not only effective in reducing RLS symptoms these agents reduce symptoms of PLMS
  - Augmentation and potential to worsen RLS is a problem
  - Long term treatment is successful in less than half of cases
Pharmacologic Treatment

- Dopamine Agonists
  - Impulse control disorders
    - Occurs in 6-17% of patients taking DAs
    - Pathologic Gambling
    - Compulsive Shopping
    - Compulsive Eating
    - Hyper-sexuality
    - Symptoms usually resolve with discontinuing the drug or dose reduction
    - Patients should be warned about development of these symptoms and should be asked about them on follow-up visits
  
- Cornelius JR, et.al. Sleep 2010;33:81-87

Restless Legs Syndrome
Pharmacologic Treatment

- Dopamine Agonists
  - Ropinirole
    - First dopamine agonist to be approved in US and Europe for RLS treatment
    - Starting dose is 0.25 mg. Dose can be increased in 2 days to 0.5 mg and to 1 mg at the end of 1 week.
    - Maximum recommended dose is 4 mg/day
    - Minimum effective dose should be used as higher doses increase risk of augmentation
    - Side effects include nausea, vomiting, dizziness, headache and fatigue
Pharmacologic Treatment

☐ Dopamine Agonists

■ Pramapexole

☐ Efficacious in moderate to severe RLS

☐ Starting dose is 0.125 mg taken 2-3 hours prior to bedtime or the onset of symptoms.

☐ Maximum recommended dose is 0.75 mg.

☐ Effective dose ranges from 0.25-1 mg.

☐ Little added benefit noted after 0.5 mg.

☐ Common side effects- sleepiness, nausea, insomnia

☐ Renal metabolism- caution in patients with renal failure
Pharmacologic Therapy

- Dopamine Agonists
  - Rotigotine
    - Direct dopamine agonist with activity predominantly at the D2 receptor but also at D1 and D3 receptors. Also has B2 receptor antagonist and 5HT1a agonist activity.
    - Transdermal patch provides steady state plasma levels over 24 hrs.
    - Starting dose is 1 mg/24h
    - Can be increased weekly by 1 mg/24h to a maximum of 3mg/24h

Restless Legs Syndrome
Pharmacologic Therapy

- Dopamine Agonists
  - Rotigotine
    - Side effects - application site reaction, nausea, headache, and fatigue
    - In an open label study over 5 years, 43% of 295 patients continued on the patch at a mean dose of 3mg/d. 57% discontinued treatment due to adverse effects or lack of efficacy. 13% developed significant augmentation resulting in 4% discontinuing treatment.
Update to the AASM Clinical Practice Guideline: “The Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder in Adults—An Update for 2012: Practice Parameters with an Evidence-Based Systematic Review and Meta-Analyses”

R. Nisha Aurora, MD; David A. Kristo, MD; Sabin R. Bista, MD; James A. Rowley, MD; Rochelle S. Zak, MD; Kathren R. Casey, MD, MPH; Carin L. Lam, MD; Sharon L. Tracy, PhD; Richard S. Rosenberg, PhD

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In January 2012, the AASM Board of Directors approved the Standards of Practice paper titled “The Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder in Adults - An Update for 2012: Practice Parameters with an Evidence-Based Systematic Review and Meta-Analyses.” The 2012 update included a new drug not reviewed in the previous 2004 AASM guidelines for the treatment of Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD) — rotigotine. Rotigotine was originally approved by the US Food and Drug Administration (FDA) for the treatment of signs and symptoms associated with early stage idiopathic Parkinson’s disease. Additionally, rotigotine had been shown in clinical trials to be effective for the treatment of moderate-to-severe RLS. In 2008, rotigotine was withdrawn from the US market due to concerns about inconsistent absorption from the patch; therefore, rotigotine was not an FDA-approved treatment option for RLS or PLMD when the 2012 update was accepted for publication. Thus, despite high level evidence supporting the efficacy of this drug for the treatment of moderate-to-severe RLS, the Standards of Practice Committee (SPC) made no recommendation regarding the use of rotigotine in the setting of RLS.

The issue of drug absorption was subsequently resolved by the manufacturer, and the new formulation of rotigotine received FDA approval in April 2012. Rotigotine is currently FDA approved both for the treatment of signs and symptoms associated with advanced stage idiopathic Parkinson’s disease, as well as for moderate-to-severe primary RLS. The change in the FDA status of rotigotine occurred after finalization and approval of the 2012 update and, therefore, is not reflected in the published paper. The new FDA status of rotigotine necessitated a change in the published recommendation level for the use of this medication in the treatment of RLS. Accordingly, the SPC has revised the recommendation level from “NO RECOMMENDATION” to a “GUIDELINE” level of recommendation. This new recommendation level reflects the high level of evidence for rotigotine coupled with uncertainty in the benefits/harms ratio due to limited clinical experience with this medication.

CITATION
Aurora RN; Kristo DA; Bista SR; Rowley JA; Zak RS; Casey KR; Lam CI; Tracy SL; Rosenberg RS. Update to the AASM clinical practice guideline: “the treatment of restless legs syndrome and periodic limb movement disorder in adults—an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses.” SLEEP 2012;35(8):1037.

DISCLOSURE STATEMENT
This is not an industry supported study. The authors have indicated no financial conflicts of interest.
Pharmacological Therapy

- Cabergoline and Pergolide
  - Ergot Dopamine Agonists
  - Effective for treatment of RLS but should not be used due to increased incidence of valvular fibrosis and other fibrotic side effects.
Pharmacologic Therapy

- **Levodopa**
  - In combination with a decarboxylase inhibitor provides the most rapid relief in primary and secondary RLS.
  - Most studies show a high risk of tolerance, augmentation, and late night or early morning rebound symptoms.
    - Augmentation may occur in up to 70% of patients taking Levodopa daily.
    - Risk increases with doses of 200 mg or more.
    - Rebound occurs in 20%-35%
Pharmacologic Therapy

- Levodopa
  - Should not be taken with high protein foods
  - The most frequent reasons for discontinuation were loss of efficacy, adverse effects, and augmentation.
  - Can be used for RLS that occurs intermittently in the evening, at night, or specific activities such as airplane travel, lengthy car rides, or theater events.
  - Avoid using for chronic treatment of RLS
Pharmacologic Therapy

- Calcium Channel Alpha-2-Delta Ligands

  - Binds with high affinity alpha-2-delta subunit of the in patients voltage activated calcium channels leading to reduced neurotransmitter release and attenuation of postsynaptic excitability.
  
  - Does not cause augmentation or impulse control disorder
  
  - Useful in patients with painful RLS or RLS associated polyneuropathy
Pharmacologic Therapy

- Calcium Channel Alpha-2-Delta Ligands
  - Gabapentin
    - Dosage 300 mg given 2-3 hours before bedtime or before the onset of symptoms.
    - Increase dose on a weekly basis until symptoms improve and a maximum dose of 900-2000 mg is reached.
    - A smaller dose may be used in the elderly.
    - Dose should be adjusted in patients with renal failure.
    - Side effects - dose dependent - Dizziness, somnolence, peripheral edema
    - Additional doses can be given earlier in the day if daytime symptoms occur.
Pharmacologic Therapy

- Gabapentin enacarbil
  - Prodrug of Gabapentin
  - FDA approved in April 2011 for treatment of moderate to severe RLS in adults.
  - Developed to address pharmacologic limitations of gabapentin.
  - Allows for once daily administration.
  - Dosage 600 mg daily with food at 5:00pm
  - Results of recent post hoc meta analyses suggest that 1200 mg once daily was effective in relieving not only subjective RLS symptoms but also severe sleep disturbance associated with RLS.

- Kume A. Neuropsychiatr Dis Treat 2014;10:249-62
Treatment

- Pregabalin
  - Gabapentin analogue
  - Initial Dosage - 50 mg daily
  - Can be increased every few days
  - Maximum dosage 450 mg./day
  - Adverse effects include unsteadiness, daytime sleepiness, increased suicidal ideation, dizziness, weight gain.
  - In a short term study of 12 weeks duration, Pregabalin 300 mg, was found to improve RLS symptoms, increase N3 and reduce WASO.

Treatment

- **Opiates**
  - Have long been used for treatment of RLS however concerns of addiction and exacerbation of sleep apnea have limited their use.
  - Typically not first line agents
  - Low potency opioids (codeine, pentazocine) or medium potency opioids such as hydrocodone or tramadol can be used for intermittent or mild RLS and also for breakthrough symptoms.
  - Can be extremely useful in patients who have failed other classes of therapy.
  - Can be used as combination therapy with alpha-2-delta ligands, DAs or as monotherapy
  - Augmentation has been reported with Tramadol
Treatment

☐ Opiates

■ Methadone

☐ A long acting opioid agonist.

☐ Can be used in patients who have failed other therapies particularly due to augmentation.

☐ Doses should be kept low (5mg-20mg) due to concerns for addiction and tolerance.

☐ Can be taken at bedtime or during the day if breakthrough symptoms occur

☐ Adverse effects- Constipation, nausea, dizziness, sedation, respiratory depression, and worsening of sleep apnea
Treatment

- Insomnia
  - Irregular sleep-wake cycles can exacerbate RLS
  - Cognitive Behavioral Therapy (CBT) has better maintenance of effect than hypnotics.
  - Melatonin can be useful.
  - GABA receptor agonists (Benzodiazepines) - Temazepam
    - May be of benefit when used sparingly
  - Benzodiazepine receptor agonists - eszopiclone, Zolpidem
    - May be of benefit when used sparingly
  - Sedating antihistamines (Amitriptyline, Mirtazapine) should be avoided as they can worsen RLS and PLMS.
Restless Legs Syndrome

Treatment

- Intrathecal Morphine Pump
  - Effective in patients with refractory RLS who have failed other treatments.
  - Daily morphine dose used in the first two reported cases was very low (0.25 and 0.08 mg.) compared to doses used in chronic pain (4.5-5.5 mg.)
  - Patients remained symptom free after several years of treatment
  - Promising results but further studies needed
Treatment

- Surgery

- Deep Brain Stimulation of the bilateral posteroventral lateral globus pallidus internus was shown to be beneficial in one patient with “malignant RLS” refractory to all other treatments.

- Some patients showed reemergence of symptoms following subthalamic nucleus DBS for Parkinson’s Disease while another study showed improvement in RLS symptoms.

- Further studies are needed to better understand the role and optimal target selection of DBS.
Augmentation

- First described in 1996 by Allen and Early
- Characterized by progressively earlier onset of RLS symptoms with a gradual shift of onset to early evening, afternoon, or even morning
- Associated with increased intensity of symptoms, shorter latency after rest, expansion of symptoms to the upper extremities, and shorter duration of medication effect
- Patients typically describe their RLS symptoms as worse than before treatment.
- Usually develops within the first 6-18 months of treatment
Augmentation

- Treatment can be challenging.
  - Use the lowest effective dose of DA
  - "Chasing" symptoms by adding an earlier dose of medication or giving the usual dose earlier
  - Can be tried in patients with mild symptoms, on low doses of DAs and symptoms that remain in the evening
  - Need to follow closely for progressive symptoms
  - Switch to a long acting DA
  - Transdermal Rotigotine or extended release Pramipexole or Ropinirole
Augmentation

Treatment

- Adding a non-dopaminergic agent and keeping the DA dose low
  - Gabapentin, Pregabalin, or Gabapentin enacarbil
  - Low dose long acting opioid (Methadone, extended release Oxycodone)
- Discontinuing the DA is usually eventually necessary.
- Restarting a DA after a drug holiday can lead to a more rapid development of augmentation.

- Check serum ferritin
  - If low (< 75ng/ml) start oral iron
- Consider referral to a sleep medicine specialist

Restless Legs Syndrome
Tolerance

- Loss of efficacy of a specific treatment
- Symptoms are similar in severity, timing, and anatomic distribution to those occurring before treatment.
- Occurs commonly in all medications used over a long period of time
- Requires increasing the dose
Rebound

- Appearance of symptoms late at night or early in the morning
- Related to half life of the medications, mainly DAs or Levodopa
- Sometimes difficult to differentiate from augmentation
### Summary of Recommendation Statements

#### Standards for use in RLS

<table>
<thead>
<tr>
<th>Practice Parameter</th>
<th>Strength of Recommendation</th>
<th>Body of Evidence Level</th>
<th>Harm/burden Assessment</th>
<th>FDA status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicians should treat patients with RLS with pramipexole.</td>
<td>(STANDARD)</td>
<td>High</td>
<td>Benefits clearly outweigh harms</td>
<td>Approved for indication</td>
</tr>
<tr>
<td>Clinicians should treat patients with RLS with ropinirole.</td>
<td>(STANDARD)</td>
<td>High</td>
<td>Benefits clearly outweigh harms</td>
<td>Approved for indication</td>
</tr>
</tbody>
</table>

#### Standards against use in RLS

<table>
<thead>
<tr>
<th>Practice Parameter</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Clinicians should not treat RLS patients with pergolide because of the risks of heart valve damage.</td>
<td>(STANDARD)</td>
<td>High</td>
<td>Harms clearly outweigh benefits</td>
<td>Discontinued</td>
</tr>
</tbody>
</table>

#### Guidelines for use in RLS

<table>
<thead>
<tr>
<th>Practice Parameter</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Clinicians can treat RLS patients with levodopa with dopa decarboxylase inhibitor.</td>
<td>(GUIDELINE)</td>
<td>High</td>
<td>Benefits closely balanced with harms. This is particularly true for those with intermittent RLS who use this medication sporadically.</td>
<td>Approved, but off-label use</td>
</tr>
<tr>
<td>Clinicians can treat RLS patients with opioids.</td>
<td>(GUIDELINE)</td>
<td>Low</td>
<td>Benefits clearly outweigh harms</td>
<td>Approved, but off-label use</td>
</tr>
<tr>
<td>Clinicians can treat patients with RLS with gabapentin enacarbil.</td>
<td>(GUIDELINE)</td>
<td>High</td>
<td>Uncertainty in balance between benefits and harms</td>
<td>Approved for indication</td>
</tr>
<tr>
<td>Given the potential of side effects, including heart valve damage, clinicians can treat RLS patients with gabapentine only if other recommended agents have been tried first and failed, and close clinical follow-up is provided.</td>
<td>(GUIDELINE)</td>
<td>High</td>
<td>Benefits closely balanced with harms</td>
<td>Approved, but off-label use</td>
</tr>
</tbody>
</table>

#### Options for use in RLS

<table>
<thead>
<tr>
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<th>FDA status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicians may treat RLS patients with gabapentin.</td>
<td>(OPTION)</td>
<td>Low</td>
<td>Unclear benefit/harm balance</td>
<td>Approved, but off-label use</td>
</tr>
<tr>
<td>Clinicians may treat patients with RLS with pregabalin.</td>
<td>(OPTION)</td>
<td>Low</td>
<td>Benefits closely balanced with harms</td>
<td>Approved, but off-label use</td>
</tr>
<tr>
<td>Clinicians may treat RLS patients with carbamazepine.</td>
<td>(OPTION)</td>
<td>Low</td>
<td>Benefits closely balanced with harms</td>
<td>Approved, but off-label use</td>
</tr>
<tr>
<td>Clinicians may treat RLS patients with clonidine.</td>
<td>(OPTION)</td>
<td>Low</td>
<td>Unclear benefit/harm balance</td>
<td>Approved, but off-label use</td>
</tr>
<tr>
<td>Clinicians may use supplemental iron to treat RLS patients with low ferritin levels.</td>
<td>(OPTION)</td>
<td>Very Low</td>
<td>Unclear benefit/harm balance</td>
<td>Approved, but off-label use</td>
</tr>
</tbody>
</table>

#### PLMD

<table>
<thead>
<tr>
<th>Practice Parameter</th>
<th>Strength of Recommendation</th>
<th>Body of Evidence Level</th>
<th>Harm/burden Assessment</th>
<th>FDA status</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is insufficient evidence at present to evaluate the use of pharmacological therapy in patients diagnosed with PLMD alone.</td>
<td>(NO RECOMMENDATION)</td>
<td>Insufficient</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Treatment Algorithm in Restless Legs Syndrome

RLS Therapeutic Strategies

- Check serum ferritin
  - If <75 ng/ml, treat with oral iron
- Non-pharmacological measures
  - Good sleep hygiene, exercise
  - Eliminate medications that worsen RLS
  - CBT, vibrational device

Intermittent RLS
- Medications taken as needed
  - Codeine, oxycodone, levodopa

Moderate Daily RLS
- As monotherapy
  - Alpha-2-delta ligand (gabapentin, gabapentin enacarbil, pregabalin)
  - DA (ropinirole, pramipexole, rotigotine)

Severe RLS
- As monotherapy
  - Alpha-2-delta ligand, gabapentin enacarbil, pregabalin
  - DA (ropinirole, pramipexole, rotigotine)

Use combination therapy
- Alpha-2-delta ligand, DA or opioid

Augmentation with DA
- Check serum ferritin, if low oral iron
  - Reduce dose or change to another class of medication:
    - Alpha-2-delta ligand (gabapentin, gabapentin enacarbil, pregabalin) or an opioid.

ICD with DA
- Reduce dose or discontinue DA
  - Change to alpha-2-delta ligand (gabapentin, gabapentin enacarbil, pregabalin) or an opioid.

Severe RLS
- Methadone as monotherapy or as add on therapy
- Refractory RLS
- IV iron (even with low normal ferritin)
  - IT morphine

Wiljemanne, Jankovic, p 684
RESTLESS LEGS SYNDROME

QUESTIONS?
## Restless Legs Syndrome: Differential Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg cramps</td>
<td>Complaint of a painful sensation in the leg with muscle hardness or tightness that causes awakenings from sleep because of painful leg sensations, often improved with massage, movement, or application of heat</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Pain in both feet and/or tingling that is usually present during the day time, but may be worse during the evening</td>
</tr>
<tr>
<td>Radiculopathy</td>
<td>Shooting pains down one leg, often present during the day and with activity</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Pain localized to a joint that usually is associated with swelling of the joint; often worse with the use of the joint or weight-bearing</td>
</tr>
<tr>
<td>Positional discomfort</td>
<td>Discomfort that occurs with a particular position; a single movement can relieve the discomfort</td>
</tr>
<tr>
<td>Frequent unconscious foot or leg movements</td>
<td>Not preceded by abnormal sensations or an urge to move the leg; often without conscious awareness of the movement</td>
</tr>
<tr>
<td>(hypnic jerks, foot-tapping, leg-shaking, nervous movements)</td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>Generalized restlessness not localized to the legs and occurring without a circadian pattern; often associated with dopamine receptor antagonist or as a feature of Parkinson disease</td>
</tr>
</tbody>
</table>

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