Update on the Pharmacologic Approach to Restless Legs Syndrome

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RLS (aka Willis Ekbom disease): The Basics

- Characterized by an uncomfortable sensation, typically in the lower extremities
  - Usually felt between knee and ankle
- Sensations are often difficult to characterize
  - Originates deep within limbs
  - Common descriptions include burning, creeping, crawling, itching or “vaguely painful”
- Typically occur at rest and become more intense during evening/nighttime hours
  - Minority will have daytime symptoms
- Most have idiopathic or “primary” RLS
  - 60% with family history
  - Secondary causes include iron deficiency, pregnancy, severe renal disease
- Frequently associated with periodic leg movement in sleep (PLMS)
### RLS: Diagnostic Criteria

- An urge to move the legs that...
  - *usually* accompanied by uncomfortable/unusual sensations
  - along with accompanying unpleasant sensations begins or worsens while at rest
  - is partially or totally relieved by movement (such as walking or stretching) for at least as long as the activity continues
  - only occur or are worse in the evening or night vs. the day
  - are not accounted for by another medical or behavioral condition

### RLS: Pathophysiology

- **Multiple theories**
  - Several risk alleles have been identified
  - **Dopaminergic role**
    - Neuroleptic drugs can exacerbate symptoms
    - May be due to abnormal binding
  - **Iron deficiency in the putamen and substantia nigra**
    - Iron in a cofactor for an enzyme involved in the rate limiting step of dopamine synthesis
    - Low ferritin is associated with increased symptom severity
  - **Other theories**
    - GABA abnormalities
    - Decreased endogenous opioid levels in the brain
RLS Treatment: Iron

- All patients should be screened for iron deficiency
- Serum ferritin does not correlate well with brain ferritin
  - Most patients with RLS have normal serum ferritin
  - Serum iron studies reflect concentrations in the erythron only
    - Patients with “normal” serum iron status may have diminished brain iron levels
- Iron replacement should be initiated for anyone with a serum ferritin $\leq 75$ mcg/L and transferrin saturation $< 45$
  - Do not treat empirically

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RLS Treatment: Iron

- Oral iron
  - May or may not be effective for individuals with serum ferritin $\leq 75$mcg/L
  
  - Absorption is dependent on whether there are adequate body stores for erythrocyte production
    - Only 1-2% of oral iron is absorbed when ferritin is between 50-75 mcg/L
    - Absorption can be increased by taking iron with vitamin C

- Dosing
  - Ferrous sulfate 325mg (65mg elemental iron) twice daily + vit C 100mg
  - Should be taken on an empty stomach

- Consider intravenous iron if symptoms persist after 12 weeks or oral dosing is not tolerated
  - May continue if patient is responding, though not to maximum desired effect
RLS Treatment: Iron

- Intravenous iron
  - Indicated if oral iron fails, if symptoms are too severe to wait for oral iron to be effective
    - Symptoms should be moderate to severe
  - Serum ferritin should be between 75-100 mcg/L
    - If serum ferritin is believed to be elevated due to an inflammatory process, do not administer unless transferrin saturation is <20% (otherwise the 45% threshold is adequate)

- Dosing
  - Ferric carboxymaltose 1000mg over 15 minutes
    - Best evidence
  - LMW iron dextran 975mg over 1h
    - Give 25mg test dose before infusion
  - Iron sucrose
    - Requires multiple infusions
    - Lack of evidence for efficacy
  - Iron gluconate
    - Lack of data

Post iron administration follow-up

Oral iron
- Repeat labs in 3 months
  - Skip doses for 2 days prior
- Continue every 3-6 months as long as therapy continues

IV iron
- Repeat labs 8 weeks after administration (assess efficacy), and again 8 weeks later (assess stability)
Treatment of Chronic Persistent RLS

**Dopamine Agonists**
- Pramipexole
- Pramipexole ER
- Ropinirole
- Ropinirole XL
- Rotigotine

**α2δ Ligands**
- Gabapentin
- Gabapentin enacarbil
- Pregabalin

Medications in bold italics are FDA approved for the treatment of RLS

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**Dopamine Agonists**

- Levodopa
  - Use is basically historical
  - May still be useful in intermittent RLS
  - Morning rebound

- Effectiveness across the class is assumed

- Onset is typically 90-120 minutes

- Common side effects include
  - N/V, headache, daytime somnolence, edema, application site reactions (rotigotine)
  - Must watch for compulsive behaviors related to use
  - Augmentation
Dopamine Agonists

- Best candidates for DAs as first line therapy
  - Comorbid depression
  - Obesity
  - Metabolic syndrome

- RLS Dosing
  - Pramipexole: 0.125mg-0.75mg
  - Ropinirole: 0.25mg-4mg
  - Rotigotine transdermal patch: 1mg-3mg

- Use the lowest possible dose to minimize risk of augmentation
- Discontinuation requires downward titration to avoid withdrawal symptoms

α2δ Ligands

- Mechanism of action in RLS is unclear
  - No direct effect on GABA
  - May be related to ability to regulate glutamate through calcium channel inhibition

- Efficacy data is best for gabapentin enacarbil (FDA approved) and pregabalin
  - Gabapentin may be effective for individual patients
    - Absorption limited by saturable transporter

- Not associated with augmentation

- Common side effects include
  - N/V, daytime somnolence, headache, weight gain
  - Abuse potential (euphoria in conjunction with opiates)
**α2δ Ligands**

- α2δ ligands should be considered first line therapy for most patients
  - Best candidates
    - Pain
    - Insomnia
    - Anxiety
    - Impulse control issues
    - Those on DAs for other conditions (e.g. Parkinsons disease)

**RLS Dosing**

- Gabapentin: Usual effective dose is 900-2400mg
  - Begin with 100-300mg/day and titrate slowly to minimize side effects
  - Divide doses >600mg into 1/3 given at midday and 2/3 before bedtime
- Gabapentin enacarbil: 600mg taken at 5:00 PM with food
- Pregabalin: Usual effective dose is 150-450mg
  - Begin with 50-75mg/day

- Must adjust for renal function

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**Augmentation**

- Defined as an increase in symptom severity during the previous week in a patient with previous treatment success
  - Symptoms may worsen to severity beyond initial baseline
  - Earlier onset (generally at least 4 hours)
    - If less than 4 hours, shorter latency at rest, involvement of other body parts, increase in intensity, and shorter duration of relief are diagnostic

- Exclusive to dopaminergic medications

- Will occur in more than half of patients with long term therapy

- Must rule out augmentation mimics
  - Natural progression (will show lasting improvement with dose increases)
  - Tolerance (symptoms do not appear earlier and are not worse vs. baseline)
  - Rebound (symptoms come back in early morning due to drop in medication levels without any symptom spread to other body parts)
Treating a Patient with Augmentation

- Eliminate any exacerbating factors
  - Make sure iron is adequate
  - Check for adherence
  - Change in status (pregnancy, renal disease, sleep disordered breathing)
  - Medications that may make RLS worse (antihistamines, dopamine receptor blockers, serotonergic antidepressants)

Treating a Patient with Mild Augmentation

- Defined as
  - No prior increase in dose
  - Dose is < maximum
  - Temporal shift
  - Mild symptoms

<table>
<thead>
<tr>
<th>Keep the dopamine agonist</th>
<th>Complete therapy switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Split the dose in two</td>
<td></td>
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<tr>
<td>2. Give the dose earlier</td>
<td></td>
</tr>
<tr>
<td>OR if 1 and 2 fail</td>
<td></td>
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<tr>
<td>3. Consider increasing dose but keeping at below the max recommended</td>
<td></td>
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<tr>
<td>If failure of above</td>
<td></td>
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<tr>
<td>If failure of above, treat as Severe</td>
<td></td>
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</tbody>
</table>

1. Change to α2δ ligand
2. Change to a long acting DA (rotigotine patch or extended release formulation) at less than approved dose
Treating a Patient with Severe Augmentation

- Defined as
  - DA dose exceeds maximum recommended
  - Symptoms cause more than mild distress
  - Does not respond to treatment for mild augmentation

<table>
<thead>
<tr>
<th>Cross Titration</th>
<th>Switch</th>
<th>10-Day Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add an αδ ligand and gradually reduce and D/C DA</td>
<td>Change therapy to long acting DA</td>
<td>Evaluate need for ongoing therapy, and initiate αδ ligand</td>
</tr>
</tbody>
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For failure of the above, or severe, around-the-clock symptoms, consider opioid therapy

Opioids

- For treatment resistant RLS only
  - Not FDA approved for RLS

- Mechanism in RLS unclear
  - RLS patients have demonstrated >1/3 fewer cells positive for beta-endorphins in the thalamus
  - Stimulation of mu opioid receptors stimulates dopamine release
  - Pre-treatment with a DA negates the response to opioids

- Most patients with refractory RLS will require high potency medications that are longer acting/controlled release
  - Short acting medications may be used to supplement therapy during the day

- A decrease in symptoms rather than elimination may need to be the goal
  - Doses will be lower than those used for chronic pain
## Opioids

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose (total daily dose)</th>
<th>Maintenance Dose (total daily dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone/naloxone</td>
<td>10/5mg</td>
<td>60/30mg</td>
</tr>
<tr>
<td>Oxycodone ER or IR</td>
<td>5-10mg</td>
<td>30mg</td>
</tr>
<tr>
<td>Hydrocodone ER or IR</td>
<td>10mg</td>
<td>45mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>2.5mg</td>
<td>20mg</td>
</tr>
</tbody>
</table>

References

- Mov Disord. 2018;33:1077-1091.
- Sleep Med Rev. 2018;41:50-60.
- Sleep Med. 2018;41:27-44.
- CNS Drugs. 2018;32:149-159.