The Pharmacists’ Role in Treating Restless Leg Syndrome

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Accreditation:
Pharmacists- 798-000-08-089-L01-P
Technicians- 798-000-08-089-L01-T

Program Overview:
This program will educate pharmacists on Restless Legs Syndrome and enhance their knowledge of currently available treatment options (along with their probable results and possible side effects). The program includes information on pharmacologic treatments, patient counseling and a question/answer period.

Objectives:
• Identify the symptoms of RLS and assess their impact on the patient's quality of life.
• Describe the problems associated with sleep disruption, prevalence, epidemiology and risk factors for restless legs syndrome (RLS).
• Describe the pharmacological treatments to manage RLS and their therapeutic mechanisms of action.
• Identify the key elements of patient education and counseling relevant to the pharmacological treatment for RLS.

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Pharmacists- 1.0 Credit hour or 0.1 CEU for pharmacists/technicians

Target Audience: Pharmacists & Technicians

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The Pharmacists’ Role in Treating Restless Leg Syndrome

Speaker: Dr. Geneva Clark Briggs, a board-certified Pharmacotherapy Specialist, received her Doctor of Pharmacy and Bachelor of Science in Pharmacy degrees from Virginia Commonwealth University, Medical College of Virginia. Dr. Briggs is a clinical associate with MedOutcomes, Inc. where she develops and presents educational programs for pharmacists.

Speaker Disclosure: Dr. Briggs has no actual or potential conflicts of interest in relation to this program

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Overview

- Identify the symptoms of RLS and assess their impact on the patient's quality of life.

- Describe the problems associated with sleep disruption, prevalence, epidemiology and risk factors for restless legs syndrome (RLS).

- Describe the pharmacological treatments to manage RLS and their therapeutic mechanisms of action.

- Identify the key elements of patient education and counseling relevant to the pharmacological treatment for RLS.
What is Restless Leg Syndrome?

- Described in Latin in 1672, named in 1945
- A disorder characterized by sensory symptoms and limb restlessness mainly during rest
- Tends to be life-long disorder
RLS is Prevalent and Frequently Overlooked

- 10% of people have some RLS symptoms
- 3-5% of people have severe symptoms that disrupt their sleep and quality of life
- 2:1 ratio of men to women
Required Diagnostic Clinical Features of RLS

- Urge or need to move the legs usually accompanied or caused by unpleasant sensations
- Symptoms are worse or exclusively present at rest
- Symptoms at least partially and temporarily relieved by activity
- Symptoms show a circadian pattern -- with a maximum in the evening or at night

International RLS Study Group and NIH Consensus Panel
Common Descriptions of RLS Sensations

- Creepy, crawly
- Worms crawling in veins
- Pepsi-Cola in the veins
- Nervous feet
- Itching under the skin
- Crazy legs
- Toothache feeling
- Excited nerves
- Electric-like shocks
- Just need to move
- Elvis legs

- Kids may use such words as:
  - Ouchies
  - Oowies
  - Tickle
  - Spiders on skin
  - Creepy crawlies
  - A lot of energy in my legs
  - Feel as if they are pulling apart
Symptoms of RLS

- Sensations in legs (arms in severe cases)
- Vaguely localized
- Generally no physical findings
- Periodic leg movements during sleep (PLMS) ~80% of adults with RLS
- Severe – daytime symptoms
Differential Diagnosis of RLS
(Disorders of Restlessness)

- Neuroleptic-induced akathisia
- Akathisia associated with neurodegenerative disease
- Anxiety disorders
- Hypotensive akathisia
- Nervous habit fidgeting or leg/foot shaking
Differential Diagnosis of RLS (Disorders of Leg Discomfort)

- Leg cramps
- Arthritic conditions
- Arterial and venous insufficiencies
- Myopathies
- Small fiber neuropathies
- Positional discomfort or ischemia
- Dermatologic conditions
- Growing pains (children)
Distinguishing RLS From Mimics

- Location of symptoms - usually diffuse and deep within the limb
- Duration of symptoms - usually somewhat persistent, lasting 5 or 10 minutes or longer
- Speed of relief with activity - quickly relieved with activity
- Relief with change of position - usually demands continued activity
- Provocation by rest - brought on by the resting state
Types

- **Primary RLS**
  - Also called familial, early onset, or idiopathic
  - Slowly progressive form that may be inherited
  - Onset before 45
  - Likely to have 1st degree relative with RLS
  - Most prevalent form (75%)

- **Secondary**
  - More rapidly progressive form that is associated with an underlying disorder
  - ? brain iron insufficiency
Secondary Causes
(Well Established Causes)

- Iron deficiency
- Uremia
- Pregnancy
- Rheumatoid arthritis
Secondary Causes

- Diabetes
- Parkinson's disease
- Hypothyroidism
- Fibromyalgia
- Vitamin deficiency (folate, B12)
- Peripheral neuropathy
- Attention deficit hyperactivity disorder (ADHD)
- Gastric surgery (before improved techniques]
- Sjögren's syndrome
- Radiculopathy
Secondary Causes
(Medication/Others)

- Dopamine blocking agents (neuroleptics, antinausea compounds, metoclopramide)
- Antidepressants (SSRIs, tricyclics)
- Antihistamines
- Caffeine
- Alcohol
- Nicotine
Risk Factors

- Family history
- Iron deficiency
- Rheumatoid arthritis
- Gastric surgery
- Age > 70
Pathophysiology (unknown)

- Brain scans suggest reduced D2 receptor binding and a mild nigrostriatal presynaptic dopaminergic hypofunction may cause the disorders

- Low brain iron levels
Consequences of RLS

- Sleep disturbance
- Impaired quality of life
- Depression
- Anxiety
- Possible increased risk of hypertension, heart disease, stroke
General Management of RLS

- Find any underlying disorders and treat if feasible
- Eliminate precipitants of RLS
- Practice good sleep hygiene
- Use simple behavioral interventions
- Moderate exercise
- Healthy diet
- Information and support
Patient Education Resources

- National Institutes of Health
  www.ninds.nih.gov/disorders/restless_legs

- We Move
  www.wemove.org/rls

- RLS Foundation
  www.rls.org

- www.restlesslegs.com

- www.rlsrest.com
Pharmacologic Treatment
(3 Categories)

- Intermittent or situational symptoms
- Daily symptoms
- Failure of prior first-line therapies
Intermittent RLS

- < 2 or 3 times/week
  (Sporadically, periodically, or situational)

- Medications that can be taken as needed
  - Levodopa with decarboxylase inhibitor (ie., carbidopa)
  - Pramipexole or ropinirole
  - Mild-to-moderate-strength opioid (codeine, tramadol, hydrocodone)
  - Sedative-hypnotic
## Augmentation and Rebound

<table>
<thead>
<tr>
<th>Augmentation</th>
<th>Increase in symptom severity and involvement of other limbs. Time shift of symptoms from bedtime to early evening to daytime.</th>
<th>Adding a middle-of-the-night dose. Switching to a dopamine agonist with a longer half-life or controlled-release levodopa. Using a combination of regular-release and controlled-release levodopa.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebound</td>
<td>Wearing off of drug effect, typically in the morning.</td>
<td>Reducing the dose of the provocative medication. Switching to an alternate dopaminergic medication with a longer half-life or to a different class of medication (opioid or anticonvulsant). Using a drug combination with a lower dopaminergic dose.</td>
</tr>
</tbody>
</table>
Daily RLS

- **Dopamine agonists**
  - Pramipexole (Mirapex®, 0.125-1.5 mg/day)
  - Ropinirole (Requip®, 0.25-6 mg/day)

- **Anticonvulsants**
  - Gabapentin (300-2700 mg/day)

- **Opioids**
  - Tramadol (100-400 mg/day)
  - Hydrocodone (5-20 mg/day)
  - Oxycodone (5-20 mg/day)

- **Benzodiazepines**
  - Clonazepam (0.5-4 mg/day)
Dopaminergic Agents

- Indicated for moderate to severe primary RLS

- Efficacy
  - Decrease PLMS
  - Decrease International RLS Study Group rating scale (IRLS) score compared with placebo (-12.4 vs -6.1)
  - Significantly higher response ('much improved' or 'very much improved') rate on Clinical Global Impressions-Improvement (CGI-I) scale.
  - Large placebo response in studies
### Study Data from Package Insert

<table>
<thead>
<tr>
<th></th>
<th>Pramipexole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in IRLS Score</td>
<td>-13.6</td>
<td>-9.4</td>
</tr>
<tr>
<td>% of responders on CGI-I</td>
<td>72%</td>
<td>51.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Ropinirole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in IRLS Score</td>
<td>-13.5</td>
<td>-9.8 (p&lt;0.001)</td>
</tr>
<tr>
<td>% of responders on CGI-I</td>
<td>73.5%</td>
<td>56.5% (p=0.0006)</td>
</tr>
</tbody>
</table>
Adverse Effects

- Nausea
- Postural hypotension
  - Syncope
- Compulsive behaviors
- Hallucinations
- Somnolence
- Augmentation and Rebound
Warning

- Falling asleep while engaged in activities of daily living, including the operation of motor vehicles

- May be NO warning signs such as excessive drowsiness

- Has occurred as late as 1 year after initiation of treatment
Drug Interactions

- **Pramipexole**
  - Cimetidine can increase AUC 50% and $T_{1/2}$ 40%

- **Ropinirole**
  - Ciprofloxacin can increase AUC 84% and $C_{\text{max}}$ by 64%
# Ropinirole Dose Titration Schedule for RLS

<table>
<thead>
<tr>
<th>Day/Week</th>
<th>Dosage to be taken once daily, 1 to 3 hours before bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1 and 2</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Days 3-7</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Week 2</td>
<td>1 mg</td>
</tr>
<tr>
<td>Week 3</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>Week 4</td>
<td>2 mg</td>
</tr>
<tr>
<td>Week 5</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Week 6</td>
<td>3 mg</td>
</tr>
<tr>
<td>Week 7</td>
<td>4 mg</td>
</tr>
</tbody>
</table>
### Pramipexole Dose Titration Schedule for RLS

<table>
<thead>
<tr>
<th>Titration Step</th>
<th>Duration</th>
<th>Dosage (mg) to be taken once daily, 2-3 hours before bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-7 days</td>
<td>0.125</td>
</tr>
<tr>
<td>2*</td>
<td>4-7 days</td>
<td>0.25</td>
</tr>
<tr>
<td>3*</td>
<td>4-7 days</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*if needed
Other Agents

- **Gabapentin**
  - Sedation
  - May be good choice if patient also has a neuropathy

- **Opioids**
  - Ekborn who first described RLS noted the efficacy

- **Sedatives/Benzodiazepines**
  - Don’t change symptoms
Refractory RLS

- Change to a different dopamine agonist
- Switch to an opioid or anticonvulsant
- Add a second medication, possibly with reduced agonist dose
- Consider a drug holiday
- High-potency opioids for severe, resistant cases
Special Populations

- **Pregnancy**
  Nonpharmacologic, iron and other vitamins if needed, opioids

- **Children**
  Nonpharmacologic, maybe dopaminergic medications, clonazepam, or clonidine

- **Depression**
  ? Bupropion may be agent of choice
Coming Attractions

Rotigotine (Neuropro®)

- Transdermal patch
  1, 2, 3, and 4 mg/24 hr found effective for severe RLS (Sleep Jun 2007]
- Approved for mild Parkinson’s disease
Patient Education

- Warn about potential for falling asleep during ADLs
- Taking with food can reduce nausea
- Educate about nonpharmacologic treatments
Conclusion

- RLS is common but underdiagnosed
- Ask about RLS symptoms if patient is seeking sleep medication
- Refer patients to support groups and neurologists
- RLS is treatable