Disclosures

I have no disclosures/financial interests that are relevant to the material in this presentation.

Objectives

Pharmacists:
1) Identify what iron studies are suggested for the evaluation of Restless Leg Syndrome.
2) Identify 2 classes of medications that are indicated for the treatment of Restless Leg Syndrome
3) Name one concern with the use of dopamine agonists for treatment of restless legs.

Technicians:
1) Identify when symptoms of Restless Leg Syndrome are most prevalent.
2) Identify at least 2 different dosage forms of iron.
3) Identify at least 2 uses for rotigotine patches.

70 MILLION Americans suffer from a sleep disorder
- Institute of Medicine 2005

Recommended Sleep

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Recommended Sleep (Hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older Adult</td>
<td>7-8</td>
</tr>
<tr>
<td>Adult</td>
<td>7-9</td>
</tr>
</tbody>
</table>

The Average Fitbit User

- Bedtime: 11:36 PM
- Wake Up: 7:17 AM
- Time Asleep: 6 HRS & 38 MINS
- REM Sleep: 1 HR & 37 MINS (21%)
- Light Sleep: 3 HRS & 55 MINS (52%)
- Deep Sleep: 1 HR & 7 MINS (15%)

These results are averages based on Fitbit users' sleep data collected in 2017.
Sleep vocabulary

- Rapid eye movement (REM) - dreaming
- Slow wave sleep - non-REM deep (stage III sleep)
- Polysomnogram (PSG) - sleep study
- Sleep latency
- Wake after sleep onset (WASO)
- Total sleep time (TST)
- Sleep efficiency (SE)

Graph showing sleep stages (Awake, Stage 1 and REM, Stage 2, Stage 3, Stage 4) over a 4-hour period.

Effects of Sleep deprivation

- Irritability
- Cognitive impairment
- Memory lapses or loss
- Impaired moral judgement
- Severe yawning
- Hallucinations
- Symptoms similar to ADHD
- Impaired immune system
- Risk of diabetes Type 2

- Increased heart rate variability
- Risk of heart disease
- Increased reaction time
- Decreased accuracy
- Tremors
- Aches

Other:
- Growth suppression
- Risk of obesity
- Decreased temperature

Graph showing glucose levels (Low to High) with associated symptoms.
Blue Light and Associated Decreased Sleep Time

- Impairs memory next day
- Difficulty learning
- Increased neurotoxin accumulation
- Depression
- Increased risk of obesity
- Retinal damage
- Cataract risk
- Cancer risk

Medical Problems That Can Affect Sleep

- Heartburn
- Diabetes
- Heart Failure
- Arthritis
- Fibromyalgia
- Kidney Disease
- Nocturia
- Thyroid Disease
- Breathing Problems (Asthma/COPD)

Psychiatric
- Anxiety
- Panic Attacks
- Phobias
- Depression
- Bipolar Disorder
- Schizophrenia

Neurologic
- Dementia
- Seizures
- Headache/Stroke/Tumor
- Parkinson's
Sleep Disorders - Overview

- Abnormal Sleep Behavior
  - REM Sleep Behavior Disorder
  - Sleep Talking
  - Sleepwalking
  - Nightmares
- Circadian Rhythm Disorders
  - Non-24 Sleep-Wake Disorder
  - Shift Work Disorder
  - Delayed Sleep Phase Disorder
- Excessive Daytime Sleepiness Disorders
  - Excessive Sleepiness
  - Narcolepsy
  - Idiopathic Hypersomnia
- Insomnias
  - Acute
  - Chronic
  - Comorbid
  - Mixed
  - Maintenance
- Sleep Related Movement Disorders
  - Restless Leg Syndrome
  - Periodic Limb Movements in Sleep
  - Teeth Grinding
- Sleep Related Breathing Disorders
  - Obstructive Sleep Apnea
  - Central Sleep Apnea

Sleep Disorders and Mental Health

- Sign of Depression
- Sign of Mania
- Worsening of anxiety/OCD/Panic Disorder
- Substance induced sleep disruptions
**RLS Prevalence**

Women are twice as often affected than men.1,2

<table>
<thead>
<tr>
<th>Age Groups (year)</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>1.4%</td>
</tr>
<tr>
<td>30-39</td>
<td>7.8%</td>
</tr>
<tr>
<td>40-49</td>
<td>13.6%</td>
</tr>
<tr>
<td>50-59</td>
<td>23.4%</td>
</tr>
<tr>
<td>60-69</td>
<td>30.8%</td>
</tr>
<tr>
<td>70-79</td>
<td>34.6%</td>
</tr>
<tr>
<td>80+</td>
<td>38.2%</td>
</tr>
</tbody>
</table>

**Chronic persistent RLS**

Vs.

**Intermittent RLS**

**RLS Mimics**

- Claudication
  - Relief at rest, worse during movement
  - No circadian pattern
  - Venous stasis
  - Edema and skin alteration
  - No circadian pattern

- Hypotensive akathisia
  - Relief at rest, worse with sitting
  - No circadian pattern

- Painful legs and moving toes
  - No sensory discomfort
  - No circadian pattern
  - Neuropathic pain
  - Not relieved with movement
  - Peripheral neuropathy
  - Stocking glove distribution
  - Vesper's cue
  - Lumbosacral pain

**RLS Mimics cont'd**

- Sleep-related leg cramps
  - Palpable tightening of muscle
  - Alleviated by stretching but not movement
  - Positional discomfort
  - Relaxed with change of posture
  - No circadian pattern

- Arthritis
  - Confined to a joint, joint erythema
  - Growing pain
  - Relaxed with local massage and stretching

- Anxiety
  - Volitile movements of the legs without sensory discomfort

- ADHD
  - Inattention, hyperactivity, disruptive/impulsive behavior

- Volitional foot tapping
  - No urge to move
  - Reduced awareness of the movement

- Drug induced akathisia
  - Body rocking/whole body movements in setting of neuroskeletal
Approach to Patients with Restless Legs

- URGES
  - U - URGE to move the legs
  - R - Worse with REST
  - G - GET UP helps with symptoms
  - E - Worse in the EVENING
  - S - Not secondary to SOMETHING ELSE

- Identify any current precipitants:
  - Iron deficiency
  - Medications especially antidepressants
  - Family history (genetic)

Ask about RLS!

- Uncomfortable leg sensations
  - Creepy
  - Crawly
  - Tingy
  - Painful
  - Burning
  - Achy
- 5% - 10% prevalence
- 21% during pregnancy
- “Growing pains” in peds

Check Ferritin, Transferrin Saturation, and CRP

- Ferritin goal >50 and not in setting of acute inflammation
- Transferrin saturation goal >20%

Iron

- Ferritin goal >50-75
- Ferric carboxymaltose (Injectfer) IV
  - 500mg IV q5 days x 2 doses for treatment of moderate to severe RLS
  - Evidence for use of iron sucrose or dextran is lacking
- Oral iron (ferrous sulfate, ferrous gluconate)
  - 325 mg daily, repeat ferritin in 6-12 months
  - Constipating
  - Give with vitamin C (acidic) to increase absorption
  - Enhances iron uptake by an intracellular reductive mechanism AND is capable of regulating iron iron responsive element binding proteins (IRP-IRE) and hypoxia inducible factor systems (HIF)
Why Dose Iron Supplement Once a Day?

- Oral iron once a day is almost equally effective as twice-daily dosing due to greater hepcidin induction with more frequent dosing
- Major side effects of iron supplement = nausea and constipation
- If iron not well tolerated it can be taken with food, but this will likely decrease absorption.
- Dosing once every other day may be considered, but seems likely to decrease compliance.

Baseline ferritin >100

Baseline ferritin <75

Wang et al, Sleep Medicine 2009

What's the deal?

- Dramatic response to levodopa suggested brain dopamine deficiency
  - More recent research suggests that problem is actually increased dopamine production
    - However, dopamine antagonism appears to be effective secondary to antagonism of afferent glutamatergic terminals leading to reduced hyperactivity in corticostriatal pathways
    - Increased thalamic glutamate levels have also been seen
    - Stimulation from glutamate can lead to arousal and sleep loss
- Most RLS patients have sufficient peripheral iron measures
  - Deficiency appears to be in the CNS stores
  - Hyperdopaminergic and hyperglutamatergic states → dysregulation and downregulation of adenosine A1 receptors → dopamine release in striatum
  - Impaired transport across the blood-brain barrier (genetic)
- Dopamine agonist and gabapentin/pregabalin appear to counteract glutamate release in the hypersensitive corticostriatal glutamatergic terminals

1/200 people have hemochromatosis genes
Do not give supplemental iron because their hepcidin does not shut down iron absorption
  - If transferrin saturation < 45% safe to proceed with supplemental iron;
  - If transferrin saturation > 45% do not give iron treatment.

Dopamine Agonists
- First line
- Augmentation
  - 0-30% and rebound risk (levodopa > pramipexole or ropinirole)
- Pramipexole (~$10)
  - 0.125mg QD, 2-3 hours before bed, increase by 0.125mg q4-7 days (max 0.5mg/day)
- Ropinirole (~$10)
  - 0.25mg QD, 1-3 hours before bed, increase by 0.25mg q2-3 days (max 4mg/day)
  - Augmentation <4% per year
- Rotigotine (Neupro) topical patch (~$620)
  - 1-3mg/day patch
  - Augmentation 4% per year
  - Similar efficacy to pramipexole
  - Also used for Parkinson's
  - Has antidepressant effects
**Augmentation**

- Paradoxical worsening of symptoms
- Symptoms become more severe and start at an earlier time
- Symptoms may spread to other parts of the body such as the arms

**WARNING - EXCESSIVE Pleasure Seeking**

**GABA Analogues**

- **Gabapentin (~$5-$20)**
  - 100-300mg QDAY-BID between late afternoon and 2 hours before bed. Increase 100mg q7 days (max 3600mg/day)
  - Most patients require <1800mg/day
  - Good alternative for patients who experienced augmentation with dopamine agonists

- **Gabapentin enacarbil (Horizant) (~$350)**
  - 600mg at ~5pm
  - Prodrug of gabapentin
  - Increased bioavailability (~2X) vs gabapentin
  - 600mg of enacarbil should be converted to 300mg of gabapentin

- **Pregabalin ($185-$339)**
  - 100mg 1-3 hours before bed. Increase 300mg/day q7 days (max dose 450mg/day, divided)
  - At least as effective as pramipexole 0.25-0.5mg
  - Worsening of symptoms = ~2%

**Opioids**

- **Oxycodone/naloxone ER (Targiniq ER)**
  - 100-300mg QDAY-TID, increase by 50mg q3-q7 days (max 400mg/day, divided)
  - Augmentation (≥70%). Preferred for intermittent RLS (quick onset and short duration), not non-intermittent

- **Methadone, hydrocodone, codeine, tramadol have all been used**
  - May worsen sleep apnea!
  - Negligible augmentation risk

**Others**

- **Levodopa/carbidopa (~$5-$15)**
  - 25-50mg QDAX-TID, increase by 50mg q3-q7 days (max 400mg/day, divided)
  - Augmentation (≥70%) Preferred for intermittent RLS (quick onset and short duration), not non-intermittent

- **Cabergoline ($280-$1125)**
  - 0.5mg QDAX (max 2mg/day)
  - LAST LINE (cardiac valvulopathy, fibrosis)
  - Augmentation ≤4%/year

- **Carbamazepine (~$5-$12)**
  - 100mg HS, increase up to 200mg/day q7 days (max 300mg/day)
  - Lacks evidence, bone marrow suppression risk, auto-inducer, interaction risk

- **Clonidine (~$5-$10)**
  - 0.1mg 1-2 hours before bed, increase by 0.1mg/day q7 days (max 1mg/day)
  - Lacks evidence
Mirtazapine
- Anticholinergic
- Some evidence suggests improvements in insomnia in depressed patients.
- Weight gain concerns (can be used as an appetite stimulant)
- Worsens restless leg symptoms in ~33% of patients

Risk of suicide?
- 2019 health claims database association study
- 2.7 fold higher risk for suicide or self-harm after adjustment for other potential confounders
- Given the numerous study limitations, consideration of suicide risk factors and suicidal ideation may be prudent

Alternatives
- Yoga- eight week pilot trial
- Aerobic exercise in renal patients
  - Giannaki CD et al. Nephrol Dial Transplant. 2013
  - Sakkaas GJ, ASAIO J. 2008

How about cannabis?
- One case series of 6 patients as of January 2021
- Confounders including use of dopamine agonists, gabapentin, or opioids
- Safer compared to the risk of impulse control disorders from dopamine agonists???

Key points
- Restless leg syndrome is a clinical diagnosis
- Iron supplementation and/or gabapentin/pregabalin are considered first-line therapies
- Augmentation is common with dopamine agonists
- Opioids may be indicated for severe RLS
- The horizon of RLS treatment appears to involve adenosine A1 receptors in the striatum that are responsible for inhibitory control of glutamatergic neurons
  - Dipyridamole (CV effects) inhibits presynaptic reuptake of adenosine → significant improvement
Objectives

1) What iron study goals are suggested for the evaluation of Restless Leg Syndrome?
   Ferritin >50, transferrin saturation >20%
2) Name at least one concern with the use of dopamine agonists for treatment of restless legs?
   Augmentation, Excessive pleasure seeking behavior

References

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