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Disclosure:

• A Randomized, Placebo-Controlled, Double-Blind, Crossover Study of Oral BTD-001 in Adults With Idiopathic Hypersomnia

• An Open Label Expanded Access Program Intended to Provide Treatment With HBS-101 (Pitolisant) to Adult Patients in the U.S. With Excessive Daytime Sleepiness Associated With Narcolepsy With or Without Cataplexy

• Phase 2, Placebo-Controlled, Parallel Group Dose-Finding Study to Evaluate the Efficacy and Safety of Three Dose Levels of AD036 in Adults With Obstructive Sleep Apnea
Diagnostic Criteria:

• An urge to move the legs, usually accompanied by an uncomfortable and unpleasant sensation in the legs. The symptoms must
• Begin or worsen during periods of rest or inactivity such as lying or sitting
• Be partially or totally relieved by movement—at least while activity continues
• Occur exclusively or predominantly in the evening or night
Restless Legs Syndrome

- The above features are not solely accounted for by another medical or behavioral condition:
  - ➢ leg cramps
  - ➢ is there a muscle knot?
  - ➢ positional discomfort
  - ➢ does the sx go away with a single movement
  - ➢ neuroleptic-induced akathisia
  - ➢ appear after use of an anti-dopamine medication
  - ➢ involves whole body
  - ➢ no circadian rhythmicity
  - ➢ arthritis, myalgia, venous stasis, habitual foot tapping
RLS

• The symptoms cause concern, distress, sleep disturbance, or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning.
Supportive features:

• Family History of RLS
• Response to dopaminergic medication
  • There is a placebo effect
• PLMS on a PSG
Additional Supportive Features:

• Symptoms during provocative states
• Forced immobilization
• Tell me about experience in airplanes
• Oh, you hate going on airplanes and never fly, tell me about long car rides or really boring meetings at work
• Pregnancy
• Bedsheets in disarray
Demographic features:

- Prevalence estimates vary—5% to 10%
- Lower in Asian populations—1% to 8%
- Least in African populations—<1%
- Twice as common in women but based on parity
- Nulliparous women have similar prevalence to men
- Note: no sex difference in prevalence rates in children
- Prevalence increases with number of pregnancies
- More prevalent with increasing age up to 60-70
- Age-related increase not seen in Asian populations
Secondary RLS

- Systemic Iron deficiency
- 25-35% of patients with iron-deficiency anemia
- Frequent blood donors
- Even mild iron deficiency
- Ferritin levels above normal but below 50-75 mcg/L
- Pregnancy
- Prevalence increases through the pregnancy
- Generally resolves within one month post-partum
- Often gone immediately post-delivery
- Associated with FH or personal history of RLS
Secondary RLS:

• End-Stage renal disease
• Resolves with renal transplant
• Antidepressants
  • Least with bupropion/trazodone
  • Worst with mirtazapine
Conditions associated with RLS:

- Psychological
  - Anxiety/depression/PTSD
  - ADHD
- Neurologic
  - 25% of patients with ADHD have RLS
  - 12-35% of patients with RLS have ADHD
  - MS/CVA/migraine/PD/narcolepsy/peripheral neuropathy
Conditions associated with RLS:

- Cardiovascular Diseases
  - Cross-sectional studies indicate increased odds ratio for cardiovascular disorders in patients with RLS
  - Prospective studies have mixed results
  - Mechanism could be increase in sympathetic activity with PLMS

- General Medical disorders
  - DM, COPD, DM, rheumatoid arthritis, thyroid disease
Exacerbating Factors:

• Sleep Deprivation
• Alcohol
• Smoking
• Caffeine
Genetics:

- Early Onset RLS (younger than 45 y.o.) often familial
- 40-92% with FH
- If RLS is present, 1st degree relatives had a 2 to 6 x greater prevalence than general population
- Inheritance is complex
Genetics:

- GWAS nucleotide polymorphisms seen in
  - BTBD9
  - MEIS1
  - MAP2K5
  - PTPRD
  - SKOR1
  - TOX3
Pathophysiology:

• Two clinical issues
• Hyperarousal
• PLMS/akathisia
Pathophysiology:

- BID -> ? Dopamine hyperactivity -> DR2 downregulation.
- Circadian influences of dopamine level
Pathophysiology:

• Dopamine Dysfunction
  – Hyper-dopaminergic state resulting in downregulation of D-2 receptors
  – Extreme circadian falls in DA levels
  – OK early in day
• Relatively dopamine-deficient (hypo-dopaminergic) later in the day
• Secondary to low iron in the brain
• Involves Adenosine (low) and Glutamate (high) as well
RLS and iron deficiency

• Noted in early descriptions of RLS by Ekbom and Nordlander
• High prevalence of RLS in iron-deficient anemia population (c. 30%)
• RLS is present without systemic iron deficiency
• BID (brain iron deficiency)
• Decreased iron in SN, putamen, caudate, thalamus
• Impaired iron transport into the brain combined with regional neuronal deficiencies
Augmentation

- Paradoxical worsening of RLS symptoms
- Increase in intensity
- Moving earlier
- Involving more body parts
- Long-term or high-dose DA agonist use
Diagnostic tests:

- PSG not necessary
- History and Physical exam
- Check for peripheral neuropathy
- Check iron stores
- Ferritin
  - Normal 20-500 mcg/L (some variability)
  - Below 50-75 mcg/L is considered precipitating factor for RLS
Is Polymonography needed?

- Diagnosis is uncertain
- No circadian rhythmicity (often occurs when long-standing)
- Pt uncertain if symptoms are relieved with motion
- RLS symptoms minimal but subjective sleep disruption is high
- Look for other disorders such as OSA
- Sleep disruption continues despite RLS treatment
- To diagnose PLMD
Treatment of RLS

- Eliminate exacerbating factors
- Behavioral therapies
- Non-pharmacologic treatments
- Medications
Exacerbating factors

• Medications
  • Antidopaminergics
  • not just antipsychotics—anti-nausea medicines such as metoclopramide
  • Sedating antihistamines
  • Antidepressants
  • NB: Wellbutrin least likely to be a problem
• Low iron stores
• Substances
• Coffee/alcohol/tobacco
• Sleep deprivation
• Sedentary Lifestyle
Behavioral modifications

- Eliminate exacerbating factors
- Maintain a healthy sleep schedule
- Look for sedating antihistamine use
- Discuss potential role of antidepressants on RLS/WED
- Eliminate tobacco
- Avoid caffeine/alcohol near bedtime
- Evaluate iron stores
- Engage in regular exercise
- Massage the legs before bedtime
- Warm bath
Treatment of RLS

• First-line treatments, after assuring adequate serum iron levels:
  • – DA-ergic
  • – Alpha-2-delta ligands
  • Scales are tipping more toward the latter
• • Comorbid depression, prominent daytime symptoms consider DA-ergic
  • Lowest dose
  • Longest half-life
• • Comorbid pain, insomnia, contraindication to DA-ergic medication, consider alpha-2-delta ligand
Dopaminergic treatment:

- Lowest effective dose
- Worrisome side effect
- Impulse control disorders
- Gambling/hypersexuality/compulsive shopping
- May not show up until 9 months after beginning treatment
- Augmentation
- Most common side effect
- Nausea
- Other side effects
- Orthostatic hypotension (dizziness)/Nightmares/Fatigue/Sleepiness/insomnia
- Metabolism
- Most renal
- Pramipexole, rotigotine (some hepatic), carbidopa/levodopa
- Hepatic
- ropinirole
Alpha-2-delta Ligands

- No significant augmentation
- Particularly effective if sensory symptoms or sleep complaints are primary
- Concern for dizziness, unsteadiness, daytime sleepiness (morning hangover) can limit tolerance
- Less frequently depression, weight gain
- Inhibit glutamate release presynaptically
Iron supplementation:

• 1. Serum ferritin <= 75 mcg/L
• 2. TSAT% < 45% Worried about hemochromatosis
• 3. No contraindications
• 4. Ferrous sulfate 325 mg with vitamin C 100 mg once to twice a day
• 5. Repeat iron studies after 3 months
Treatment with IV iron

1. Serum ferritin between 75 and 100 mcg/L with TSAT% < 45%
2. Oral iron treatment failure or oral iron contraindicated
3. IV preparations:
   1. Ferric carboxymaltose 1000mg over 15’ or 500 mg over 7.5 minutes twice, 5-7 days apart
   2. LMW Iron Dextra 975 mg over
   3. 4 hr after 25 mg test dose
4. Serum iron studies 6-12 weeks after infusion
5. Repeat infusion if response and RLS sx’s return or worsen >= 12 weeks after infusion and serum levels indicate fall in peripheral iron status and serum ferritin is <300 with TSAT% < 45%
RLS in pregnancy:

- Non-pharm therapies
  - Exercise/yoga/massage/Pneumatic compression devices
  - Avoid aggravating factors
  - Treat concomitant OSA
- Iron
  - Oral if ferritin <75 mcg/L—controversy over safety of vit C
  - IV 2nd or 3rd trimester to avoid embryogenesis if failed oral iron and ferritin <30 mcg/L
- Medications
  - Clonazepam
  - L-DOPA/carbi-DOPA
  - Opiates if severe and failed all of the above
RLS in pregnancy:

- **Clonazepam**
  - 2nd/3rd trimester and lactation
  - 0.25 to 1 mg qhs
  - Avoid use with anticonvulsants or diphenhydramine (increased fetal mortality possible)

- **Cabidopa/levodopa**
  - Avoid benzaseride
  - 25/100 to 50/200 ER qhs

- **Refractory or very severe**—IRLS score >30 and failure to respond to at least one non-pharm, iron, 1 non-opioid pharm
  - Oxycodone 5-20 mg/d
  - Only after 1st trimester
  - For lactation
  - Gabapentin 300-900 mg qhs
  - Low-dose clonazepam 0.25-1 mg in the evening
  - Tramadol 50-100 mg/d only if RLS very severe/refractory
Augmentation:

- Increase in symptom severity without obvious provocative factor in a pt who has responded to Rx PLUS either of the 2 below:
  - Earlier onset of symptoms
  - Either earlier onset by at least 4 hours OR
  - Earlier onset between 2 - 4 hrs with at least one of the following
    - Shorter latency to symptoms when at rest
    - Spread of symptoms to other body parts
    - Increase intensity of symptoms
    - Duration of relief from treatment is shorter
    - Paradoxic response to Rx adjustment
      - Worsening of symptoms with ↑ dose
      - Improvement of symptoms with ↓ dose
Mimics of augmentation:

- Worsening because of exacerbating factors
- Natural progression of disease
- Tolerance to medication
  - May precede augmentation
- End-of-dose rebound
Augmentation:

• Primarily seen with DA-ergics
• – Associated with shorter half-lives
• Also seen with tramadol and rarely gabapentin
Treatment of Augmentation:

• • Differential diagnosis
• – Worsening because of an extrinsic factor
• • Evaluate and eliminate exacerbating factors
• – Lifestyle changes
• • Sleep deprivation
• • ↓ mobility
• • Change in alcohol use
• – Medications
• • Watch for antihistamines
• • New antidepressant
• • Anti-nausea agent
• • Assure serum ferritin > 75 mcg/L to 100 mcg/L
Pharmacological treatment:

• A. Switch to a longer-acting dopaminergic medication
  • Rotigotine
• B. Switch to an α2δ ligand
  • Cross titrate - gradually decrease dopaminergic while titrating up the α2δ ligand
• C. Gradually decrease dose and have patient without any medication for 10 days (“10 day washout”)
  • Then treat with medication if necessary: α2δ ligand or opiate
Pharmacological treatment

• If these do not work, switch to opiate
  • A. Long-acting oxycodone
  • B. Methadone
Periodic Limb Movement Disorder

- Rare as PLMS generally associated with other disorders
- Associated with mood disorders, anxiety, attention deficits, oppositional behaviors, and parasomnias.
- See in patients with FH of RLS
- Increased prevalence with age, minimized when those with RLS or FH of RLS are excluded
- No gender preference
- More common in whites than blacks
Periodic Limb Movements of Sleep

- Duration: 0.5” to 10”
- Amplitude: ≥ 8 microvolt ↑ above baseline
- Separated between 5” and 90”
  - From onset of one to onset of another
  - If movements on 2 legs separated by <5”, then scored as a single movement
- Minimum of 4 in a row (can go thru wake)
- Associated with an arousal if overlaps with arousal or if separated from arousal by < 0.5” between end of one and onset of the other
- Must not be scored if near a respiratory event
- LM should not be scored if it occurs from 0.5” before, during, or within 0.5” after a respiratory event
PLMS

- • RLS
- • Narcolepsy
- • RBD
- • increase in frequency with age
- • Antidepressant medications