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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
 - 25% of patients with ADHD have RLS
 - 12-35% of patients with RLS have ADHD
- Neurologic
 - 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
 - 1- 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
 - • Paradoxical 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 $\alpha_2\delta$ ligand
 - Cross titrate - gradually decrease dopaminergic while titrating up the $\alpha_2\delta$ ligand
- C. Gradually decrease dose and have patient without any medication for 10 days (“10 day washout”)
 - Then treat with medication if necessary: $\alpha_2\delta$ 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 \uparrow 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

