FMC Sleep and Respiration Rounds

Presented By
Dr. Michael Braganza
University of Calgary

Wednesday, October 17, 2018
Restless Legs Syndrome
Case Presentation and Literature Update

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Dr. Michael Braganza, MD
University of Calgary

Wednesday, October 17, 2018
Lunch: 11:30am
Presentation: 12:00-1:00pm

Room 01500
O’Brien Centre
Health Sciences Centre

The Sleep and Respiration Rounds in the division of Respiratory Medicine at the University of Calgary is a self-approved group learning activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada.

Supported by an unrestricted educational grant from Fisher & Paykel
Case Presentation

**ID:** 63F referred Oct 2017

**Profile:** Migraines, Acid Reflux

**Medications:** Demerol 25-50mg qhs

**History:**
- Ropinirole > 5 years
- Symptoms worsened
  - arms
  - earlier / during wakefulness
  - symptoms were more severe
  - pain
- Rapid ↑ in ropinirole dose
  - symptoms worse
- Slept prone position
  - corneal abrasions
- Tried:
  - pramipexole, rotigotine patch
  - gabapentin, pregabalin
  - clonazepam and diazepam
  - levodopa
  - topiramate
- Suicidality on benzodiazepines
- IRLS score 40

**RFC:** Severe RLS

**Profile:** Migraines, Acid Reflux, RLS

**Medications:** Demerol 25-50mg qhs

**WHAT WE DID IN October 2017...**
- Ferritin 73μg/L (normal, but ↓ 75):
  - Started IV Iron Sucrose (Venofer) 100mg q1m x 3 months
- Follow up visits
  - Ferritin 173 ug/L
  - Symptoms: No better IRLS 40
- What now?
Restless Legs Syndrome

Goals

- Increase Awareness of RLS
- Pathophysiology
- Secondary Causes
- Treatments
  - Iron Therapy
  - Dopaminergic
  - Opioids
- Augmentation
- Case Presentation
Restless Leg Syndrome

Diagnostic Criteria
Criteria A-C must be met
A. An urge to move the legs, usually accompanied by or thought to be caused by uncomfortable and unpleasant sensations in the legs. These symptoms must:
   1. Begin or worsen during periods of rest or inactivity such as lying down or sitting;
   2. Be partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; and
   3. Occur exclusively or predominantly in the evening or night rather than during the day.
B. The above features are not solely accounted for as symptoms of another medical or a behavioral condition (e.g., leg cramps, positional discomfort, myalgia, venous stasis, leg edema, arthritis, habitual foot tapping).
C. The symptoms of RLS cause concern, distress, sleep disturbance, or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning.

Restless Legs Syndrome

• Misnomer
  • 21-57% describe arm sensation
• 50% describe pain but rarely in isolation
• Difficult to describe “unpleasant”
  • “uncomfortable”
  • “twitchy”
  • “heebie jeebies”
  • “pulling”
  • “wriggling maggots”
• “Elvis Legs”
• “fidget”
• “electric”
• “I need to move”
• “tingling”
Epidemiology

• 5-15% of adult caucasian populations
  • 2-3% are clinically significant
  • Prevalence varies by region-latitude gradient
    • <0.1% in Equatorial Regions
    • 15% in Scandinavian countries
• Female Prevalence
  • F=M when evaluating nulliparous women
  • Prevalence is 2-3X greater in pregnancy
• Age of Onset
  • <45 years old
    • Hereditary
      • 40-92% will report affected family member
      • BTBD9 / MEIS1 / MAP2K5 / LBX1
  • > 45 years old
    • Tends to secondary
    • Often more responsive to iron therapy

Restless Legs Syndrome

• Symptoms
  • Motor symptoms
    • Periodic Limb Movements of Sleep/ Wakefulness
  • Sensory symptoms
    • Akathisia
      • Feeling of restlessness the exists in the absence of moving
      • Associated with suicidal ideation
  • Excessive Daytime Sleepiness
    • Poorly characterized by ESS
    • Hyperarousal state that counters sleep homeostasis
      • Short sleep time with persistent disruptions
      • Lack of profound sleepiness expected for short sleep time
Pathophysiology

- Poorly understood
  - Multiple pathways → common clinical syndrome
  - Central and Peripheral Nervous System
- Genetics
  - Heritability in twins studies 50-60%
  - Genome wide association studies:
    - 6 Candidate Risk Loci:
      - MEIS1, BTBD9, PTPRD, MAP2K5, SKOR1, TOX3
Pathophysiology

• Central
  • Reduced Iron stores is **main consistent finding**
    • Reduced Iron stores in striatum, thalamus, red nucleus
    • CSF-Ferritin is lower compared to controls
  • Dysregulation of iron transportation by blood brain barrier
    • Transferrin serum levels are elevated in RLS vs Control


Pathophysiology

• Central
  • Reduced Iron stores is **main consistent finding**
    • Reduced Iron stores in striatum, thalamus, red nucleus
    • CSF-Ferritin is lower compared to controls
  • Dysregulation of iron transportation by blood brain barrier
    • Transferrin receptor in brain is low

Pathophysiology

- Central
  - Hyper-Dopaminergic System
    - Counterintuitive: We give DA agonists to RLS patients
    - Little pathologic evidence to prove deficiency
    - Likely hyperdopaminergic state with increased turnover
      - Dopamine metabolite 3-OMD increased in CSF
      - Presynaptic hyperdopaminergic state with increased synthesis
    - Potentially inefficient / dysregulated release of dopamine
      - May be related to brain iron deficiency
      - Bypass a blockage point?

Pathophysiology

- Central
  - Hyper-Glutamatergic System / NMDA receptor
    - Likely involved in the arousals mechanism
    - Glutamate levels are increased in thalamus
      - Ketamine (inhibits NMDA) improves RLS
      - Methadone (antagonizes NMDA) is highly effective
  - Hypo-Adenosinergic
    - Adenosine modulates ascending dopaminergic system
    - Prolonged wakefulness → Adenosine release → Mediates sleepiness
    - Brain iron deficiency is related to low central adenosine levels
  - Higher CSF hypocretin
Pathophysiology

- Peripheral
  - Fact that legs > arms are affected points to spinal cord pathology
- PLMS resembles spinal cord reflexes
  - Dorsiflexion of ankle, flexion of knee and hip
  - RLS patients have lower reflex thresholds in ESRD
    - reflex hyperexcitability might be involved in generating PLMS.
- Diencephalic Tract (A 11)
  - Involved in suppressing sensations and requires dopamine
  - Animal models where they injure this tract seems to cause ‘restlessness’
    - Dopaminergic medication administration seems to decrease this restlessness

So its complicated...

Figure 6. Integrative scheme of the pathogenetic mechanisms involved in the periodic leg movements during sleep (PLMS), akathisia and arousal components of restless legs syndrome (RLS; see text: Conclusion and Future Directions).
Secondary Causes of RLS

• Fe Deficiency
  • Free iron
  • Daily variance can be 50%
  • Ferritin
  • Serum levels ≠ CNS levels
• Renal Failure
  • 33% of IHD patients
  • RLS have higher mortality
  • Responds by renal transplant
    • Re-emerge with transplant failure
• Neuropathy
  • DM / EtOH / Idiopathic

• Pregnancy
  • 25%, typically resolves at 3rd trimester
  • May be related to estradiol levels/folate/iron levels
• Multiple Sclerosis
  • 30%
  • Spinal Cord Lesions are much more likely to have RLS vs just brain
• Medications
  • Antihistamines (CNS involvement)
    • Sedating (Benadryl)
  • Antipsychotics
  • Antidepressants

Treatment
### Restless Legs Syndrome Rating Scale

**Clinical Global Improvement Scale (#2)**

1. **Severity of Illness:**
   - Considering your total clinical experience with this particular population, how severely ill is the patient at this time?
     - 0 = Not assessed
     - 1 = Normal, not at all ill
     - 2 = Moderately ill
     - 3 = Severely ill
     - 4 = Very severely ill

2. **Global Improvement:**
   - Rate overall improvement whether or not, in your judgement, it is due entirely to drug treatment.
     - Compared to his condition at admission to the project, how much has he changed?
     - 0 = Not assessed
     - 1 = Much improved
     - 2 = Moderately improved
     - 3 = Minimally improved
     - 4 = Much worse
     - 5 = Markedly worse

3. **Efficacy Index:**
   - Rate this item on the basis of drug effect only.
   - Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

<table>
<thead>
<tr>
<th>Therapeutic effect</th>
<th>Side effects</th>
<th>Do not significantly interfere with patient's functioning</th>
<th>Significantly interferes with patient's functioning</th>
<th>Outweighs therapeutic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked</td>
<td>None</td>
<td>01</td>
<td>02</td>
<td>06</td>
</tr>
<tr>
<td>Moderate</td>
<td>02</td>
<td>03</td>
<td>04</td>
<td>07</td>
</tr>
<tr>
<td>Minimal</td>
<td>07</td>
<td>11</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Unchanged or worse</td>
<td>15</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

## Treatment

### Pharmacologic
- Iron Supplementation
- Dopaminergics
- Alpha 2 Delta Ligands
- Opioids
- Methadone
- Vit C / Vit E (ESRD)

### Non Pharmacologic
- Massage
- Warm bath
- Neurostimulation
- Exercise
- CBT

### Exacerbating Factors
- Sleep Deprivation
- EtOH
- Tobacco use
- Caffeine
- Multiple Drugs
  - Antihistamines
  - SSRIs
  - SNRIs
  - Antipsychotics
Treatment: Placebo Effect

- Ondo (2013)
  - Boehringer Ingelheim
  - Patients who took placebo in 6 RCTs for pramipexole

- IRLS (n=879) - 9.5 points
  - Predictors:
    - Worse baseline IRLS score
    - Absence of previous DA agonist
    - Female sex
    - Being American (vs being from Europe)

- CGI placebo (n=726) 41.5%
  - Predictors:
    - Worse baseline IRLS score
In RLS, can there be a true placebo group?

Level 3 Test: RDI 14, SaO$_2$ 93.7%

Which breaths are normal?
Non-Respiratory Arousal Disturbance (PLMD)

Case # 17

PLMD
Rodrigues (2006)

- Evaluate nasal CPAP on
  - Daytime sleepiness
  - Restless Leg Symptoms
- Methods:
  - 17 OSA with RLS
  - PSG
  - Diagnostic then Therapeutic
  - Full night Therapeutic on previously determined pressure
- Epworth Sleepiness Score
- Pichot Questionnaire for fatigue

Reassessed them after 3 months of nCPAP

Rodrigues (2006)

- Results
  - BMI 34
  - AHI 44
  - ESS 11→7
  - Pichot 17→10 (still fatigued)
  - PLMI 32→8
  - IRLS 17→12
- "Does not imply that CPAP is a treatment for RLS symptoms"
  - IRLS improvement due to treatment of severe OSA
  - Placebo effect
  - PLMI may worsen

| Table 3 |
| Polysomnographic data and n-CPAP titration results of the 17 patients with the association OSAS + RLS |
| Mean ± SD |
| TST (h) | 4.8 ± 0.7 |
| SE (%) | 72.9 ± 12.3 |
| PS1-2 (%) | 70.3 ± 22.4 |
| PS3-4 (%) | 14.6 ± 9.8 |
| PREM (%) | 9.1 ± 6.9 |
| IAr (number/h) | 21.4 ± 9.5 |
| AHI (number/h) | 44.3 ± 27.5 |
| n-CPAP (cmH2O) | 9 ± 2.9 |

TST, total sleep time; SE, sleep efficiency; PS1-2, percentage of stages 1 + 2; PS3-4, percentage of stages 3 + 4; PREM, percentage of REM sleep; IAr, index of arousals; AHI, apnea–hypopnea index; n-CPAP, positive pressure level.
CPAP

- Rodrigues (2007)
  - Prospective Comparison
    - 13 patients with OSA VS 17 patients with OSA+RLS
  - Methods:
    - ESS and Pichot were applied before and after 3 months of CPAP
  - Results:
    - Both groups had similar ESS and Pichot scores at baseline
    - OSA+RLS patients had higher ESS and PIC scores compared to OSA alone

<table>
<thead>
<tr>
<th>Fatigue score</th>
<th>Group 1 (OSAS)</th>
<th>Group 2 (OSAS+RLS)</th>
<th>p (between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIC (before CPAP)</td>
<td>11.7±6.6</td>
<td>16.6±7.3</td>
<td>0.08</td>
</tr>
<tr>
<td>PIC (after CPAP)</td>
<td>5.1±6.1</td>
<td>10.1±6.4</td>
<td>0.03</td>
</tr>
<tr>
<td>p (within-group)</td>
<td>0.008</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

PIC, Pichot's questionnaire.

Treatment

- Why we give iron
  - Brain iron deficiency is associated/ causative of RLS
  - Lower ferritin associated RLS severity
  - Iron ↓ anemics have 6X increased prevalence RLS
  - Iron is potentially curative
- Blood levels ≠ CNS Levels
  - Patients can have brain iron deficiency despite normal Fe and ferritin levels
Treatment

- Reviewed 31 papers
  - Iron therapy for RLS or PLMD
- Iron Homeostasis
  - Tightly regulated
  - Most iron ingested is NOT absorbed
    - Mostly goes to RBC
    - 0.5-1.5% of ingested iron is available to CNS
- Hepcidin
  - Blocks absorption
  - Stimulated by inflammation
  - Stimulated by sufficient erythropoiesis
  - If Ferritin > 75 oral iron is effectively useless

Sleep Med. 2018 Jan;41:27-44

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Treatment

- Oral Iron
  - Poorly absorbed
    - Avoid ANY cations: Ca, Mg, Multivitamin
    - Should be taken with Vitamin C
  - Should be taken on an empty stomach
    - ↑ Nausea - Low compliance
  - Reassess RLS symptoms after 12 weeks

Sleep Med. 2018 Jan;41:27-44
Treatment

• Iron Therapy Review (Allen, 2017)
• IV Iron
  • Multiple formulations
  • Carbohydrate carrier that releases elemental Iron into the blood
• IV Brands: They are not all the same
  • Iron sucrose (Venofer)

5.4. IV Iron sucrose

5.4.1. Evidence-based guidelines
Iron sucrose, at a dose of 200 mg administered in five infusions is probably not effective (level B) for treatment of RLS in patients with serum ferritin <45 μg/L and at a dose of 500 mg given in two infusions over 24 h is possibly not effective (level C) for the treatment of RLS with serum ferritin <300 μg/L.

Sleep Med. 2018 Jan;41:27-44.

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Treatment

• Free Iron → RBCs and marrow
• Iron → Transferrin → WBC may reach CNS
• Faster Release
  • Higher doses overwhelm available transferrin
    • Must be given slowly, in smaller doses, over consecutive days
• Slower Release
  • Show greater increase in WBC iron concentrations

Labile Iron Pools in Parenteral Iron Products

Sleep Med. 2018 Jan;41:27-44.
Treatment

• Iron Therapy Review (Allen, 2017)
• Overall Message:
  • Iron most accurately assessed fasting AM
    • May not reflect CNS levels
  • Try oral iron if ferritin < 75 ug/L
  • Switch to IV iron if
    • Oral iron not tolerated
    • After 12 weeks of PO iron
  • Start with IV iron if
    • Moderate to Severe RLS
    • Ferritin 75-100ug/L
  • IV Iron Target
    • Ferritin 300ug/L, TSAT < 45%
Treatment

• Dopaminergics
  • Levodopa
  • Pramipexole
  • Ropinirole
  • Rotigotine
  • Cabergoline

• Originally anecdotal evidence from PD
  • Letter to the Editor in 1982
  • 5 patients treated for RLS
    • 200mg of Levodopa / 50 benserazide
    • RLS was cured
  • Levodopa was discontinued
    • RLS reappeared
    • Bromocriptine (DA agonist) worked

Treatment of Restless Legs Syndrome With Levodopa Plus Benserazide

To the Editor.—We treated five patients, three men and two women, with restless legs syndrome. Their ages ranged from 33 to 54 years, and the duration of their symptoms from two to 20 years. Their symptoms were moderate to severe in degree, and they were followed up for six to 18 months.

The symptom common to all subjects was a disturbing feeling in the legs urging them to move their legs; one also had pain. These symptoms appeared only during attempts to sleep and relaxation periods. Involuntary jerking movements of the legs, which occurred along with the preceding symptoms, made the patients uncomfortable and caused insomnia.


Treatment

• Dopaminergic Medication
  • Incredibly effective for limb movements
  • Long considered to be 1st line treatment for RLS

• Adequate iron levels may be necessary:
  • Iron is a cofactor for tyrosine hydroxylase
    • Rate limiting step for Dopamine synthesis
  • Iron may be regulating dopamine receptors
  • Iron may be involved in regulating dopamine release
  • Iron may increase D2R density in striatal cells

• They are extremely effective in short term
Treatment

• Dopaminergic Medications
• Side Effects
  • Impulse Control Disorders (gambling)
  • Nausea
  • Sedation
  • Nasal Congestion

Augmentation

• Worsening of RLS after initial improvement with dopamine medication
  • Can also occur with tramadol (weak opioid)
• Criteria
  • Earlier onset by at least 2 hours
  • Increased intensity of symptoms
  • Quicker onset with rest
  • Medication benefit does not last
  • Spread to other body parts
  • PLMW occur or get worse
• National RLS Program
  • 75% of referrals are due to Augmentation

Risk Factors
• Dopamine dose and time
• Shorter acting DA meds
• Family history of RLS
• Lack of Neuropathy
• Low Iron or Low Ferritin
Augmentation

- Levodopa 82%
- Pramipexole / Ropinirole
  - 7-8% / year
  - By 10 years 80%
- Rotigotine patch
  - 5% after 5 years (1-3mg)
  - Longer acting Is this a masking effect?
Augmentation

- Consider augmentation if a patient who has been stable (6 months) requests more medication

- Rule out
  - Triggers / Low Iron
  - Tolerance to current regime
    - Benzos / Opioids
  - End of Dose Rebound
    - Ropinirole 6-7 hours
    - Pramipexole 7-8 hours
  - Worsening of RLS / Natural progression
    - Very difficult to differentiate

Augmentation

- Prevention
  - Use A2Delta ligand
  - Keep ferritin levels high
  - Do not use DA agonists (or Tramadol)
    - Use the lowest dose possible
    - Do not increase the dose more than once
  - Do not change to another short acting DA
  - Consider long acting DA (rotigotine)
  - Use intermittent therapy
    - Up to 3d /week
    - Alternate with another drug
Treatment

• Alpha 2 Delta Voltage Gaited Calcium Channel
  • Receptors in Spinal Cord and Thalamus
  • Gabapentin
  • Gabapentin enacarbil
    • FDA approved
    • Better bioavailability and longer lasting effect
  • Pregabalin

Only FDA approved RLS drug in this class
Pregabalin vs Pramipexole

Richard (2014) - Efficacy and Augmentation

- Compared Pregabalin vs Pramipexole
  - 12 week placebo controlled
  - 40 week comparator controlled

Methods:
- IRLS ≥ 15
- Symptoms > 15/month X 6M
- No Augmentation
- Pfizer was sponsor
Comparison of Pregabalin with Pramipexole for Restless Legs Syndrome

Richard P. Allen, Ph.D., Crystal Chen, M.D., Diego Garcia-Borreguero, M.D., Ph.D., Olli Polo, M.D., Sarah DuBrava, M.S., Jeffrey Miceli, Ph.D., Lloyd Knapp, Pharm.D., and John W. Winkelmann, M.D., Ph.D.

Visits:
Week 0, 2, 6, 10, 14, then monthly
- IRLS severity scale
- Clinical Global Impression of Improvement (CGI-I scale)

Augmentation Review Board

Richard(2014)

Methods:
- Primary Endpoints
  - Pregabalin vs placebo:
    - Change from baseline to week 12 in IRLS score
    - Change from baseline to week 12 in CGI-I
  - Pregabalin vs pramipexole
    - Change from baseline to week 40 or 52 in augmentation
- Secondary Endpoints
  - Pregabalin vs pramipexole
    - Change from baseline to week 12 in IRLS score (short term comparison)
• Richard(2014)
• Results:
  • 719 patients from 102 centres
    • Pramipexole 0.5mg and pregabalin were effective compared to placebo
  • 52 weeks
    • Pregabalin vs Pramipexole 0.5mg
      • Noninferior

Comparison of Pregabalin with Pramipexole for Restless Legs Syndrome

- Richard Allen, Ph.D., Crystal Chen, M.D., Diego García-Borroregu, M.D., Ph.D.,
  Olli Polo, M.D., Sarah Dufra, M.S., Jeffrey Micieli, Ph.D., Lloyd Knapp, Pharm.D.,
  and John W. Winkelmann, M.D., Ph.D.

Table 1: Primary and Secondary Efficacy End Points, According to Study Group.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Pregabalin</th>
<th>Pramipexole, 0.25 mg Daily</th>
<th>Pramipexole, 0.5 mg Daily</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRLS score</td>
<td>Patients assessed — no.</td>
<td>177</td>
<td>169</td>
<td>178</td>
</tr>
<tr>
<td>Baseline</td>
<td>22.3±6.7</td>
<td>22.4±5.4</td>
<td>22.1±5.2</td>
<td>22.4±5.6</td>
</tr>
<tr>
<td>12 wk</td>
<td>10.9±7.3</td>
<td>14.6±7.3</td>
<td>12.0±7.5</td>
<td>15.4±7.1</td>
</tr>
<tr>
<td>Mean change from baseline vs. placebo (95% CI)</td>
<td>-4.5 [-5.8 to -3.2]</td>
<td>-0.4 [-2.0 to 0.7]</td>
<td>3.2 [4.5 to -1.5]</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>0.16</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Augmentation at 52 weeks
- 235 patients received pregabalin
  • 5 (2.1%) had augmentation
- 225 patients received 0.25mg pramipexole
  • 12 (5.3%) had augmentation
- 235 patients received 0.50mg pramipexole
  • 18 (7.7%) had augmentation
• Richard(2014)
• Results:
  • Adverse Events
    • Higher Discontinuation Rate
      • 27.5% (pregabalin)
      • 18.5% (0.25mg pramipexole)
      • 23.9% (0.50mg pramipexole)
    • Dizziness, Somnolence, Fatigue, HA
    • Suicidal Ideation
      • 6 patients vs 3(0.25mg pramipexole) vs 2 (0.50mg pramipexole)

• Richard(2014)
• Conclusions
  • Pramipexole 0.5mg is more efficacious than 0.25mg dose
    • 0.50mg is associated with significant augmentation
  • 300mg of pregabalin was as effective as pramipexole but had lower augmentation
  • Most patients who augmented did so >6 months into study
    • Treatment implications
Recommended 1st Line Drugs

Table 4
Factors that affect selection of an agent for initial treatment in patients with restless legs syndrome/Willis-Ekbom disease (adapted from Garcia-Borreguero et al. [43]).

<table>
<thead>
<tr>
<th>Factor that impacts the choice of agent</th>
<th>Treatment choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of day (daytime symptoms)</td>
<td>Preferably a long-acting agent</td>
</tr>
<tr>
<td>Sleep disturbance disproportionate to other symptoms of RLS/WED, eg. severe insomnia</td>
<td>Twice-a-day dosing of a short-acting agent</td>
</tr>
<tr>
<td>Pregnancy risk</td>
<td>α2A ligand</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>Avoid both DAAs and α2A ligands</td>
</tr>
<tr>
<td>Increased risk of falls</td>
<td>Consider the use of iron</td>
</tr>
<tr>
<td>Painful restless legs</td>
<td>Select a drug that is not renally excreted or reduce dose of renally excreted drugs</td>
</tr>
<tr>
<td>Constipated pain syndrome</td>
<td>Dopamine-receptor agonist</td>
</tr>
<tr>
<td>History of impulse control disorder</td>
<td>α2A ligand</td>
</tr>
<tr>
<td>History of alcohol or substance abuse</td>
<td>Dopamine-receptor agonist or α2A ligand</td>
</tr>
<tr>
<td>Very severe symptoms of RLS/WED</td>
<td>Dopamine-receptor agonist</td>
</tr>
<tr>
<td>Excess weight, metabolic syndrome</td>
<td>Dopamine-receptor agonist</td>
</tr>
<tr>
<td>Availability or cost of drug</td>
<td>Dopamine-receptor agonist</td>
</tr>
<tr>
<td>Constipated generalized anxiety disorder</td>
<td>Dopamine-receptor agonist</td>
</tr>
<tr>
<td>Higher potential for drug interactions</td>
<td>Select drug that is not hepatically metabolized</td>
</tr>
<tr>
<td>Symptomatic PLMS</td>
<td>Dopamine-receptor agonist</td>
</tr>
</tbody>
</table>
Side Effect Profiles

• Opioids
  • RLS involves both sensory (akathisia) and motor (PLM) which both respond to opioids
    • May treat sensory more than motor symptoms
  • This population is NOT the same as chronic pain population
    • Much less addiction
    • Much less tolerance
    • Doses can be stable for years
Natural CNS opiod System

Opioid Pathophysiology

• Treats both sensory (akathisia) and motor (PLM)
• Opioids Receptors found in CNS
  • Mu receptors
    • Morphine derivatives (synthetics) act here
  • Kappa receptors
  • Delta Receptors
  • Opioid like 1 receptors
• Post mortem of RLS patients
  • Thalamus:
    • Beta endorphin cells were reduced by 37.5%
    • Metenkephalin cells were reduced by 26.4%
  • Suggests imbalance in natural opiate system
Opioid Pathophysiology

- Opioids Mu receptors
  - Associated with dopamine receptors
  - Can also stimulate dopamine release
  - Pre treatment with a DA antagonist will negate benefits of opioids on RLS
  - Naloxone “antidote” to opioids
    - Give naloxone to RLS patient who is opioid naïve
      - No effect
    - Give naloxone in a blinded fashion to opioid treated RLS patients
      - RLS signs and symptoms reappear/worsen

Opioids

- Slightly different geometry
  - Different receptors interact with different pathways
  - If one fails, try another...
• Claudia Trenkwalder 2013
  • 12 week randomized, blinded, placebo controlled trial (N=276)
    • Oxycodone 5.0mg + Naloxone 2.5mg bid vs. placebo
      • Multicentre: 55 sites in Europe
        • Up titrated to max dose 40mg Oxycodone ER
        • Drug Company Funded (Mundipharma, maker of Reloxyn / Targin)
  • 40 week open label extension phase (N=197)
  • Primary outcome
    • Change in IRLS score at 12 weeks
      • Response = **50% decrease in score**
    • CGI score
      • “much improved” or “very much improved”

• Claudia Trenkwalder 2013
  • Inclusion
    • 6 months minimum of symptoms
      • Intolerable side effects or lack of efficacy on 1st line meds
      • Daytime onset of symptoms before 6PM 4 days per week
    • IRLS >15 (moderate to severe)
  • Excluded
    • Secondary RLS
    • Ferritin < 30
    • Previous/current use of DA antagonist
      • **AUGMENTATION**
• Claudia Trenkwalder 2013
  • Placebo-Controlled Phase (Week 1-12)
    • Tapered off meds for RLS x 7 days
    • Randomized to treatment vs placebo
    • Assessed
      • Week 1, 2, 3, 4, 8, 12
    • Both placebo and treatment were up titrated X 6 weeks
    • At week 12 both placebo and treatment were down titrated to
      5/2.5 mg dose prior to open label phase
  • Open Label Phase (Week 12-52, 40 weeks)
    • Assessed q4w

• Results- RCT 12 week phase
  • 304 enrolled
  • 67% completed 12 weeks
  • Discontinuation
    • 37% in placebo vs 29% in treatment
  • Mean oxycodone dose was 22mg vs 34mg of placebo
  • Modified Intent-to-treat analysis
  • “Responders” oxycodone vs placebo
    • IRLS 57% vs 31% (p=0.001)
    • CGI-2 67% vs 35% (p=0.001)
  • No augmentation
• Claudia Trenkwalder 2013
  • Results
    - 42% of patients were remitters
    - 0 on IRLS
    - No Augmentation @ 52 weeks
    - Mean dose Oxycodone 18mg

• Side Effects
  - 84% of treatment vs 73% placebo
    - In treatment group:
      - GI disorders
      - Pruritus
Methadone

- Fully synthetic, No morphine backbone
  - Mu
  - Delta
  - Kappa
- Non competitive inhibitor of NMDA Glutamate receptor
  - Antagonizes spinal cord NMDA receptors
  - Unique to methadone
- Half life it 10-60hrs
  - Less abuse potential

Methadone

- Average dose
  - 2.5-20mg/day
  - Far more effective for RLS than pain
  - Less tolerance to methadone for RLS than for pain
- Resensitizes Mu receptors
- Decreases opioid induced pain
Methadone

- 2 open label studies for refractory RLS
  - Onda (2005)
    - 27 patients who failed 2 DA
    - Tried 5.9 medications (range 3-9)
    - 74% had tried a narcotic
    - Most who stopped did so in Month 1
    - 23 had ‘sustained relief’
    - No Augmentation
    - 17 continued for 2 years
      - Average dose 15.5mg, max dose 40mg

- Silver (2011)
  - Retrospective review of patients treated between 1997-2007
  - Discontinuation rates
    - 9%/year pramipexole
    - 8%/year pergolide
    - 0%/year methadone
  - Max dose increase was only 10mg
  - No augmentation and persistent response
Case Presentation

ID: 63F referred Oct 2017
RFC: Severe RLS
Profile: Migraines, Acid Reflux, RLS
Medications: Demerol 25-50mg qhs

Progress:
- Venofer
  - Ferritin → 150
- Exercise Prescription
  - Made things worse. (Re ruled out claudication)
- Added small amount of ropinirole
  - Severe Augmentation
- Oxycodone/naloxone August 2018
  - Sleep time increased to 5hrs
  - Pain resolved
  - IRLS score 31→ Is this placebo?

Potential Next steps:
- Behavioural:
  - Day / Night Reversal
- IV Iron (isomaltoside)
- Methadone
- Gabapentin enacarbil
- Pneumatic Compression Devices
- Vitamin C
- Vitamin D
- Carbamazepine
- Clonidine
- Amantadine
- Clinical Trials

Questions?

Canada legalizes marijuana...
Extra slides

Neurostimulation

- Movement is effective in treating RLS
  - Counter stimulation
    - Rubbing thumb when you get hurt
  - Vascular theories
    - Low O2 causes movement
    - Improve vascular supply
- Transcranial direct current stimulus
- Transcranial magnetic stimulation
- Transcutaneous electrical nerve stimulation (TENS)

- Pneumatic Compression Device
- Vibratory stimulation in RLS
- Near infrared stimulation
- Acupuncture
Augmentation Severity Rating Scale

Pathophysiology

• Brain Iron Homeostasis
  • Most RLS patients do not show systemic iron deficiency (though iron deficiency confers a 6X elevated risk compared to general population)
  • CNS iron deficiency was first demonstrated in 2000
    • 10/12 imaging studies have shown reduced iron in the substantia nigra
  • BID has been shown in the epithelial cells of chorid plexus / brain microvasculature in RLS patients
Opioids

- Kappa Receptor Agonists
  - Pentazocine
    - ONLY kappa agonism
    - Not a very good pain medication
    - No constipation/bladder retention
    - Good for RLS
    - Tmax 1 hour, half life 4-6 hours
  - Oxycodone (mild)
  - Fentanyl (synesthetic) (mild)

Tramadol

- Synthetic opioid
- Effects serotonergic and NA pathways
- Mu receptor
  - 6000x less potent
- Associated with AUGMENTATION
Opioids

• Delta Receptor Agonists
  • Hydromorphone

• Opioid receptors are in
  • Dorsal Root Ganglia
  • Brainstem
  • Basal ganglia
    • Striatum
    • Substantia nigra

• Retrospective Case Series 2004
• 27 patients who failed 2 DA
  • Tried 5.9 medications (range 3-9)
  • 74% had tried a narcotic
• Range methadone 5-30mg day
  • Average initial 13mg
  • Average final dose was 15.5
Efficacy (Defined by 3/5) was sustained relief in 23 patients
1 person became addicted
11% became constipated

Pathophysiology

- Central
  - Reduced Iron stores is **main consistent finding**
    - Reduced Iron stores in striatum, thalamus, red nucleus
    - CSF-Ferritin is lower compared to controls
    - Reduced transferrin receptors (would be expected to be higher in deficiency state)
    - Dysregulation of iron transportation by blood brain barrier

- Central
  - Reduced Iron stores is **main consistent finding**
    - Reduced Iron stores in striatum, thalamus, red nucleus
    - CSF-Ferritin is lower compared to controls
    - Reduced transferrin receptors (would be expected to be higher in deficiency state)
Pathophysiology

- Peripheral
- Response to Dopaminergics
  - Iron is a cofactor for tyrosine hydroxylase
  - Rate limiting step for DA synthesis
  - Iron may be regulating dopamine receptors
  - Iron may be involved in regulating dopamine release
  - Iron may increase D2R density in striatal cells

- Supportive features
  - Near universal initial response to dopaminergic medication
  - PLM seen on PSG
  - Family History of RLS

Restless Leg Syndrome

- Comorbidities
  - Depression
  - GAD
  - PTSD
  - OCD
  - ADHD

- HRQoL
  - Osteoarthritis
  - CHF
  - Parkinson’s Disease
  - Stroke
• Decreased D2R Receptors in corpus striatum
  • Involved in motor movements and reward systems

Pathophysiology

• Garcia-Borreguero (2018)
  • Low adenosine associated with brain iron deficiency
    • Down regulation of Adenosine A1 receptors in the striatum / cortex
    • Lead to presynaptic hyperdopaminergic and hyperglutamatergic states
  • Dipyridamole increases levels of adenosine
  • Open label, non placebo trial 15 patients with RLS
    • 8 weeks of dipyramidole (100-400mg)
    • PSG and Multiple Suggested Immobilizations Tests
  • Results
    • Reduction of PLMI and IRLS
• Garcia-Borreguero (2014)
  • Multicentre double blind placebo controlled 3 way crossover trial
  • 23 centres in USA
  • Patients had moderate to severe RLS
  • Pregabalin 300mg day vs pramipexole 0.50mg day vs placebo
  • 4 x 2 consecutive night PSGs
    • During placebo run-in period (Day 7/14 day)
    • 2 consecutive night PSG at end of each treatment phase
**Garcia-Borreguero (2014)**

- **Patients**
  - IRLS $\geq 15$
  - Moderate to severe sleep disturbance
  - $> 6$ months of symptoms
  - PSG
    - WASO $\geq 60$ minutes over 2 nights
    - WASO $< 30$ minutes on **neither**
    - PLMI $> 10$
    - Mean Total Sleep time between 3-6.5hrs.

- **Excluded**
  - Secondary RLS
  - Ferritin $< 10$ ug/L
  - $>50\%$ improvement in RLS during placebo
• Garcia-Borreguero (2014)
  • Endpoints
    • WASO
    • NAASO (number of awakenings after sleep onset)
    • TST
    • Sleep Efficiency
    • Sleep Latency
    • Arousal Index
    • PLM Arousal Index

• Garcia-Borreguero (2014)
  • Results
  • 85 participants
    • 62 completed all 3 periods of the trial
Table 2—Polysomnography endpoints

<table>
<thead>
<tr>
<th>Study variable</th>
<th>PGB mean (SEM)</th>
<th>PPG mean (SEM)</th>
<th>PBO mean (SEM)</th>
<th>PGB vs PBO P value*</th>
<th>PGB vs PPO P value*</th>
<th>PPG vs PPO P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep maintenance</td>
<td>51.5 (4.2)</td>
<td>78.4 (4.1)</td>
<td>78.6 (4.2)</td>
<td>-27.1 (-35.8 to -18.4) &lt; 0.0001</td>
<td>-35.9 (-53.5 to -18.3) NA</td>
<td>-35.9 (-53.5 to -18.3) NA</td>
</tr>
<tr>
<td>NAASO, count</td>
<td>18.1 (1.1)</td>
<td>26.3 (1.0)</td>
<td>21.1 (1.0)</td>
<td>-2.7 (-4.6 to -0.7) NA</td>
<td>-7.9 (-9.8 to -5.5) &lt; 0.0001</td>
<td>-7.9 (-9.8 to -5.5) &lt; 0.0001</td>
</tr>
<tr>
<td>TST, min</td>
<td>402.4 (6.0)</td>
<td>376.5 (5.8)</td>
<td>369.7 (6.0)</td>
<td>32.7 (22.0 to 43.4) NA</td>
<td>52.0 (35.2 to 68.9) NA</td>
<td>52.0 (35.2 to 68.9) NA</td>
</tr>
<tr>
<td>SE, %</td>
<td>83.8 (12.1)</td>
<td>78.6 (12.1)</td>
<td>77.0 (12.2)</td>
<td>6.8 (4.6 to 9.0) NA</td>
<td>5.2 (3.0 to 7.5) NA</td>
<td>5.2 (3.0 to 7.5) NA</td>
</tr>
<tr>
<td>Sleep architecture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage N1 sleep, min</td>
<td>38.1 (2.6)</td>
<td>48.4 (2.5)</td>
<td>43.7 (2.6)</td>
<td>-5.7 (-9.8 to -1.5) NA</td>
<td>-10.3 (14.4 to -6.2) NA</td>
<td>-10.3 (14.4 to -6.2) NA</td>
</tr>
<tr>
<td>Stage N2 sleep, min</td>
<td>227.1 (6.1)</td>
<td>241.5 (5.9)</td>
<td>204.4 (6.1)</td>
<td>22.7 (10.7 to 34.7) NA</td>
<td>-14.5 (26.6 to -2.6) NA</td>
<td>-14.5 (26.6 to -2.6) NA</td>
</tr>
<tr>
<td>SWS (stage N3 sleep), min</td>
<td>68.9 (4.6)</td>
<td>34.8 (4.5)</td>
<td>40.6 (4.6)</td>
<td>20.9 (12.6 to 29.3) NA</td>
<td>-32.1 (23.8 to 40.4) &lt; 0.0001</td>
<td>-32.1 (23.8 to 40.4) &lt; 0.0001</td>
</tr>
<tr>
<td>Stage R (REM) sleep, min</td>
<td>70.4 (3.1)</td>
<td>51.8 (3.0)</td>
<td>75.4 (3.1)</td>
<td>-5.0 (-10.5 to 0.7) NA</td>
<td>-18.6 (13.0 to 29.4) NA</td>
<td>-18.6 (13.0 to 29.4) NA</td>
</tr>
<tr>
<td>Arousal Index, number of arousals/h</td>
<td>2.8 (0.3)</td>
<td>4.2 (0.3)</td>
<td>3.4 (0.3)</td>
<td>-0.7 (-1.2 to -0.2) NA</td>
<td>-1.4 (-1.9 to -1.0) NA</td>
<td>-1.4 (-1.9 to -1.0) NA</td>
</tr>
<tr>
<td>Sleep induction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPS, min</td>
<td>31.1 (4.6)</td>
<td>31.5 (4.5)</td>
<td>38.9 (4.6)</td>
<td>-7.7 (-11.1 to -1.6) NA</td>
<td>-0.4 (9.7 to 8.9) NA</td>
<td>-0.4 (9.7 to 8.9) NA</td>
</tr>
<tr>
<td>Periodic limb movements</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PLMA, PLMA/h</td>
<td>3.9 (0.7)</td>
<td>2.7 (0.7)</td>
<td>7.6 (0.7)</td>
<td>-3.7 (-5.4 to -1.9) &lt; 0.001</td>
<td>1.3 (0.5 to 3.0) NA</td>
<td>1.3 (0.5 to 3.0) NA</td>
</tr>
<tr>
<td>PLMSI, PLMSI/h</td>
<td>22.4 (2.5)</td>
<td>8.0 (2.4)</td>
<td>37.0 (2.5)</td>
<td>-14.3 (20.8 to -3.2) NA</td>
<td>14.4 (8.2 to 20.7) NA</td>
<td>14.4 (8.2 to 20.7) NA</td>
</tr>
</tbody>
</table>

*P value, PGB vs PBO: < 0.0001, PGB vs PPO: NA, PPG vs PPO: < 0.0001

Trenkwalder exclusions and side effects
Table 1

| Trade name(s) | INFeD® | Ferrlecit® | Venofor® | Ferumoxides (Ferumoxtran-10®) | Monoferr® | USA: Injectafer®
|---------------|--------|------------|----------|-------------------------------|----------|-----------------
| Generic name  | LWI gaitran | Iron gluconate | Iron sucrose | Ferrumoxides AMAG Pharmaceuticals | Iron ison溏teide 1000 Pharmacemis AS | Ferric carboxymaltose USA: American Regent Inc |
| Distributor   | Watson Pharmaceuticals Inc. | Sanofi Aventis Inc. | American Regent Inc. | 750,000 | Europe Only |
| Molecular weight measured by manufacturer (Da) | 165,000 | 289,000–444,000 | 34,000–60,000 | 150,000 | Not USA: Viver Pharma |
| Labeled dosage (mg) | 100 | 125 | Adult: 200 Pediatric: 100 | 510 | USA: 750 mg |
| Does for RLS | 1000 mg single dose | 1000 mg single dose | 1000 mg single dose | 1000 mg single dose | USA: 1500 mg (if weight >50 kg) 2 doses: 5–7 days apart |
| Dose administration | IV infusion 1 h (usually with 250 ml normal saline) | Slow IV 10 m | Slow IV 2–5 m | Slow IV 1–2 m | Europe: single dose 1000 mg 2 doses: 5–7 days apart |
| Test dose required | Yes | No | No | No | Europe: single dose 1000 mg |
| Iron concentration (mg/dl) | 50 | 125 | 20 | 30 | 100 |
| Vial volume (ml) | 2 | 5 | 5 | 17 | 1, 5 & 10 in Europe |
| Black box warning | No | No | Yes | No | 2 and 10 in Europe, 15 US |
| Preservative | Benzyl alcohol | None | None | None | None |

Abbreviations: N/A, not available; TDL, total-dose infusion. *Injectafer is marketed outside the US under the brand name Ferinject.

REFERENCES:

INFeD® Prescribing Information. Morristown, NJ: Watson Pharmaceuticals, Inc.
Ferinject prescribing information from http://www.ferinject.co.uk/prescribing-information/downloaded 30 Jan 17.

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Treatment

Functional studies show increased activity in the thalamus
Opioid receptors are abundant in the thalamus