

## Restless Leg Syndrome: NMPHA Winter Conference

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January 23, 2021, 1130-1230

1

### Disclosures

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

2

### 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.

3

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

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7

### 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)

8

### 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

9



10



11



12

Progress in Brain Research  
Volume 261, 2018, Pages 1-18

### Effects of sleep deprivation on cognition

Abstract  
Sleep deprivation is commonplace in modern society, but the far-reaching effects on cognitive performance are only beginning to be understood from a scientific perspective. While there is broad consensus that insufficient sleep leads to a general slowing of response speed and increased variability in performance, particularly for simple measures of attention, attention and vigilance, there is much less agreement about the effects of sleep deprivation on more highly skilled cognitive operations, including perception, memory and executive functions. Central to this debate has been the question of whether sleep deprivation affects overall cognitive capacities in a global manner through depleted attention and attention, or whether sleep loss

**RESEARCH ARTICLE**  
 **$\beta$ -Amyloid accumulation in the human brain after one night of sleep deprivation**

Elhan Shubik-Kayal, Chen, Jack Wang, Corinne E. Wilentz, Sukun D. Damaris, Mei Qian, Dong Wook Kim, Eyal Linggler, Victoria Roman, Anna Zilber, Clara Ferman, Orna Shikler, Pinar Maral, Tamar Shtroumova, Susan De Santis, David Torralba, Hakimeh Behaveshian, and Henry D. Zimmerman

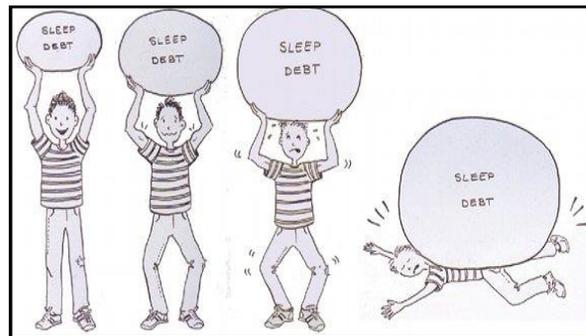
Published April 24, 2018, 1117-1123, e0483. doi:10.1016/j.pbs.2018.03.001

Editorial Board: P. Paus, University of California, Los Angeles, CA, and accepted March 11, 2018 (received for review December 16, 2017)

Also: Figures & SI | Info & Metrics | PDF

**Significance**  
There has been an emerging interest in sleep and its association with  $\beta$ -amyloid burden as a risk factor for Alzheimer's disease. Despite the evidence that acute sleep deprivation elevates  $\beta$ -amyloid levels in mouse interstitial fluid and in human cerebrospinal fluid, not much is known about the impact of sleep deprivation on  $\beta$ -amyloid burden in the human brain. Using positron emission tomography, here we show that acute sleep deprivation impacts  $\beta$ -amyloid burden in brain regions that have been implicated in Alzheimer's disease. Our observations provide preliminary evidence for the negative effect of sleep deprivation on  $\beta$ -amyloid burden in the human brain.

13



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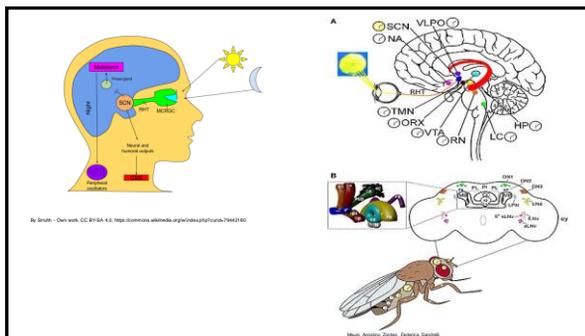


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### Blue Light and Associated Decreased Sleep Time

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

16



17

### 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(s)
  - Depression
  - Bipolar Disorder
  - Schizophrenia
- Neurologic
  - Dementia
  - Seizures
  - Headache/stroke/tumor
  - Parkinson's

18

### Sleep Disorders- Overview

- Abnormal Sleep Behavior**
  - REM Sleep Behavior Disorder
  - Sleep Talking
  - Sleepwalking
  - Nightmares
- Circadian Rhythm Disorders**
  - Non-24 Sleep-Wake Disorder
  - Shiftwork Disorder
  - Delayed Sleep Phase Disorder
- Excessive Daytime Sleepiness Disorders**
  - Excessive Sleepiness
  - Narcolepsy
  - Idiopathic Hypersomnia
- Insomnias**
  - Acute
  - Chronic
  - Comorbid
  - Onset
  - 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

19

### Sleep Disorders and Mental Health



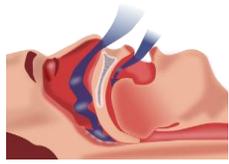
- Sign of Depression
- Sign of Mania
- Worsening of anxiety/OCD/Panic Disorder
- Substance induced sleep disruptions



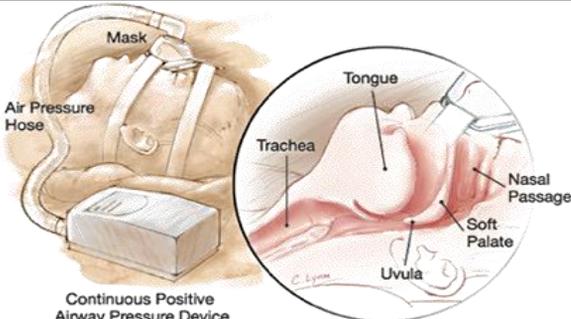
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### Sleep Related Breathing Disorders

- Obstructive Sleep Apnea
- Central Sleep Apnea



21



Mask  
Air Pressure Hose  
Tongue  
Trachea  
Nasal Passages  
Soft Palate  
Uvula  
Continuous Positive Airway Pressure Device

22



Nasal      Nasal Pillow      Full Face

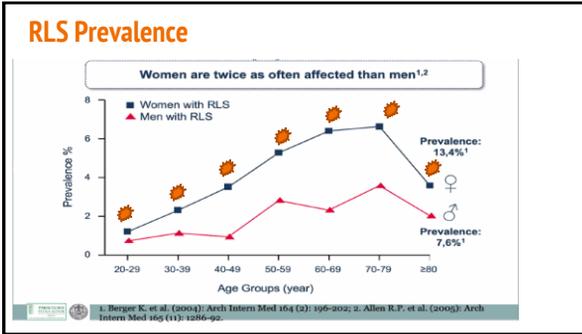
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**Table 3: Medications that may affect sleep**  
A number of drugs steal sleep, while others may cause unwanted drowsiness. Your doctor may be able to suggest alternatives that do not disrupt sleep.

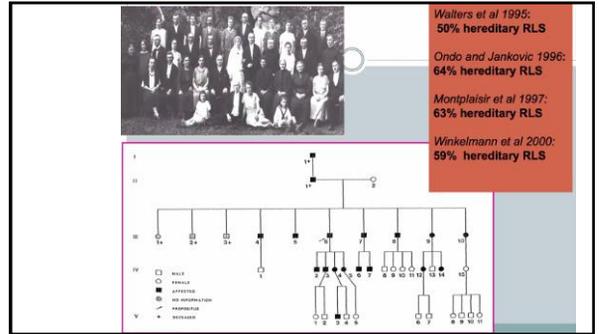
| MEDICATION                                      | USED TO TREAT   | COMMON EXAMPLES  | POSSIBLE EFFECT ON SLEEP AND DAYTIME FUNCTIONING   |
|---|---|--|--|
| Beta blockers*                                  | High blood pressure, heart rhythm problems, angina  | metoprolol (Lopressor), pindolol (Visken), propranolol (Inderal), clonidine (Catapres)   | Insomnia, nighttime awakenings, nightmares   |
| Clonidine                                       | High blood pressure; sometimes prescribed off-label for alcohol withdrawal, smoking cessation, or other health problems |  | Daytime drowsiness and fatigue, disrupted REM sleep; less commonly, restless legs, early morning awakening, nightmares |
| Corticosteroids                                 | Inflammation, asthma  | prednisone (Sterapred, others)   | Daytime sleepiness, insomnia, decreased REM sleep  |
| Diuretics                                       | High blood pressure   | chlorthalidone (Diatril), chlorthalidone (Hygroton), hydrochlorothiazide (Easid, HydroDiuril, others)                            | Increased nighttime urination, painful calf cramps during sleep  |
| Medications containing alcohol                  | Cough, cold, and flu  | Contact Cold and Flu, Nyquil Cough, many others  | Suppressed REM sleep, disrupted nighttime sleep  |
| Medications containing caffeine                 | Headaches and other pain  | Caffeine, NoDoz, Vivarin   | Wakefulness that may last up to six to seven hours   |
| Nicotine replacement products                   | Smoking   | Anacin, Exceirin, ibutil nicotine patches (Nicoderm), gum (Nicorette), nasal spray or inhalers (Nicotrol), and lozenges (Commit) | Insomnia, disturbing dreams  |
| Sedating anticholinergics**                     | Cold and allergy symptoms   | chlorpheniramine (Chlor-Trimeton), diphenhydramine (Benadryl), dimenhydrinate (Dramamine)  | Drowsiness   |
| Selective serotonin reuptake inhibitors (SSRIs) | Motion sickness   | fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft)   | Decreased REM sleep, daytime fatigue   |
| Sympathomimetic stimulants                      | Depression, anxiety   | dexamfetamine and amphetamine (Adderall), methylphenidate (Ritalin, Concerta)  | Difficulty falling asleep, decreased REM and non-REM deep sleep  |
| Theophylline                                    | Attention deficit disorder  | theophylline (Clio-bid, Theo-Dur, others)  | Wakefulness similar to that caused by caffeine   |
| Thyroid hormone                                 | Asthma, chronic obstructive pulmonary disease (COPD)  | levothyroxine (Lexoxy), Synthroid, others  | Difficulty falling asleep, fragmented sleep, insomnia (at higher doses)  |
|   | Hypothyroidism  |  |  |

\*Some beta blockers do not affect sleep; they include atenolol (Tenormin) and sotalol (Betosol).  
\*\*These medications are also found in over-the-counter sleep aids.

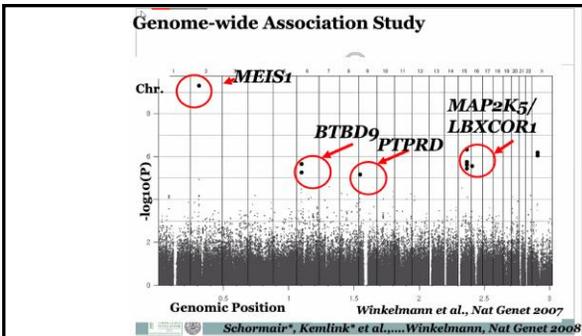
24



25



26



27

### Chronic persistent RLS

Vs.

### Intermittent RLS

Special Section in Sleep Medicine:  
 Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria – history, rationale, description, and significance  
 Richard F. Allen<sup>1</sup>, Daniel L. Picchetti<sup>2,3</sup>, Diego Garcia-Borreguero<sup>4</sup>, William G. Ondo<sup>5</sup>, Arthur S. Walters<sup>6</sup>, John W. Winkelmann<sup>7</sup>, Marco Zucconi<sup>8</sup>, Raffaele Ferri<sup>9</sup>, Claudia Trenkwalder<sup>10</sup>, Hochang B. Lee<sup>11</sup>, on behalf of the International Restless Legs Syndrome Study Group

**Changes :**  
 Addition of Criterion 5.  
**Specifiers for clinical course of RLS/WED:**  
**A. Chronic-persistent RLS/WED:** symptoms when not treated would occur on average at least twice weekly for the past year.  
**B. Intermittent RLS/WED:** symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events.

28

### RLS Mimics

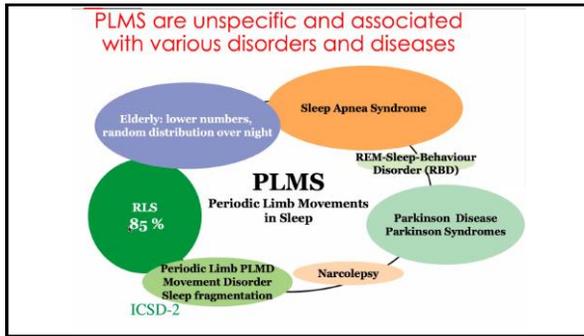
- Claudication
  - Relief at rest, worse during movement
  - No circadian pattern**
  - Skin alterations
- Venous stasis
  - Edema and skin alteration
  - No circadian pattern**
- Hypotensive akathisia
  - Relief at rest, worse with sitting
  - No circadian pattern**
- Painful legs and moving toes
  - No sensory discomfort
  - No circadian pattern**
- Neuropathic pain
  - Not relieved with movement
- Peripheral neuropathy
  - Stocking glove distribution
- Vesper's cue
  - Lumbosacral pain

29

### RLS Mimics cont'd

- Sleep-related leg cramps
  - Palpable tightening of muscle
  - Alleviated by stretching not movement
- Positional discomfort
  - Relieved with change of posture
  - No circadian pattern**
- Arthritis
  - Confined to a joint, joint erythema
- Growing pain
  - Relieved with local massage and stretching
- Anxiety
  - Volitional 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 neuroleptic

30



31

### 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)

32

### Ask about RLS!

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

33

### IRLS

Assess the Severity of Restless Legs Syndrome

**USING THE INTERNATIONAL RLS IRLS RATING SCALE**

The IRLS Rating Scale was developed by the International Restless Legs Syndrome Study Group (IRLSSG) to assess the severity of a patient's RLS symptoms. Ask your patient the 10 questions listed below and have them rate their symptoms from 0 to 4 (0=none, 1=mild, 2=moderate, 3=severe, 4=worst imaginable) and enter their IRLS score. It will range from 0 to 40.

The IRLS Rating Scale was validated in a controlled study and found to have high levels of internal consistency, inter-rater reliability, and test-retest reliability. The IRLS Scale is an instrument of continuous construction by submitting data and clinical reports to the IRLS. To learn more about this group, visit [www.irls.org](http://www.irls.org).

| In the past week:   | Score                 |
|---|-----------------------|
| Overall, how would you rate the RLS discomfort in your legs or arms?<br>* Very severe 4<br>* Severe 3<br>* Moderate 2<br>* Mild 1<br>* None 0   | <input type="radio"/> |
| Overall, how much pain do you feel due to RLS symptoms?<br>* Very severe 4<br>* Severe 3<br>* Moderate 2<br>* Mild 1<br>* None 0  | <input type="radio"/> |
| Overall, how much rest of your RLS arms or legs do you get from resting or sleeping?<br>* Not at all 4<br>* Almost none 3<br>* Some 2<br>* A fair amount 1<br>* A lot 0   | <input type="radio"/> |
| How severe was your sleep disturbance from your RLS symptoms?<br>* Very severe 4<br>* Severe 3<br>* Moderate 2<br>* Mild 1<br>* None 0  | <input type="radio"/> |
| How severe was your tiredness or sluggishness during the day due to your RLS symptoms?<br>* Very severe 4<br>* Severe 3<br>* Moderate 2<br>* Mild 1<br>* None 0   | <input type="radio"/> |
| How often did you get RLS as a vehicle?<br>* Very severe 4<br>* Severe 3<br>* Moderate 2<br>* Mild 1<br>* None 0  | <input type="radio"/> |
| When you had RLS symptoms, how severe were they on average?<br>* Very severe 4<br>* Severe 3<br>* Moderate 2<br>* Mild 1<br>* None 0  | <input type="radio"/> |
| Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example, carrying out a professional, family, home, social, school, or work task?<br>* Very severe 4<br>* Severe 3<br>* Moderate 2<br>* Mild 1<br>* None 0 | <input type="radio"/> |
| How severe was your mood disturbance from your RLS symptoms-for example, angry, depressed, sad, anxious, or irritable?<br>* Very severe 4<br>* Severe 3<br>* Moderate 2<br>* Mild 1<br>* None 0   | <input type="radio"/> |
| <b>Add the scores from above and share the total with your patient.</b><br>Add (0 to 40) <b>Score: 0 to 40</b> Very Severe (37 to 40)      Total Score  | <input type="text"/>  |

34

### Check Ferritin, Transferrin Saturation, and CRP

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

*B12, folate, thyroid function also important*

35

### Iron

- Iron studies (ferritin goal >50-75)
- Ferric carboxymaltose (*Injectafer*) 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)

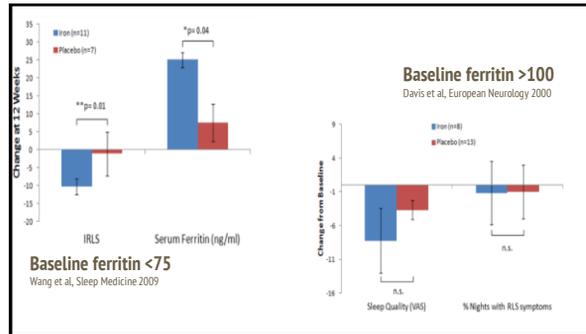
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### \*Why Dose Iron Supplement Once a Day?

- 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.



37

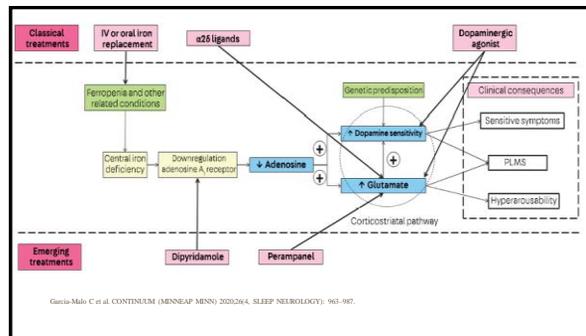


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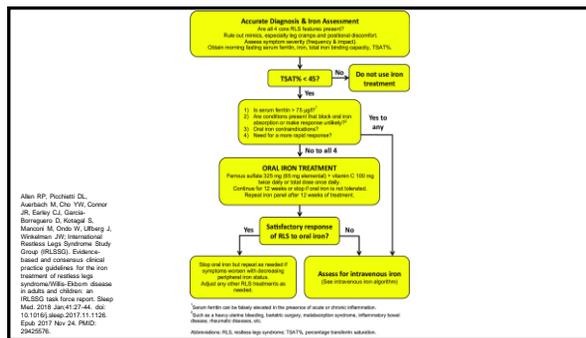
### What's the deal?

- 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 hyper glutamatergic 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

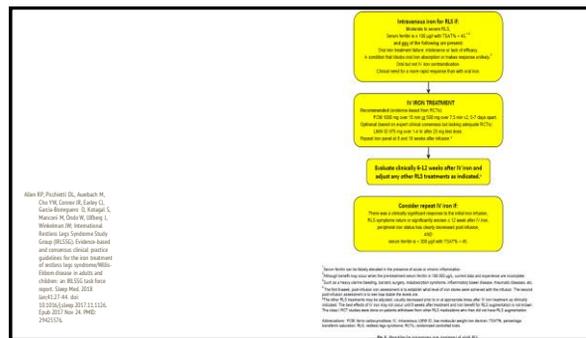
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42



## 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



49

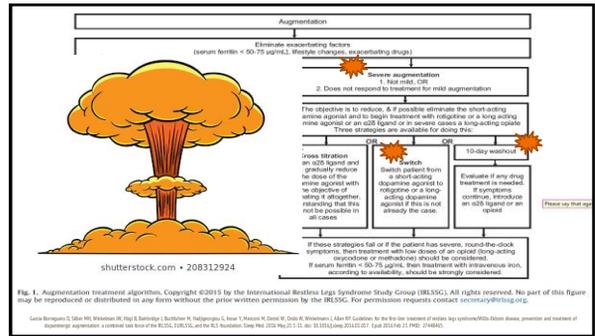


Fig. 1. Augmentation treatment algorithm. Copyright ©2015 by the International Restless Legs Syndrome Study Group (IRLSSG). All rights reserved. No part of this figure may be reproduced or distributed in any form without the prior written permission by the IRLSSG. For permission requests contact secretary@irlssg.org.

50

## WARNING- EXCESSIVE Pleasure Seeking



51

## 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 <math>< 1800\text{mg/day}</math>
  - 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%

52

## Opioids



- Oxycodone/naloxone ER (*Targiniq ER*)
  - **Last line**
  - Limited evidence
    - May be considered if adverse effects/failures of other treatments
- Methadone, hydrocodone, codeine, tramadol have all been used
- **May worsen sleep apnea!**
- Negligible augmentation risk

53

## Others

- Levodopa/carbidopa (~\$5-\$15)
  - 25-50mg QDAY-TID, increase by 50mg q3-7 days (max 400 mg/day, divided)
  - **Augmentation (<math>\leq 70\%</math>)** - Preferred for intermittent RLS (quick onset and short duration), not non-intermittent
- Cabergoline (\$280-\$1125)
  - 0.5mg QDAY (max 2mg/day)
  - **LAST LINE** (cardiac valvulopathy, fibrosis)
  - Augmentation <math>< 4\%/year</math>
- Carbamazepine (<math>< \\$5-12</math>)
  - 100mg HS, increase upto 200mg/day q7 days (max 300mg/day)
  - **Lacks evidence**, bone marrow suppression risk, **auto-inducer**, **interaction risk**
- Clonidine (<math>< \\$5-10</math>)
  - 0.1mg 1-2 hours before bed, increase by 0.1mg/day q7 days (max 1mg/day)
  - **Lacks evidence**

54

## 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



55

## 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



56

## Alternatives

- Yoga- eight week pilot trial
  - Innes KE et al, *J Altern Complement Med.* 2013.
- Aerobic exercise in renal patients
  - Giannaki CD et al, *Nephrol Dial Transplant.* 2013
  - Sokkos GK, *ASAIOJ.* 2008



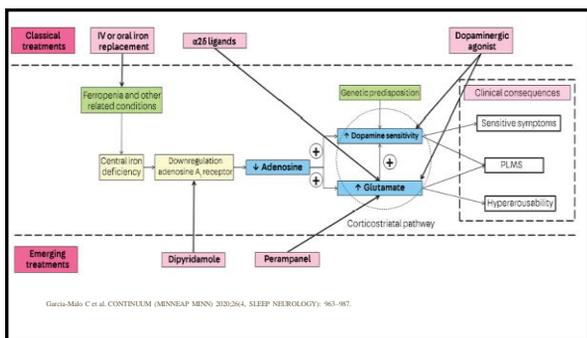
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## How about cannabis?

- 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 agonist???



58



59

## 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



60

### 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**



61

### References

1. [Iron treatment in restless leg syndrome: a meta-analysis](#)
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62

### Questions



63