RLS and Parasomnias: Treatment Updates and Considerations

Michael Howell MD
Associate Professor of Neurology
University of Minnesota
Minnesota Regional Sleep Disorders Center
Hennepin County Medical Center
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1. I do not have any relationships with any entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients, OR

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3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

   1.
   2.
   3.
Introduction

• RLS
  – Presentation Challenges
  – Treatment Update
    • Dopamine augmentation and other complications
• Parasomnias
  – NREM Parasomnias
  – RBD
“Bad medicine: restless legs syndrome”

- On December 19, 2013, the British Medical Journal (Impact Factor 17.445) published an opinion piece by Dr. Des Spence, General Practitioner from Glasgow.
- Describes RLS as a “Pharma classic”
- Subjective scales are “pseudoscientifically converted to an illegitimate numerical rating”
- Claims no objective correlates
- “Implausible biological basis”
- “The benefit of treatment is marginal, involving the usual suspects such as gabapentin derivatives, strong opioids, and benzodiazepines.”
RLS as a misnomer, an update

• RLS is a descriptor that fails to recognize that 21 to 57 percent of patients complain of arm symptoms instead.
• Limbs, abdomen, and genitals may be involved
• Non-motor urges:
  – Eating, Cigarette Smoking

Management Update

- Iron
- Dopaminergics
- Alpha-2 Delta Ligands
- Opioids
- Vibratory Counter-stimulation

(Wikimedia Commons)
The Role of Iron

- Iron affects dopamine production, synaptic density, myelin synthesis, and energy production in the brain.
- Autopsy, MRI, brain sonography, and CSF analysis support the role of iron in RLS.
- Serum ferritin levels are routinely assessed
  - <50 μg/L-Increased severity of RLS symptoms
  - <75 μg/L-recommended by consensus statement

Iron Replacement Among Deficient

- 325 mg of ferrous gluconate (with 65 mg of elemental iron)
  - With 100 mg of Vitamin C
- ½ to 1 tablet up to three times daily
- Take on an empty stomach (2 hours before or after meals) to aid absorption
  - Watch for dyspepsia and constipation
- Recheck ferritin levels after 6 months of repletion to avoid rare iron overload

(Silber et al 2013)
IV Iron Administration

- IV iron dextran associated with anaphylaxis and IV iron sucrose/gluconate is not helpful due to short duration of benefits
- IV ferric carboxymaltose (FCM) for parental iron replacement seems to be a safe and effective option when needed; 2 doses of 500 mg IV 5 days apart
- Side effects include: diarrhea, infections, transient blood phosphorus decrease, headache

(Wikimedia Commons)

(Silber et al 2013)
Choosing an Agent

<table>
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<tr>
<th>• Dopamine Agonists</th>
<th>• Alpha-2 Delta Ligands</th>
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<td>– pramipexole</td>
<td>– gabapentin</td>
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<td>– ropinirole</td>
<td>– gabapentin enacarbil</td>
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<td>– rotigotine transdermal patch</td>
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<td>altered GI absorption</td>
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<td>• Side Effects</td>
<td>– pregabalin</td>
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<td>– Nausea</td>
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<td>– Headaches</td>
<td>– dizziness,</td>
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<td>– Impulsive behaviors</td>
<td>– sleepiness</td>
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<td>– augmentation</td>
<td>– weight gain</td>
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<tr>
<td>– sleep attacks</td>
<td>(Silber et al 2013)</td>
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(Silber et al 2013)
Sleep Attacks

(Minnesota Regional Sleep Disorders Center)
Choosing an Agent

• Dopamine Agonist
  – Severe Symptoms
  – Comorbid Depression
  – Obesity/metabolic syndrome

• Alpha-2 Delta Ligands
  – Pain
  – Anxiety
  – Insomnia
  – Previous Impulse Control Disorder
  – Young Age

(Silber et al 2013, Allen et al 2014)
Only Head-to-Head Study

• 2014 NEJM Article
• Pregabalin 300mg versus Pramipexole 0.5mg
  – Relatively equivalent treatment efficacy
  – But greater augmentation over 1 year (Pregabalin 2.1% pramipexole 7.7%)
• Industry Funded

(Allen et al 2014)
Once Augmentation Begins

- Recheck Ferritin and Replace if appropriate
- Add alpha-2 delta ligand
- Consider sustained release formulations or rotigotine patch.
- Start talking about opioid therapy

(Wikimedia Commons)
Opioids

- Long Acting Opioids
  - Methadone
- Narcotic medications are highly effective for intractable symptoms
- Methadone
  - 5-20mg po up to tid
  - Typically sustained treatment response

- Rate of discontinuation after first year up to 10 years: 0%
- Rate of augmentation: 0%
- Stigma associated with use

(Silver et al., 2011)
Alternative Therapies

- Consider in pregnancy or with polypharmacy
- Avoiding triggers
  - Caffeine
  - Situations (theaters, meetings, uninterrupted car or airplane trips)
- Stretching
- Vibratory pads
  - Relaxis

(Wikimedia Commons)
Counterstimulation

- FDA approved medical device
  - However no improvement in IRLS Scores or QOL
- Place pad under the area of discomfort
- Choose the vibration intensity that feels best
- Provides 35 minutes of vibration ("vibratory counter-stimulation"), gradually ramping down and shutting off without waking the user.

- Side effects:
  - Temporary worsening of symptoms
  - Leg cramping
  - Tingling
  - Soreness
  - Motion sickness

- Requires a prescription
- Not covered by insurance and costs $626
Parasomnias

• Sleepwalking and related behaviors
  – Confusional Arousals
  – Sleep Terrors
  – Sleep Related Eating Disorder
• Recent insights on etiology

Sleepwalking Lady Macbeth
## New Criteria

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<td><strong>NREM Parasomnias</strong></td>
<td><strong>Confusional Arousals</strong></td>
<td><strong>Disorders of Arousal</strong></td>
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<td><strong>RBD</strong></td>
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<td>Recurrent Isolated Sleep Paralysis</td>
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<td><strong>Other Parasomnias</strong></td>
<td><strong>Sleep Related Eating Disorder</strong></td>
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<td>Sleep Related Groaning (Catathrenia)</td>
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<td><strong>Isolated Symptoms</strong></td>
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*(AASM 2005, AASM 2014)*
Epidemiology Update

- Prevalence of benign sleepwalking in adults may be higher than previously appreciated.
  - 1-4% most commonly cited for the disorder sleepwalking
  - However recently it was shown that 12% of adults describe Non-distressing sleepwalking
  - Prolonged episodes more likely secondary to sedative medication.

(Frauscher et al 2014, AASM 2014)
Possible Sleepwalking Fatality

• 60 year old male with zolpidem induced sleepwalking post herpetic neuralgia
  – Admitted to hospital for epidural block
  – Next day found dead from drowning in water storage tank.

(Fuseli-Sleepwalking Lady Macbeth

(Usomoto et al 2015)
Recent insights in predicting sleepwalking frequency

- Environmental sleep disruption
  - Evening screen time increases risk of SW X 4 in adolescents.

- Frequency of cortical arousals from N3 sleep (on PSG) can predict more frequent sleepwalking episodes.

(Arora et al 2014, Buskova et al 2014)
Genetics of Sleepwalking

- Clear family history in many cases.
  - Monozygotic twins more concordant for SW than dizygotic twins.
- Haplotype HLA-DQB1
- Chromosome 20q locus in one family

Recent insights on daytime function of sleepwalking

• Patients with SW describe more fatigue and sleepiness compared to controls.
  – However MSLT study does not demonstrate hypersomnolence.

• Sleep related verbal memory consolidation is not impaired in sleepwalkers.
  – Despite having fragmented SWS

New Data on Hypersynchronous Delta Activity

• A burst of slow wave activity (SWA) may immediately precede disorders of arousal
• May be an attempt by the cortex to block an arousal by increasing the depth of sleep.
  – Ultimately the arousing stimulus partially overcomes the brains attempt to maintain sleep and the individual is awoken in a disoriented state.
  – Not present when sleepwalkers having a normal non-disoriented arousal.

(Guilleminault et al 2005, Perrault et al 2014)
Update in Slow Wave Activity.

• Among sleepwalkers
  – EEG spectral analysis prior to sleepwalking episodes as well as normal awakenings.
  • Increase in SWA and slow oscillation density in the 3 minutes prior to SW episodes.
    – Not present when sleepwalkers having a normal non-disoriented arousal.
  • In parallel there is EEG activation (low amplitude fast frequency) in regions of the motor cortex.

(Perrault et al 2014, Januszko et al 2016)
Dream imagery and injurious behaviors in SW

• Distinctive themes
  – Sleepwalking/Sleep Terrors: Sudden need to escape, ceiling is collapsing, fire
  – RBD-counter attacking animal/assailant.

(Wikimedia Commons)

(Ugccioni et al 2013)
New Clinical Tools

• Home video monitoring
  – Case of a 33 year old female sleepwalker who had two normal laboratory PSGs.
  – Home monitoring over 36 nights
    • 199 diverse episodes

(Mwenge et al 2013)
New Clinical Tools

- Paris Arousal Disorders Severity Scale
  - Self rated scale of 17 behaviors, as well as their frequency and severity
- Ranges from 0-50
- Score > 13 = active sleepwalking problem
  - Sens 84%
  - Spec 88%

(Arnulf et al 2014)

Fuseli-Sleepwalking Lady Macbeth
Sleep Related Eating Disorder

Previously classified: Other Parasomnia

(University of Minnesota)

(Minnesota Regional Sleep Disorders Center)

(ICSD-2 2005)

(Brion 2012)
Sleep Related Eating Disorder

Now a NREM parasomnia

(Minnesota Regional Sleep Disorders Center)

(ICSD-3 2014)

(University of Minnesota)

(Brion 2012)
Darwins Predisposition

- Cryptic motor restlessness
  - Medication induced sleepwalking
    - Strongest Evidence among cases of Sleep Related Eating Disorder
  - Counter argument

(Howell 2015, Lopez et al 2016)
The Zolpidem-Sleepwalking Sequence

1. An RLS pt presents to a clinician with difficulty initiating sleep.
2. RLS symptoms are unrecognized and zolpidem is prescribed (cryptic)
3. The hypnotic agent suppresses executive function (judgment) and memory.
4. The urge to ambulate (and some cases eat and/or smoke) in the RLS patient is then unleashed and manifests as complex amnestic behaviors.
Management Update—Still Lacking Treatment Data

- Pharmaceutical Treatment is often pursued when potentially injurious behaviors persist.
- Purported therapies include:
  - Benzo’s
    - Clonazepam
    - Diazepam
    - Flurazepam
  - Biperiden
  - Hypnosis
- Patients should be educated on the paucity of clinical data for these treatments.

(Harris 2009, Howell 2012)
Management Update

• The best strategy is still to identify and treat co-morbid conditions
  • Predisposing
    – restlessness
  • Priming
    – sleep deprivation
    – sedatives
  • Precipitating
    – Sleep Disordered Breathing
    – Environmental (Noise)

(Pressman 2007, Harris 2009, Howell 2012)
REM sleep behavior Disorder

- Disorder of Dream Enactment
- Increasingly recognized as a common disorder which increases in prevalence with age.
  - General population: 0.5%
  - Age > 60: 2%
    - Symptoms 9%

(Molano et al 2009, Kang et al 2013, ICSD-3 2014)
Original 6 RBD Cases

(Used with permission, Dr. Carlos Schenck)
Subtle DEB (hand babbling)

(University of Minnesota)
REM Behavioral Events
RBE’s
DEB but only marginal RSWA

(University of Minnesota)
REM Sleep Behavior Disorder

RBD is most commonly associated with neurodegenerative disease, particularly α-Synucleinopathies:

- Parkinson’s disease
- Dementia with Lewy Bodies
- Multiple System Atrophy

Courtesy Alon Avidan
RBD Predicts Neurodegeneration

Postuma, et al.
Neurology 2009
Predicting Conversion to Neurodegeneration

• Patients with the following are more likely to convert in < 5 years
  – hyposmia, constipation, orthostasis
  – Impaired color vision
  – Family history of dementia
  – absence of antidepressant medication

(Charcot 1879)

(Postuma 2015)
RBD indicates more aggressive disease

• PD + RBD patients are more likely to have:
  – Gait instability
  – Severe Parkinsonism
  – Greater motor fluctuations
  – More cognitive decline, hallucinations, autonomic instability

(Charcot 1879)

Tonic REM motor activity predicts freezing of gait

(Videnovic et al 2013)

(University of Minnesota)

(Charcot)
Tonic REM motor activity predicts freezing of gait

(Courtesy of Dr. Anthony Santiago)
RBD Treatment - Medications

No large randomized placebo controlled studies. Treatments are based off of small clinical trials and consensus

Clonazepam (0.25-2.0mg)

Primary treatment for the first 30 years
Suppresses dream enactment but increased muscle tone persists
Sedation is a concern in the setting of parkinsonism and progressive cognitive decline.

RBD Treatment

Melatonin (3-18mg)

Decreased DEB and partial restoration of REM atonia

Effect appears to linger for several nights after agent is discontinued.

Minimal sedating effects suggest that it may be more appropriate in the setting of advanced neurodegeneration.

Normal Variants-Sleep Talking

(University of Minnesota)
Thank You

To all my colleagues and staff at the Minnesota Regional Sleep Disorders Center and University of Minnesota Sleep Disorders Center.
References

• Scott LJ. “Gabapentin enacarbil in restless legs syndrome.” *CNS Drugs* 2012;26(12):1172-7047.


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