Restless Legs Syndrome

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Learning Objectives

By the end of this presentation participants should be able to:

- Describe the 4 key characteristics of RLS
- Explain advantages and disadvantages of common treatments for RLS
- Recognize signs of “augmentation”
- Recommend appropriate options for the management of augmentation.
- Provide appropriate patient counseling for the common agents used to treat RLS.

Case Presentation

Mrs. Antoine is a 77 year old woman. She tells you the visiting nurse found her husband asleep on the couch this morning because he “just can’t take my jumpy legs anymore. Neither of us is getting enough sleep!”

She complains of “weird numb sensations down the sides of her legs” when she is falling asleep. Home Healthcare Nurse 2005:23(4):207-9.

Case Presentation

Her symptoms began 4 months ago and occur only at night. They do feel better if she gets up to walk around.

Her current medications include sertraline for depression and a senior multivitamin.

Her physician advised her to take 60mg of iron and 250mg magnesium daily, but she reports the symptoms aren't getting any better.

Home Healthcare Nurse 2005;23(4):207-9.

Diagnostic Criteria

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in legs.
   - Sometimes RLS affects the arms or other body parts
   - Patients may have trouble describing the urge to move or the sensations
   - Common themes include:
     - "uncomfortable"
     - Movement "inside the leg"

Sleep Medicine 2003;4:101-119.

Diagnostic Criteria

2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity.
   - Rest may be physical or mental
   - The more restful the situation and longer the duration, the more likely the patient will experience RLS symptoms.

Sleep Medicine 2003;4:101-119.

Diagnostic Criteria

3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
   - Relief is usually quick, though it may not be complete.

Sleep Medicine 2003:4:101-119.

Diagnostic Criteria

4. The urge to move or unpleasant symptoms are worse in the evening or night than during the day, or only occur in the evening or night.
   - Even with more severe symptoms, the morning should represent a relative ‘protected time.’

Sleep Medicine 2003:4:101-119.

Supporting Features

- Family History
- Sleep Disturbance
- Response to dopaminergic therapy
- Presence of periodic limb movements in sleep (PLMS) or during wakefulness
- Otherwise normal medical/ physical evaluation

Chest 2006:130:1596-1604.
Sleep Medicine 2003:4:101-119.

Case Presentation

Does Mrs. Antoine have RLS?

A. Yes
B. No
C. We need more testing to be sure

Case Presentation

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Associated Conditions

- End-Stage Renal Disease
- Pregnancy
- Iron Deficiency

Medications That May Provoke RLS

- Agents with dopamine blocking activity
  - Antipsychotic agents
  - Antiemetics (metoclopramide)
- Antidepressants (SSRIs, TCAs, lithium)
- Antihistamines
- Alcohol
- Nicotine
- Caffeine

Am J Med 2007:120(1A):S22-S27.
AJHP 2006:63:1599-612.

Clinical Presentation

Early-Onset RLS

- Symptoms before age 45
- Family History
- Common among 1st degree relatives
- Symptoms progress slowly

Late-Onset RLS

- Symptoms tend to progress more rapidly
- More often a secondary form of RLS
- Neuropathy more common

Am J Med 2007:120(1A):S13-S21.

Epidemiology

- Estimated prevalence is 5-15%
- About 3% report 'significant' symptoms
- More likely in women than men
- Symptoms more common with advancing age
- Little information on prevalence in African American or Asian groups

Am J Med 2007:120(1A):S13-S21.

RLS Treatment Goals

- Goals of treatment include:
  - Adequate restorative sleep
  - Enable the patient to enjoy quiet, relaxing activities

Am J Med 2007;120(1A):S22-S27

RLS Treatment

- Treatment should be individualized for each patient based on the following factors:
  - Iron status
  - Disease severity
  - Symptom pattern: intermittent vs. daily
  - Presence of pain
  - Adverse effects of medications used.

Chest 2006;130:1596-1604.
Mayo Clin Proc 2004;79(7):916-922.
Am J Med 2007;120(1A):S22-S27.

Treatment Options

- Non-pharmacologic Interventions
- Pharmacologic Options include:
  - Dopaminergic agents
  - Anticonvulsants
  - Opioid Agonists
  - Benzodiazepines (BZD) and BZD agonists

Mayo Clin Proc 2004;79(7):916-922.
Am J Med 2007;120(1A):S22-S27.

Non Pharmacologic Approaches

- Treat underlying disorders
- Discontinue medications that may worsen symptoms
- Practice good sleep habits
- Behavioral interventions: brief walks before bedtime, hot or cold showers, massage
- Encourage moderate exercise
- Provide information and support

Mayo Clin Proc 2004:79(7):916-922.
Am J Med 2007:120(1A):S22-S27.

Intermittent Symptoms

- May be situational or predictable
- May be treated with PRN medications
- Recommended treatment options:
  - Levodopa/ carbidopa
  - Mild-to-moderate potency opiates
  - Sedative-hypnotics

Mayo Clin Proc 2004:79(7):916-922.
Am J Med 2007:120(1A):S22-S27.

Daily Symptoms

- Frequent or daily symptoms likely require daily medications
- Treatment options:
  - Dopamine agonists (pramipexole, ropinirole)
  - Gabapentin
  - Mild-to-moderate potency opioids
  - Sedative-hypnotics
- Levodopa is associated with rebound and augmentation, not first-line for daily use

Mayo Clin Proc 2004:79(7):916-922.
Am J Med 2007:120(1A):S22-S27.

Refractory Symptoms

- Consider change of medications
- Consider combination therapy (dopamine agonist + another class of drug)
- May use more potent opioid agonist
- Consider ‘drug holiday’ with symptoms temporarily treated by another drug

Mayo Clin Proc 2004:79(7):916-922.
Am J Med 2007:120(1A):S22-S27.

Levodopa/Carbidopa (Simemet®)

- Regular or CR effective for intermittent RLS
- Initial dose: levodopa/carbidopa 25mg/100mg ½ to 1 tablet HS
- Recommended maximum: 200mg levodopa HS
- A high-protein diet may interfere with absorption, should keep protein consumption consistent.

Chest 2006:130(5):1596-1604.
Am J Med 2007:120(1A):S22-S27.

Levodopa / Carbidopa

- Avoid concurrent use of non-selective MAO inhibitors
- Common ADRs in RLS trials:
  - Nausea
  - Headache
  - Dry mouth
- Rebound occurs in up to 35% of patients

Chest 2006:130(5):1596-1604.
Am J Med 2007:120(1A):S22-S27.

Augmentation

- A change or worsening in RLS symptoms after beginning therapy including:
  - RLS symptoms earlier in the day after HS dose
  - Increased intensity of symptoms
  - Spread of symptoms to arms
- Occurs in up to 70% of patients taking levodopa
- Reduced risk with doses <200mg / day or <3 times per week use
- Treat by discontinuing medication for $\geq$ 3 months

J Gen Intern Med 2006;21:C1-C4.

Case Presentation

A patient comes into the pharmacy for a refill on Sinemet® CR for RLS. He mentions that his symptoms now start around 4pm instead of at bedtime.

Which of the following best describes this phenomenon?

A. Drug resistance
B. Augmentation
C. Rebound
D. Tolerance

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Dopamine Agonists

- 2 agents FDA approved for RLS
  - Ropinirole
  - Pramipexole
- Ergoline derivatives associated with cardiac ADRs
  - Pergolide
  - Cabergoline
- Longer onset and duration of action
  - Take $\geq$2 hrs prior to symptom onset
- Less augmentation risk than levodopa

Am J Med 2007;120(1A):S22-S27.

Ropinirole (Requip®)

- FDA approved for moderate to severe RLS
- Non-ergot derived agonist at dopamine D_2 and D_3 receptors
- Significantly decreases RLS symptoms and improve sleep and QOL measures
- Initial doses: 0.25mg
- Recommended maximum 3 mg divided BID or TID

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Am J Med 2007;120(1A):S22-S27.

Ropinirole

- Interactions:
  - Strong inhibitor of CYP450 2D6
  - Substrate of CYP450 1A2
  - CNS depressants may worsen somnolence
- Common ADRs:
  - Nausea /vomiting
  - Headache
  - Dizziness
  - Somnolence / daytime sleepiness
- Augmentation Risk

Chest 2006;130:1596-1604.

Pramipexole (Mirapex®)

- FDA approved for moderate to severe RLS
- Non-ergot derived agonist at dopamine D_2 and D_3 receptors
- Significantly decreases RLS symptoms and improve sleep and QOL measures
- Initial doses: 0.125 – 0.25 mg
- Recommended maximum 1.5 mg divided BID or TID

Formulary 2007:42:165-174.

Pramipexole

- Interactions:
  - CNS depressants may worsen somnolence
- Common ADRs:
  - Nausea
  - Headache
  - Fatigue
  - Nasal congestion
  - Fluid retention/ edema
  - Daytime sleepiness/ sleep attacks
- Augmentation Risk

Formulary 2007:42:165-174.
Chest 2006:130:1596-1604.

Pergolide (Permax®)

- Ergot derived dopamine agonist
- Used to treat Parkinson's Disease and RLS.
- Withdrawn from US market in August 2007
- Associated with valvular heart disease
- Patients advised NOT to stop treatment abruptly, but to consult a healthcare professional

http://www.fda.gov/cder/drug/advisory/pergolide.htm

Cabergoline (Dostinex®)

- Ergot derived dopamine agonist
- Risk of heart valve disease and fibrotic syndromes
- Improved RLS symptoms and quality of life in a placebo-controlled study.
- ADRs included nausea, dizziness, somnolence, and vomiting
- Dosing: 0.5 – 4mg

AJHP 2006:63:1599-612.
Mov Disorder 2007:22(5):696-703.

Anticonvulsants

- Several agents studied:
  - Gabapentin
  - Valproic Acid
  - Carbemazepine
  - Lamotrigine
- Gabapentin is well tolerated and similarly effective when compared to ropinirole
- Anticonvulsants considered first-line therapy for RLS and neuropathy

Am J Med 2007:120(1A):S22-S27.
Chest 2006:130:1596-1604.

Opioid Agonists

- Effective to improve RLS symptom severity, and sleep quality
- Propoxephene, codeine used for initial treatment
- Tramadol may also be considered
- Use may be limited by ADRs and risk of dependence
- High-potency agents, multiple daily dosing or CR formulations may all be needed in some cases.

Mayo Clin Proc 2004:79(7):916-922.
Am J Med 2007:120(1A):S22-S27.

Benzodiazepine Agonists

- Not as effective as dopamine agonists for RLS
- Clonazepam most often studied
  - Improved subjective sleep quality
- Best used for those with intermittent nighttime symptoms
- May also be considered for use in combination

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AJHP 2006:63:1599-612.

Special Populations: RLS in Children

- Diagnostic criteria differ:
  - 4 adult criteria plus either:
    - a description of leg discomfort in their own words
    - 2 of: a sleep disturbance, 1st degree relative with RLS, or sleep study documenting periodic limb movements
- Use non-pharmacologic strategies first
- Dopaminergic agents may be effective to reduce symptoms

Am J Med 2007:120(1A):S22-S27.

Special Populations: Pregnancy

- Symptoms more common in pregnancy
  - Worst in 3rd trimester
  - Usually remit with delivery
- Treat iron or folate deficiency
- Avoid drug treatment, may consider opiates

Am J Med 2007:120(1A):S22-S27.

RLS Counseling Points

- Information about RLS
- Non-drug strategies
- Medication information
  - Adverse effects
    - Warn of possible sedation, daytime sleepiness
    - With ergot-derived agents, monitor for valve disease or fibrosis
  - Signs and symptoms of augmentation
  - Take drug treatments prior to symptom onset

Case Presentation

Which of the following medications might be worsening Mrs. Antoine's RLS symptoms?

A. Magnesium
B. Iron
C. Sertraline
D. Potassium (in mvi)

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Case Presentation – Assessment and Plan

- No current RLS treatment
  - Low dose of iron
  - Magnesium not generally used to treat RLS
- Using an SSRI, may worsen RLS
- Discuss symptom pattern
- Consider non-drug interventions
- Discuss dopaminergic treatment

For More Information:

- RLS Foundation http://www.RLS.org
- We Move http://www.wemove.org/rls
- National Sleep Foundation http://www.sleepfoundation.org
- International RLS Study Group (IRLSSG) http://irlssg.org
- Movement Disorders Society http://www.movementdisorders.org

Am J Med 2007;120(1A):S28-S29.

Summary

- RLS can significantly impact sleep and quality of life.
- Current treatment guidelines recommend the use of dopaminergic agents
- Pramipexole and ropinirole have been FDA approved for moderate to severe RLS
- Additional research and comparative studies are needed

Take the Post-Test

Please click on the following link to take the post-test:

http://neu.ceedutest.com/student-create-account.html