the FOUNDATION for PERIPHERAL NEUROPATHY®

Welcome!

FPN Webinar:

Navigating Sleep *with* Peripheral Neuropathy

Friday, November 15, 2024

We will begin our presentation shortly.

the FOUNDATION for PERIPHERAL NEUROPATHY®

Today's moderator:

Lindsay Colbert
Executive Director
the Foundation *for* Peripheral Neuropathy

the FOUNDATION for PERIPHERAL NEUROPATHY®

Before We Begin

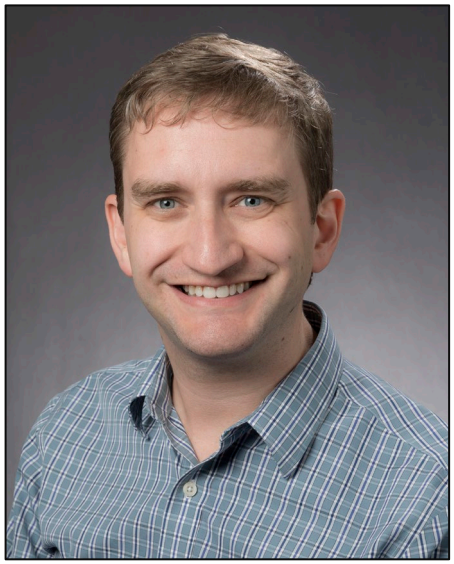
This presentation is being recorded. The recording link will be emailed to you so you can view it again later.

Submit your questions anytime via the Questions Box. We will try to answer them during this webinar.

If you are having trouble with the audio using your computer, you can dial in by phone (check your email for dial-in instructions).

the FOUNDATION for PERIPHERAL NEUROPATHY®

Today's speaker:



Brandon R. Peters, MD, FAASM
Virginia Mason Franciscan Health, Seattle

Navigating Sleep with Peripheral Neuropathy

November 15, 2024

Brandon R. Peters, MD, FAASM
Virginia Mason Franciscan Health, Seattle

Learning Objectives

- Discuss the complex relationship between peripheral neuropathy, pain, and sleep.
- Review how restless legs syndrome and periodic limb movements of sleep connect to peripheral neuropathy and sleep disruptions.
- Learn about some of the most commonly used medications that may aid pain and sleep.

Peripheral Neuropathy

- Pain associated typically fluctuates, often worse at night
- Various descriptors: ache, burning, cold, electric, itchy, sharp, shooting, and tingling
- Linked to numbness and problems with balance, coordination, and movement
- Nerves that automate bodily functions may also be affected, impacting: blood pressure, heart rate, digestive tract mobility, sexual/bladder function, and sweating/temperature regulation

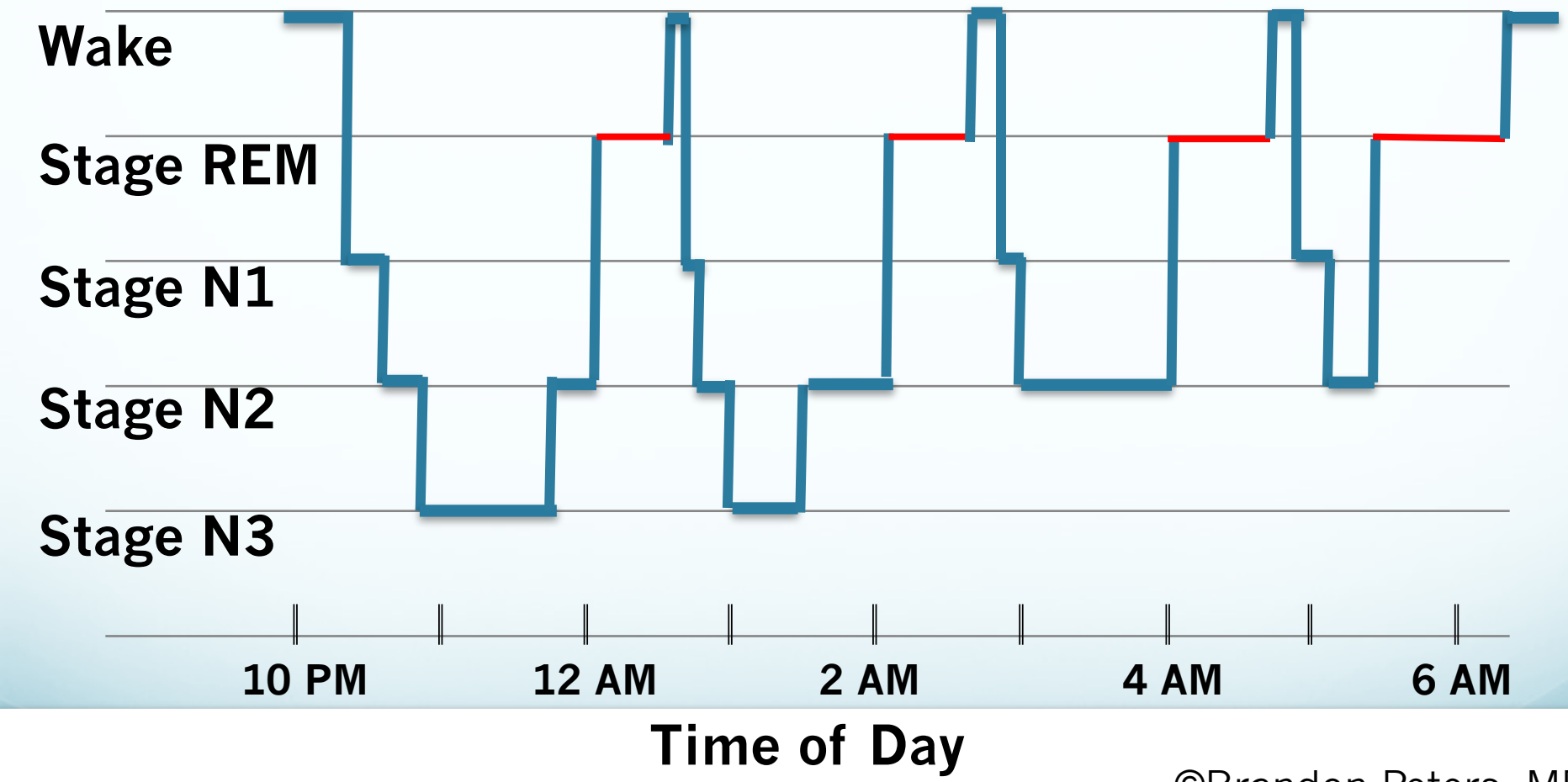
Why Pain Worse at Night?

- Not fully understood
- Gate control theory of pain
  - Body processes pain signals via gatekeepers that allow pain signals to travel to the brain (or not)
  - If the gates are opened, pain awareness occurs.
  - If the gates are closed, your brain doesn't receive the pain signal.
  - Regulators: movement (activity closes the gates), physical sensation/pressure (massage or gentle heat may close the gates), and stress/anxiety (open the gates)
- Cold worsens neuropathic pain
- Circadian rhythm
  - Daytime production of hormones/chemicals (i.e., cortisol) that suppress pain
- Lack of attention redirection or cognitive distraction

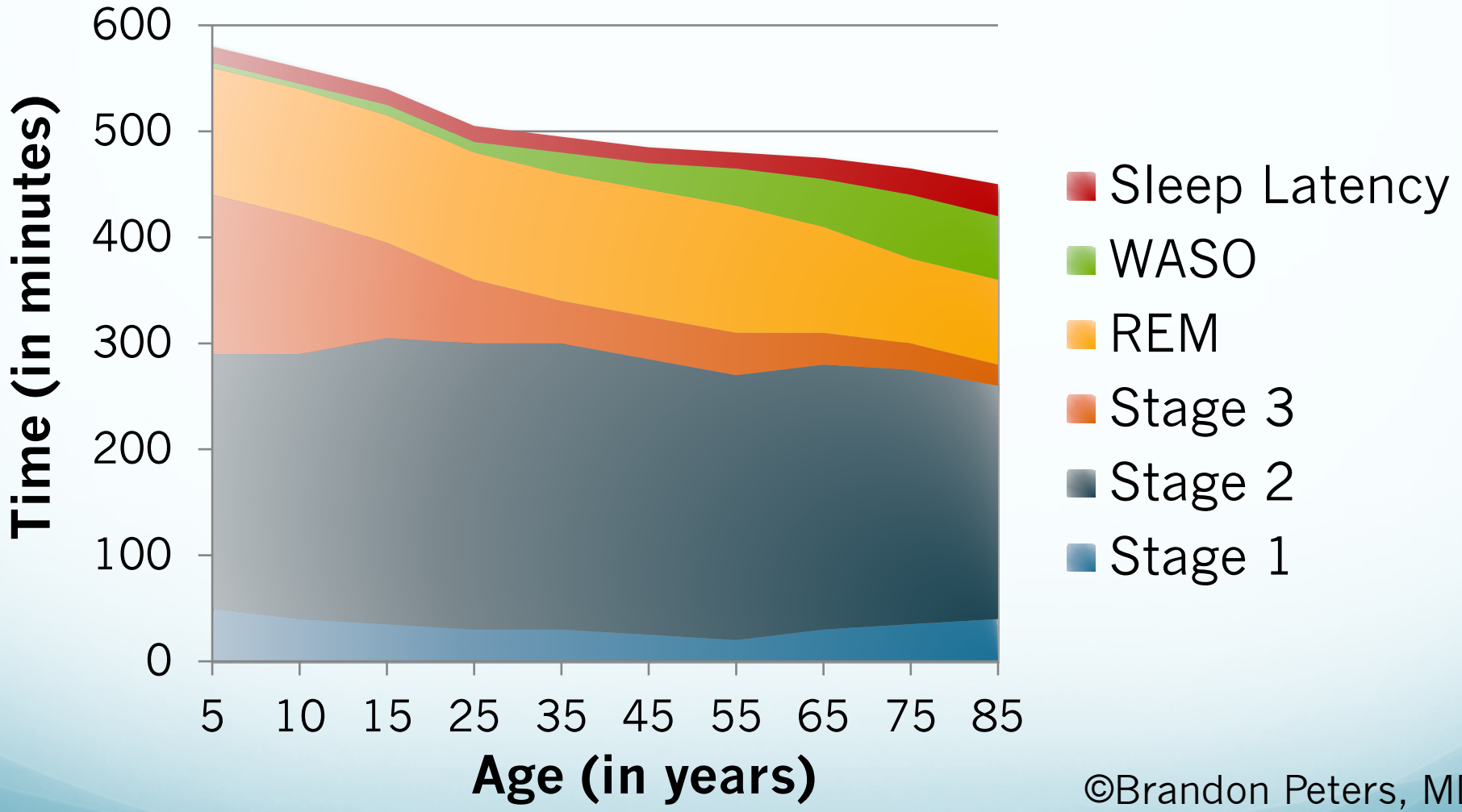
What Is Sleep?

- Sleep is a transient and reversible loss of conscious awareness of the external environment important to growth and restoration of the body as well as memory processing, learning, and creative thinking.
- Sleep cycles include a regular pattern of non-REM and REM sleep stages that last 90 to 120 minutes
- Slow-wave sleep (deep or N3) occurs more in the first third of the night, declines as we age, and is associated with growth hormone release, necessary for repair of tissues and building of muscle mass.

Idealized Sleep Pattern



Sleep Changes in Aging



Sleep and Pain Perception

- Pain may make it difficulty to fall asleep or to get back to sleep, contributing to insomnia.
- In sleep, sensation and pain are generally not recognized, but there are correlated EEG changes.
- Poor sleep due to inadequate total sleep time, poor sleep quality, and sleep disorders may increase pain
- Many people with chronic pain disorders have an associated sleep disorder (i.e., 50% have insomnia)

Neuropathy and Sleep

- Peripheral neuropathy may be associated with restless legs syndrome and periodic limb movement of sleep, the latter undermines sleep maintenance.
- Untreated sleep apnea may contribute to diabetes and it also independently worsens RLS symptoms.
- Many treatments that target RLS/PLMS will also provide relief from neuropathic pain.

Restless Legs: Historical Context

- In 1672, Sir Thomas Willis first described restlessness and movements affecting the limbs in bed disruptive of sleep as "if they were in a place of the greatest torture" in *De Anima Brutorum.*
- He coined the term neurology, first numbered the cranial nerves, and described the Circle of Willis.
- In 1945, Swedish neurologist Karl-Axel Ekbom first described "restless legs" as part of his doctoral thesis.
- Ekbom's syndrome is another eponym for delusional parasitosis (suggesting a persistent interest in creepy-crawly sensations under the skin).

Image sources: http://www.willisfleming.org.uk/images/drthomaswillis.jpg
http://1.bp.blogspot.com/-FwpU-A_CWXI/UapvIlVusOI/AAAAAAAAGkI/V2fCt3oF4VM/s1600/Karl-Axel-Ekbom-Father-of-Restless-Leg-Syndrome-Research.jpg

Misnomers and Eponyms

- Restless legs syndrome (RLS) is a descriptor that fails to recognize that 21 to 57 percent of patients complain of arm symptoms instead.
- Willis-Ekbom disease (WED) recognizes the variable presentations and emphasizes the impacts of the disorder.
- RLS/WED is a sensorimotor disorder characterized by a nearly irresistible urge to move the limbs, often accompanied by an uncomfortable sensation.

Image Source: https://s-media-cache-ak0.pinimg.com/236x/91/7e/35/917e35f24190abdfde49091c1daa4eef.jpg

URGE: 4 Key Features of Clinical Diagnosis

- **Urge** to move the limbs usually accompanied by uncomfortable and unpleasant sensations
- **Rest** or inactivity (lying down or sitting) precipitates or worsens the symptoms
- **Getting up** or moving provides partial or total relief as long as the activity continues.
- **Evening** or night worsens the symptoms (circadian pattern)

Image source: http://curerestlessleg.com/wp-content/uploads/2013/03/RestlessLeg-th.gif

Curveballs: Didn't They Read the Book?

- Numerous descriptors: restless, tingling, electrical, squeezing, painful, twitchy, need to stretch, urge to move, want to move
- Children use age-appropriate words
- Limbs, genitals, and the chest may be involved
- The urge to move may occur without discomfort.
- When very severe, movement may not provide relief.
- Augmentation from dopamine agonists may exacerbate the symptoms, masking the prior circadian rhythm.

Clinical Diagnosis of RLS/WED

- No objective testing is required
- Differentiate mimics:
  - Leg cramps
  - Positional discomfort
  - Myalgia
  - Venous stasis
  - Leg edema
  - Habitual foot tapping
  - Arthritis
  - Periodic limb movements of sleep (PLMS)
- Specificity improves with a careful history:
  - 40% of normal people have an urge to move the legs at rest
  - Improvement with movement and circadian rhythmicity captures 70% with RLS/WED
  - Ruling out leg cramps and positional discomfort brings it up to 94% specificity
  - All without a single test!

Epidemiology: Onset and Prevalence

- 5-10% of European and North American populations are affected
- 2-3% reach clinical significance with consequential life disruption
- 2-4% of children are afflicted
- Prevalence increases until the age of 60-70
- Study results vary, but 5-54% of people with peripheral neuropathy may have RLS
- Familial (idiopathic) has a mean onset in the 20s-30s (1 in 3 have symptoms prior to age 21)
- Progression can be slow or stable and remission may occur
- Late-onset disease often has a rapid progression due to the associated causes

Image source: http://www.doctortrey.com/wp-content/uploads/2012/09/rls.jpg

What Causes RLS/WED?

- The occurrence likely depends on genetic predisposition, brain iron deficiency, and improper dopamine regulation within the central nervous system.
- May be idiopathic (familial) or secondary.
- Genome association studies implicate 4 single nucleotide polymorphisms: BTBD9, MEIS1, MAP2K5/LBXCOR, and PTPRD.
- First-degree relatives of those affected have 2-6 times the risk.

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 deficiency in RLS/WED.
- Serum ferritin levels are routinely assessed (<50 µg/L suggests deficiency).

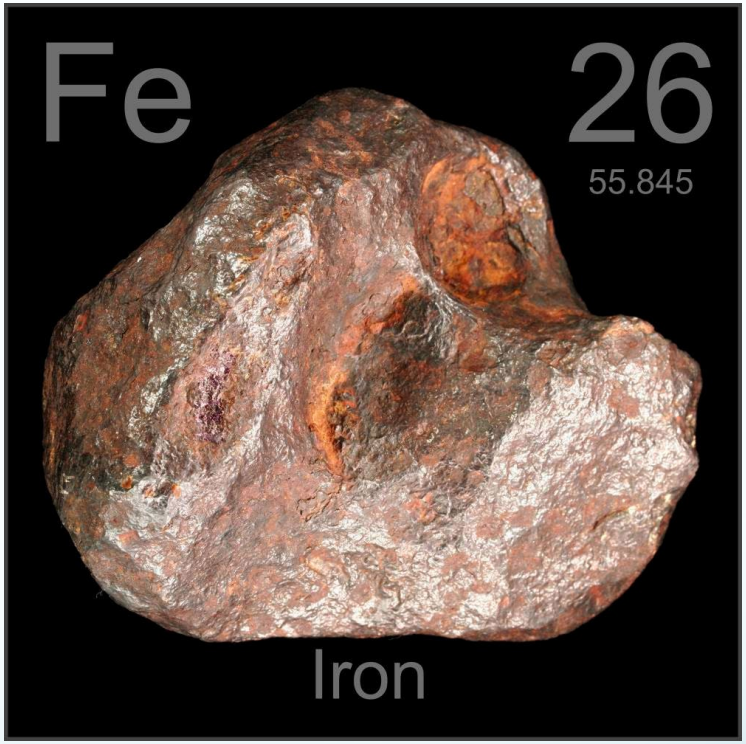


Image source: http://www.periodictable.com/Samples/026.32/s13.JPG

Dopamine Dysfunction

- Improper regulation of dopamine in the CNS appears to be important to the pathophysiology of RLS/WED.
- Supported by functional MRI (fMRI), positron emission tomography (PET), and autopsy studies.
- Explains benefit of dopaminergic medications.

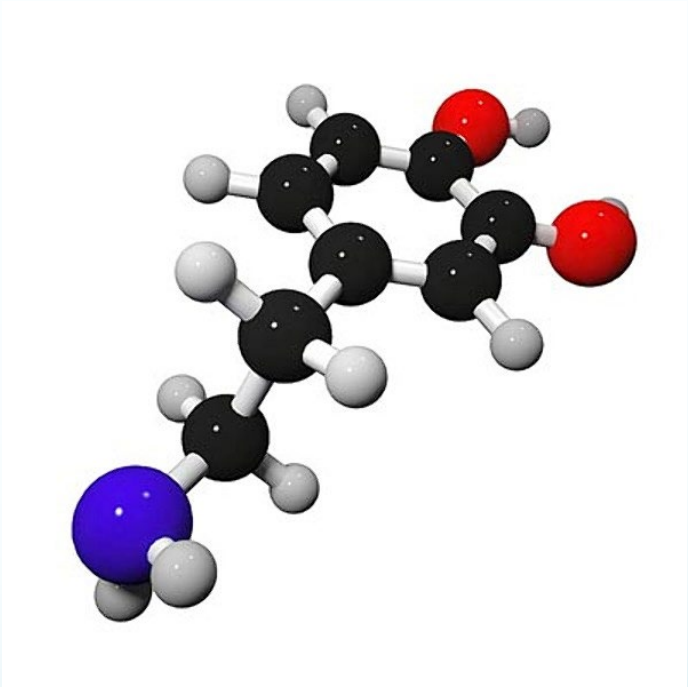


Image source: http://previewcf.turbosquid.com/Preview/2014/05/25__20_10_45/dopamine-c-01.jpg

Laundry List of Causes and Associations

- Iron deficiency
- Chronic renal failure (2-5x risk)
- Pregnancy (affects 1 in 4)
- Prolonged immobility
- Medications
  - Diphenhydramine
  - Antidepressants except bupropion
  - Centrally active dopamine receptor antagonists
- Mood disorders (anxiety, depression, panic disorder, PTSD)
- ADHD (12-35% have RLS/WED)
- Diabetes (affecting 18%)
- Multiple sclerosis (affects 19%)
- Parkinson's disease (up to 21%)
- Rheumatic disease (25%)
- Varicose veins (22%)

Consequences of RLS/WED

- Insomnia (60-90% affected)
- Sleep disruption (increased arousals)
- Bed partner impacts
- Sleepiness/fatigue
- Decreased quality of life
  - Major disease burden similar to or worse than congestive heart failure, depression, Parkinson's disease, and stroke
- Children: growing pains and ADHD

Image source:
http://eltridente.files.wordpress.com/2010/03/20091224145237_15_sindrome_piernas_inquietas.jpg

Periodic Limb Movements of Sleep (PLMS)

- Occur in first 1/3 of the night
- Usually extension of the great toe and partial flexion of ankle, knee, and sometimes hip
- Cortical/autonomic arousals
- May disturb bed partners
- Significant when >15 per hour in adults, >5 per hour in children and lead to sleep disturbances
- Not treated in isolation
- Affects 70% of those with RLS/WED

Image source: http://previous.presstv.ir/photo/20110409/mortazavi20110409080815217.jpg

Choosing to Treat Restless Legs

- Consider the frequency and severity of symptoms
- Many will forego therapy until the consequences are sufficiently impactful
- By the time patients come to specialists, they are probably interested in treatment and may have already failed other therapy

Iron Replacement Among Deficient

- Check a serum ferritin level and CBC
- If serum ferritin level < 75 µg/L, recommend oral iron replacement
- Consider the use of 325 mg of ferrous gluconate (with 65 mg of elemental iron)
- Take ½ to 1 tablet up to three times daily as needed
- Take iron with 100 mg of vitamin C to aid absorption
- Take on an empty stomach (2 hours before or after meals) to aid absorption
- Common side effects include dyspepsia and constipation
- Recheck ferritin levels after 6 months of repletion to avoid rare iron overload

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

Image source: http://media.renalandurologynews.com/images/2015/10/07/adverseeventsivironckd_846191.jpg?format=jpg&zoom=1&quality=70&anchor=middlecenter&width=320&mode=pad

Medications Enhancing GABA

- Often first-line therapy includes GABA-nergic medications
- Options include:
  - Neurontin (Gabapentin) – helpful for PRN use with breakthrough symptoms
  - Horizant (Gabapentin enacarbil) – long-acting with altered GI absorption
  - Lyrica (pregabalin)
- Common side effects include: dizziness, sleepiness, and weight gain

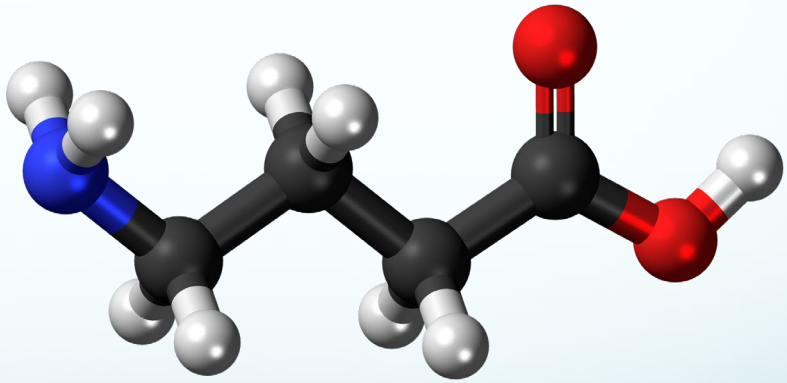


Image source: https://upload.wikimedia.org/wikipedia/commons/5/55/GABA_3D_ball.png

The Use of Horizant

- Moderate to severe RLS and post-herpetic neuralgia
- Prodrug of gabapentin; unknown mechanism of action; half-life 5.8 hours; renal excretion (dosing)
- Novel absorption via high-capacity nutrient transporters
- Dose 600 mg with food ~5 PM
- Well tolerated, few side effects (sleepiness in 19.7%, dizziness in 11.5%)
- PIVOT trials, 80% response rates in trials at 1 year
- Side effects more common in first month. Sleepiness persists in 30% and dizziness in 20%; 11.2% withdrew from treatment
- Caution about suicidal thoughts or behaviors
- Higher doses had no additional benefit and increased adverse reactions

Off-Label Role of Dopamine Agonists

- Frequently used treatment, especially among PCPs
- Options include:
  - Mirapex (pramipexole)
  - Requip (ropinirole)
  - Neupro (rotigotine) transdermal patch
- Mirapex: 9% annual discontinuation rate; 7% annual augmentation
- Response is initially seen in almost all cases
- Augmentation (worsening of symptoms, earlier, in other limbs) may limit long-term use
- Compulsive behaviors are rarely seen as a side effect
- Levodopa is no longer considered the standard of care due to the severe risk of augmentation

Neupro (Rotigotine) Patch

- Moderate to severe RLS and Parkinson's disease
- Start 1 mg and increase by 1 mg weekly up to 3 mg max as needed; taper by 1 mg QOD to D/C
- Once daily patch replaced in the morning; rotation sites, used once in 14 days
- Non-ergot dopamine agonist; stable plasma concentrations
- Side effects: skin rash, nausea, fatigue, headache, dizziness
- Skin reactions (37% in year 1 with 19% discontinuing therapy)
- Augmentation affected 13% of patients
- 5 year trial of 295 patients; 57% discontinued treatment (30% due to adverse events, 11% due to lack of efficacy)

Image source: http://www.askdrray.com/wp-content/uploads/2006/12/Rotigotine-Patch-For-Parkinsons-Also-Helps-Restless-Leg-Syndrome.jpg

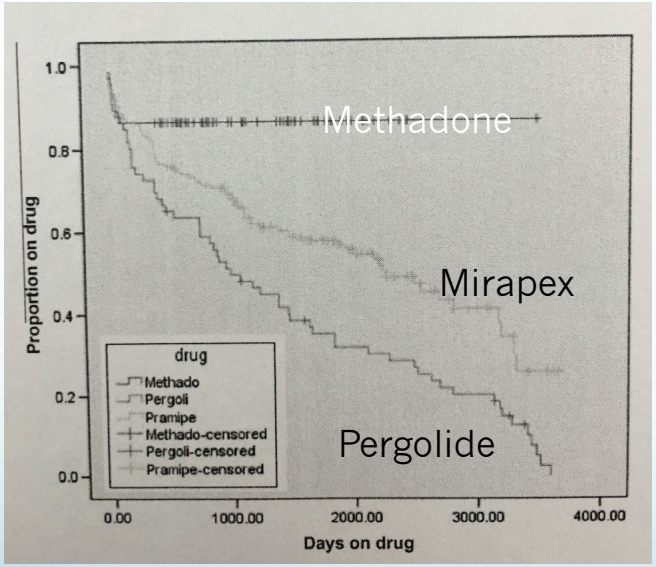
The Role of Benzodiazepines

- Not considered first-line due to the potential risk of abuse, dependence, and overdose
- With intractable symptoms, may be an option to consider
- Helpful for comorbid insomnia
- Consider agents with long half-lives such as Klonopin (clonazepam) and Valium (diazepam)

Image source: http://www.inspiremalibu.com/wp-content/uploads/2015/10/popular-benzodiazepines.jpg

Long-Acting Opioid Medications

- Narcotic medications are highly effective for intractable symptoms
- Consider patients carefully



- Methadone
  - Use 5 mg ½ tablet to 2 tablets as needed up to three times daily
  - Most patients respond well to low doses for sustained periods (>5 years)
  - If escalating doses are "required" consider secondary gains
  - Rate of discontinuation after first year up to 10 years: 0%
  - Rate of augmentation: 0%
  - Stigma associated with use
  - State laws may restrict access

Figure adapted from Silver *et al.*, 2011

Alternative Therapies

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

Image source: http://www.medgadget.com/wp-content/uploads/2015/03/2015-03-17-15-20-10-423475663.jpg

Relaxis Pad

- FDA approved medical device
- Place pad under the area of discomfort
- Choose the vibration intensity that feels best
- Provides 35 minutes of vibration (“vibratory counterstimulation”), gradually ramping down and shutting off without waking the user.

- Side effects:
  - Temporary worsening of symptoms
  - Leg cramping
  - Tingling
  - Soreness
  - Pain
  - Motion sickness
- Requires a prescription
- Not covered by insurance and costs $626

Home Relief for Neuropathic Pain

- A warmer bedroom – direct fan away
- Good sleep hygiene
- Soft diabetic socks to avoid touch of sheets/covers
- Evening dose of pain medication
- Topical pain relief (capsaicin or lidocaine)

The Role of CBTI

- Cognitive behavioral therapy for insomnia (CBTI) is a 6-week program that is the best treatment for chronic insomnia.
- Components include:
  - Sleep education
  - Sleep consolidation
  - Relaxation techniques
  - Mindfulness
- May be done with a therapist, workshop, online course (Insomnia Solved), or book (*Sleep Through Insomnia*)

Image source: https://expertbeacon.com/sites/default/files/avoid_the_cycle_of_chronic_insomnia_poor_sleep_and_exhaustion.jpg

General Guidelines for Medical Therapy

- Optimal therapy should reduce bothersome symptoms and consequences while minimizing any adverse effects.
- Begin therapy when the affected person is impacted.
- Medications that enhance GABA are often first-line therapy.
- Consider the use of PRN medications to address situational exacerbations.
- Benzodiazepines and opioids are often used as a last resort due to the potential for dependence and abuse.
- Consider seeing a specialist for optimized care management.

Questions?

E-mail: BrandonPetersMD@gmail.com

Twitter/X: @BrandonPetersMD

www.BrandonPetersMD.com

References

- Allen R, Picchietti D, Hening W, *et al*. "Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health." *Sleep Med* 2003;4:101-19.
- Allen RP *et al*. "Clinical efficacy and safety of IV ferric carboxymaltose (FCM) treatment of RLS: A multi-centred (sic), placebo controlled preliminary clinical trial." *Sleep Medicine* 12(2011):906-913.
- American Academy of Sleep Medicine. *International classification of sleep disorders*, 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014.
- Buchfuhrer MJ. "Strategies for the treatment of restless legs syndrome." *Neurotherapeutics* 2012;9(4):776-90.
- Burbank F *et al*. "Sleep improvement for restless legs syndrome patients. Part 1: Pooled analysis of two prospective, double-blind, sham-controlled, multi-center, randomized clinical studies of the effects of vibrating pads on RLS symptoms." *Journal of Parkinsonism and Restless Legs Syndrome* 2013;3:1-10.
- Coccagna G, Vetrugno R, Lombardi C, and Provini F. "Restless legs syndrome: an historical note." *Sleep Med* 2004;4(3):279-83.
- Dauvilliers Y, Winkelmann J. "Restless legs syndrome: update on pathogenesis." *Curr Opin Pulm Med* 2013;19:594-600.
- Ekbom K. "Restless legs: a clinical study." *Acta Med Scand* 1945;158:1-122.

References (cont.)

- Ferni-Strambi L, Walters AS, and Sica D. “The relationship among restless legs syndrome (Willis-Ekbom Disease), hypertension, cardiovascular disease, and cerebrovascular disease.” *J Neurol* 2013 Aug 21.
- Kryger MH, *et al*. "Principles and Practice of Sleep Medicine." Elsevier. 5th edition. 2011.
- Merlino G *et al*. “Association of restless legs syndrome in type 2 diabetes: a case-control study.” *Sleep* 2007 Jul;30(7):866-71.
- Oertel W *et al*. “Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study.” *Lancet Neurol* 2011;10:710-20.
- Ohayon MM, O’Hara R, Vitiello MV. “Epidemiology of restless legs syndrome: A synthesis of the literature.” *Sleep Med Rev* 2012;16:283-95.
- Scott LJ. “Gabapentin enacarbil in restless legs syndrome.” *CNS Drugs* 2012;26(12):1172-7047.
- Silver N, *et al*. “A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome.” *Sleep Medicine* 2011;12:440-444.
- Spence D. “Bad medicine: restless legs syndrome.” *BMJ* 2013;347:f7615.

the FOUNDATION for PERIPHERAL NEUROPATHY®

Questions?

DEDICATED to REVERSING the IRREVERSIBLE

www.foundationforpn.org

the FOUNDATION for PERIPHERAL NEUROPATHY®

Thank You for Watching!

Did you like this webinar? Please take our survey at the end of this webinar. A recording will be uploaded on our website at www.foundationforpn.org shortly. Stay tuned.

Do you like us? Please consider supporting us so that we can continue to fulfill our mission of improving the lives of people living with Peripheral Neuropathy. You can give securely online, via mail or via phone. Every dollar matters!

Can we help with anything else? Call 847-883-9942 or email info@tffpn.org. You may also mail inquiries and donations to *the* Foundation *for* Peripheral Neuropathy at 485 E. Half Day Road, Suite 350, Buffalo Grove, Illinois 60089.