

Medications Used to Treat Restless Legs Syndrome

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Introduction

- Restless legs syndrome (RLS)
 - Common, under-diagnosed, treatable condition
 - Symptoms are most consistent with sensory-motor feelings
 - Neurological movement disorder associated with sleep disorder
 - Prevalence 2 - 15%
 - Incidence increases with age
 - Most common in women 2:1
 - Diagnosis is based on clinical features

Prevalence by Severity

- RLS at any frequency or severity 7.2%
- RLS at least weekly 5.0%
- RLS >2/week and distressing 2.7%
- Prevalence in subpopulation of those with RLS
 - Men ~ 1.7%
 - Women ~ 3.7%

Allen RP, et al. *Arch Intern Med.* 2005;165:1286-1292.

RLS: Diagnostic Criteria

- NIH characteristics of RLS
 - Urge to move the limbs with or without sensations
 - Worsening at rest
 - Improving with activity
 - Worsening in the evening or night
- Validated diagnosis is based on these criteria

Allen, Picchietti et al., *Sleep Med*2003;4:101-119.

Sensations of RLS

•Terms used to describe RLS by patients:

- Creeping
- Crawling
- Itching
- Burning
- Searing
- Jimmy legs
- The gotta moves
- Tugging
- Indescribable
- Pulling
- Drawing
- Aching
- Flowing water
- Elvis legs



RLS: Associated Conditions

- Attention deficit disorder
 - Adults and children
- Anxiety
 - ~ 13 times the risk of panic attacks
- Depression
 - ~ 5 times the risk in RLS

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RLS: Associated Conditions

- Evidence suggests that patients with long standing RLS leads to chronic sleep deprivation and may be at higher risk for:
 - Cardiovascular disease
 - Hypertension

RLS: Clinical Course

- Chronic condition
- Occasional remissions
- Exacerbations
- Onset at any age
- Severity increases with age
 - Most common disorder in people >65 yo

Quality of Life

- General discomfort
- Sleep problems – getting to sleep and staying asleep
- Cognitive dysfunction
- Emotional dysfunction

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Exacerbation of Symptoms

- Triggers or worsening of conditions
 - Antihistamines (cold/sinus medicines)
 - Chlorpheniramine (Coricidin®)
 - Diphenhydramine (Benadryl®)
 - Brompheniramine (Dimetapp®)
 - Caffeine, nicotine, alcohol, lack of exercise, lack of sleep, long flights or meetings, low iron stores
 - Sympathomimetics (cold medicines)
 - Tyramine
 - Amphetamine
 - Dopamine Antagonist (Anti-nausea)
 - Metoclopramide (Reglan®)
 - Prochlorperazine (Compazine®)
 - Droperidol (Inapsine®)
 - Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRI's) (in some individuals)
 - Mirtazapine (Remeron®)

RLS: Etiology

- Primary RLS
 - A CNS disorder, not caused by psychiatric factors/stress
 - Dysfunction of the dopamine receptor in the basal ganglia, perhaps
 - Imbalance of neurotransmitters in the dorsal horn of the spinal cord or spinal excitability
 - Genetic-Evidence to suggest it is hereditary
 - > 40% have a family history
 - Three main chromosome defects: This accounts for 70% of RLS cases
 - MEIS1 on chromosome 2p
 - BTBD9 on chromosome 6p
 - MAP2K5 and LBXCOR1 on chromosome 15q
- Secondary RLS
 - Non-genetic causes

Secondary RLS

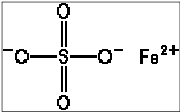
- Iron deficiency anemia
 - Iron is the cofactor for the rate limiting step in production of levodopa
- End-stage kidney disease
 - 6-60%
- Peripheral neuropathy, Parkinson's Disease (~ 21%)
- Pregnancy
 - Risk increased up to 27%
- Diabetes
 - Type II DM a risk factor
- Other: Folate and Mg deficiencies, vitamin E, C, B12 deficiencies, hypothyroidism

Treatment of Secondary RLS

Iron

- Measuring iron deficiency
- Ferritin is a good predictor of iron stores
- Can be falsely elevated with inflammation
- % iron saturation and TIBC can be helpful
- Normal is ~ 11 to 30%
- Low normal is not good enough for RLS
- Treatment goal of ferritin > 50ng/ml

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Treating Iron Deficiency

- Oral iron
 - Ferrous sulfate 325 mg, one 2 to 3 x/day
 - Slow Fe 160 mg, one 2 to 3 x/day
 - Ferro-sequels – contains a laxative
- Absorption enhanced
 - Take each dose with 250 mg of vitamin C, empty stomach, no calcium with the dose, avoid tea
- IV iron for severe unresponsive iron deficiency
- Treat constipation with stool softener

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RLS Treatment: Pregnancy

- Non-pharmacologic first line
 - Hot baths, massage, elastic stockings, sleep
- Iron replacement
- Opiate medications
- Methadone safest
- 3rd trimester safest for drug treatment

Primary RLS: Therapy

- Non-medical
 - Lifestyle changes
- Medical
 - Primary therapy
 - Secondary therapy

RLS: Non-Medical Therapies

- Good sleep hygiene
 - May change sleep time
- Moderate physical activity (e.g. walking, stationary bike riding, kickboxing, etc.)
- Hot or cold packs, baths, massage
- Rubbing or pressure, stretching
- Engage the mind (yoga, meditation)

How Many People Here

- Take hot showers or baths???



RLS: Medical Therapy

- Dopaminergic agonists
- Benzodiazepines
- Opioids
- Antiepileptic drugs
- Iron
- Levodopa/carbidopa
- Other

RLS Treatment: Dopaminergics

- **Requip® (ropinirole)**
 - 0.75mg daily-24mg daily for Parkinson's disease
 - 0.25mg daily week 1 (typical starting dose for RLS) and increase to relief of symptoms (max dose 3 mg/daily)
 - Requip XL total daily ropinirole dose given once daily
- **Mirapex® (pramipexole)**
 - 1.5 – 4.5 mg daily for Parkinson's disease
 - 0.125mg-1.5mg daily (in 2-3 divided dose) for RLS
- **Sinemet® (carbidopa/levodopa)**
 - Parkinson's Disease dose varies
 - 50 - 200 mg hs or 25/100 given 30 to 60 minutes before bedtime and may repeat once
 - Controlled Release (CR) may be best in RLS
- **Rotigotine (Neupro® patch)**
 - Currently not on the market

Dopaminergics: Side Effects

- Class effects:
 - Nausea
 - Vomiting
 - Orthostatic hypotension
 - Hallucinations
 - Augmentation of symptoms
 - Insomnia
 - Compulsive behavior, rare but potentially devastating

Dopaminergic Agent Withdrawal

- Symptoms occur after sudden discontinuation of drug
- Symptoms include anxiety, panic attacks, depression, sweating, nausea, dizziness, generalized pain, and drug cravings
- Only occurs in patients with Impulse Control Disorders (ICDs)
- Possible solutions:
 - Avoid high doses of dopamine agonists
 - Closely monitor patients for symptoms of ICDs
 - Warn patients of risks
 - Taper off drug at first sign of ICDs
 - Closely monitor patients when tapering off dopamine agonists

www.medicalnewstoday.com/articles/75634.php

Dopaminergics: Drug Interactions

- Increase blood levels of pramipexole (Mirapex®):
 - Cimetidine (Tagamet®) – increases blood levels by ~ 50% and extends the half-life by ~ 40%
 - Ranitidine (Zantac®) decreases clearance by ~ 20%
 - Diltiazem, verapamil decreases clearance by ~ 20%
 - Triamterene decreases clearance by ~ 20%
- Increase blood levels of ropinirole (Requip®):
 - Ciprofloxacin (Cipro®)
 - Estrogens
- Decrease blood levels of pramipexole (Mirapex®):
 - Cephalosporins
 - Penicillins
 - Indomethacin (Indocin®)
 - Hydrochlorothiazide

Symptom Augmentation

- Increased symptom intensity related to increased dosage of medications
- There is a lag to beneficial symptom relief
- Duration of treatment benefit is shorter
- Symptoms extend to previously unaffected body parts (arms, etc.)
- Symptoms begin presenting earlier in day
- More patients on levodopa have augmentation than those on a dopamine agonist

Treating Augmentation

- Lack of controlled trials with evidence to guide
- Possible strategies
 - Decrease or split dose and increase non-medicine treatments
 - Treat to ferritin above 50 ng/ml
 - Consolidate sleep
 - Discontinue levodopa
 - Change dopamine agonist
 - Change to a different class of medication
 - Drug holiday
 - Combination of agents with different mechanisms of action

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Other Treatments

- Look around, there are other options to be considered!
 - Opiate receptors
 - GABA, NMDA, AMPA
 - Glutamate: an excitatory neurotransmitter

RLS Treatment: Sedative Hypnotics

- Benzodiazepines (BZD's)
 - Improves sleep
 - Off label use
 - Clonazepam (Klonopin®) 0.5 to 4 mg/day
 - Temazepam (Restoril®) 15-30 mg/day
- Side Effects
 - Constipation, urinary complications, cognitive dysfunction

RLS Treatment: Opioids

- Codeine 15 to 120 mg/day
- Oxycodone 2.5 to 20 mg/day
- Methadone 5 to 30 mg/day
- Side Effects
 - Constipation, tolerance or loss of effect

RLS Treatment: Antiepileptic drugs

- Valproic Acid (Depakote®)
- Carbamazepine (Tegretol®)
- Lamotrigine (Lamictal®)
- Gabapentin (Neurontin®)
- Pregabalin (Lyrica®)
- Side effects
 - Sedation, blood count abnormalities, rash, weight gain, edema, tremor, cognitive dysfunction



Other RLS Medications

- Liorasel® (baclofen)
- Catapres® (clonidine)
- Ambien® (zolpidem)
- Ultram® (tramadol)
- Side effects
 - Constipation, sedation, seizures (rare), cognitive dysfunction

Other RLS Medications

- Amantidine – non-dopamine agonist
- Selegiline – MAO-B inhibitor indirectly effects dopamine
- Bupropion – weak blocker of serotonin and norepinephrine and reuptake inhibitor of neuronal dopamine
- Apomorphine – dopamine system
- Intrathecal pumps – helpful in pain syndromes
- Acupuncture
- Estrogen
- Ketamine (NMDA receptor antagonist)
- CPAP for sleep apnea
- Cognitive behavioral therapy

On The Horizon/Future Research

- BGP15 – heat shock protein, just completed phase IIb studies in DMII
- XP-13512 – Phase III – Xenoport/GSK (decision pending FDA review on 2/9) – prodrug of Gabapentin (extended release) and has good absorption and BBB penetration
- Aplindore/Neurogen - Wyeth - Phase II clinical trials - better efficacy than placebo
- Ropinirole gel (topical)/Jazz pharmaceuticals – plans to restart clinical trials in the future
- Rifaximin (Xifaxan®) – approved by the FDA for travelers diarrhea - may improve IRLS
- Carbergoline (Dostinex®) – approved by the FDA for hyperprolactinemia
- Histamine and orexin (hyperarousal)
- Heat shock proteins

Generic vs. Brand Name Drugs

Brand



Generic

Benefits of Generic Drugs

- Decrease cost
 - Patient
 - Third party payer
- Increase availability
 - Multiple manufacturing sources
- Potential better adherence



Generic Drugs for RLS

- Requip® generic
- Manufacturers
 - Roxane Laboratories Inc.
 - Teva Pharmaceuticals USA
 - Par Pharmaceuticals Inc.
 - Mylan Pharmaceuticals Inc.
- Mirapex® generic
- Manufacturers
 - Teva
- Some narcotics, antiepileptic drugs, and other medications may also come generic

Conclusion

- RLS is a common and an underdiagnosed treatable condition that can have significant effect on quality of life
- Onset can occur in childhood, although prevalence increases with age
- Numerous secondary causes treated the same as primary
- Dopamine agonists are 1st line therapy
- The availability of generic medications could dramatically increase the number of patients who get treatment for RLS