

Restless Legs Syndrome: Update on Diagnosis, Treatment, and Exciting Research

Charles H. Adler, M.D., Ph.D.
Professor of Neurology
Mayo Clinic College of Medicine
Senior Clinical Scientist
Banner Sun Health Research Institute

Restless Legs Syndrome (RLS): Criteria for Diagnosis

- *Urge to move* the limbs \pm uncomfortable sensations
- Symptoms are worse or exclusively *at rest* or during periods of inactivity
- Symptoms are partially or totally *relieved by movement*
- *Circadian rhythm*: symptoms must be worse or exclusively in the evening or night

Allen et al. *Sleep Med* '03

RLS Features



- Sensory symptoms:
 - Creepy, crawly, tingly, painful, burning, achy
 - Like worms or bugs crawling deep in the muscle; Like water running under the skin
- Usually affects both legs simultaneously but can be unilateral or alternating
- Arms may be involved
- Many patients experience symptoms daily

Allen et al. *Sleep Med* '03

Epidemiology of RLS

- Very common disorder, 5-15% of population
- ~2%-3% of the U.S. population report RLS symptoms that may require Rx
- Prevalence increases with age
- Age of onset is often < 30 yo
- Gradually progressive-so age at diagnosis is often in mid-life

Phillips et al. *Arch Int Med* '00; Rothdach et al. *Neurol* '00; Ulfberg et al. *Eur Neurol* '01; Allen et al. *Sleep Med* '03; Ondo *Sleep Med* '03; Hening et al. *Sleep Med* '04; Bjorvatn et al. *Sleep Med* '05; Allen et al. *Arch Intern Med* '05; Vogl et al. *Mov Dis* '06; Cho et al. *Sleep* '08

Periodic Leg Movements

- Results in excessive daytime sleepiness
- Involuntary, periodic (every 20-40 sec) slow leg and hip movements (1-2 sec in duration)
- Diagnosis is made by the bed partner or by a sleep study
- Treatment includes same medications used for RLS but given at HS or middle of the night only

RLS – PLMS Comparisons

Cause of RLS: Unclear

- Role of Iron Deficiency
 - Decrease in CSF ferritin and increase in transferrin indicate low brain iron stores
 - MRI shows less iron in SN and putamen
 - Iron changes found pathologically
- Role of Dopamine Deficiency
 - Dopaminergic drugs are effective for RLS
 - RLS and akathisia occur with dopamine antagonists
 - Some PET/SPECT studies support central dopamine dysfunction in RLS¹⁻³ others do not⁴⁻⁶

Early et al. Neurology '00; Allen et al. Neurology '01; Connor et al. Neurology '03; Early et al. Sleep '05; Early et al. Sleep Med '06; Turjanski et al. Neurology '99; Michaud et al. J Neurology '02; Routtinen et al. Neurology '00; Happe et al. J Neurology '03; Eisensehr et al. Neurology '01; Cervenka et al. Brain '06

Etiologies for RLS

- Idiopathic, often hereditary (mainly autosomal dominant)
 - Chromosome 12¹, 9^{2,3}, 14^{4,5}, 20⁶, 27⁷ possible loci
- Secondary
 - Iron deficiency (including multiple blood donations)
 - Pregnancy (11-27%)
 - End-stage renal disease
 - Medications- TCA, SSRI⁸, MAO-I, lithium, antihistamines, dopamine antagonists
 - Peripheral neuropathy
 - Multiple sclerosis⁹

¹Desautels et al. Am J Hum Genet. 2001; ²Chen et al. Am J Hum Genet. 2004; ³Lohmann-Hedrich et al. Neurology '9; ⁴Bonati et al. Brain. 2003; ⁵Levchenko et al. Ann Neurol '04; ⁶Levchenko et al. Neurology '06; ⁷Pichler et al. Am J Hum Genetics '06; ⁸Rottach et al. J Psych Res '08; ⁹Italian REMS Study Group Sleep '08

Assessment

- History-major method of diagnosis. Ask about the four core diagnostic features
- Neuro exam: normal if idiopathic
- Lab testing if indicated: complete blood count, serum ferritin, folate, serum chemistries, glucose, glycosylated hemoglobin
- International RLS rating scale = IRLS

RLS RATING SCALE

Each question 0–4 so max = 40

1. Overall, how would you rate the RLS discomfort in your legs or arms?
2. Overall, how would you rate the need to move around because of your RLS symptoms?
3. Overall, how much relief of your RLS arm or leg discomfort do you get from moving around?
4. Overall, how severe is your sleep disturbance from your RLS symptoms?
5. How severe is your tiredness or sleepiness from your RLS symptoms?
6. Overall, how severe is your RLS as a whole?
7. How often (days/wk) do you get RLS symptoms?
8. When you have RLS symptoms how severe (number of hrs) are they on an average day?
9. Overall, how severe is the impact of your RLS symptoms on your ability to carry out your daily affairs?
10. How severe is your mood disturbance from your RLS symptoms?

Walters et al. Sleep Med '03

Medication Treatment Issues

- Age of patient
- Distribution/frequency/severity of symptoms
- Start meds at bedtime ± evening then titrate
 - Use middle of night or day dosing only if needed
- Treatment is symptomatic, not curative
- Benefit is based on subjective response

Medication Options

- Iron
- Dopaminergic agents
- Anticonvulsants
- Benzodiazepines
- Opiates
- Others

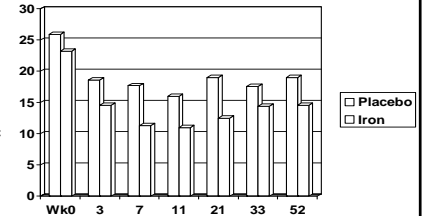
Oral Iron Treatment

- Replace iron in patients with serum ferritin levels < 50 µg/dL or iron saturation < 16%
- Ferrous sulfate 325 mg TID given concurrently with vitamin C (improves absorption)
- May take weeks to see benefit
- SE: constipation, gastric irritation
- Check ferritin level every 2-3 of months till ferritin > 50 mcg/dL or iron saturation > 20%. Beware of hemochromatosis.

Earley C.J. *N Engl J Med* '03

IV Iron Sucrose

- 60 patients:
29 IV iron
31 placebo
- 1 yr of treatment
- Drop outs (lack of efficacy):
– Placebo 19/31
– Iron 5/29



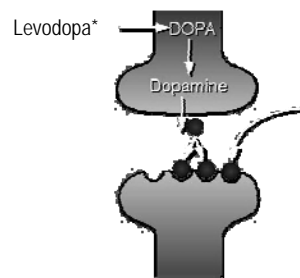
Grote et al. *Mov Disorders* '09

IV Iron (Ferric Carboxymaltose)

- 500 mg day 0 and 5
- Decrease in RLS rating scale at Day 28
- Remissions at Day 28:
7/24 (29%) iron vs. 1/21 (4.8%) placebo

Allen et al. *APSS Sleep Congress* '09

Dopaminergic Agents



- DA Agonists**
- Ropinirole (Requip)
 - Pramipexole (Mirapex)
 - Rotigotine (Neupro patch)*
 - Bromocriptine (Parlodel)*
 - Pergolide (Permax)*
 - Cabergoline (Dostinex)*

* Not an FDA approved indication for RLS

Levodopa

- Not recommended as first-line continuous therapy 2^o augmentation and rebound
- Can be used prn (plane, car, theater)
- Start ½-1 carbidopa/levodopa IR or CR 25/100
- Can add middle of night and day doses
- Very well studied, including hemodialysis pts

von Scheele et al *Arch Neurol* '90; Collado-Seidel et al *Neurol* '99; Janzen et al *Ann Pharmacother* '99

Augmentation and Rebound

- Augmentation
 - A combination of earlier onset of symptoms, increase severity, and involvement of other limbs
 - Symptoms shift to earlier in evening then daytime
 - Retrospectively up to 80% of levodopa treated and 48% of dopamine agonist treated patients
- Rebound
 - Wearing off of drug effect, typically in the AM

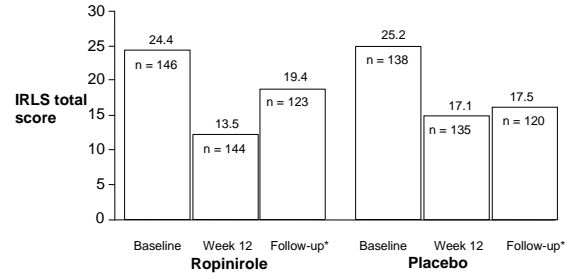
Allen and Earley *Sleep* '96; Stiasny et al. *Parkinsonism Relat Disord* '00; Winkelmann et al. *Mov Disorders* '98; Garcia-Borreguero *Sleep Med* '04; Ondo et al *Arch Neurol* '04

Ropinirole for RLS

- Double-blind placebo-controlled studies¹⁻⁷
- Improves RLS and PLMS
- Effective dose is 1.5 to 6 mg/d-single or divided doses
- Main SE: nausea, orthostasis, dizziness, sleepiness, insomnia

¹Trenkwalder et al. *JNNP* '04; ²Saletu et al. *Neuropsychobiol* '00; ³Stiasny et al. *Neurol* '01; ⁴Adler et al. *Neurol* '03; ⁵Walters et al. *Mov Dis* '04; ⁶Bogan et al. *Mayo Clin Proc* '06; ⁷Montplaisir et al. *Mov Dis* '06

Ropinirole 12 week study

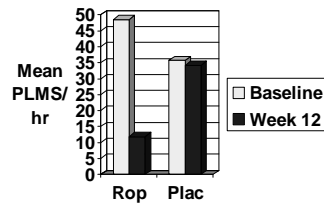


* 7 ± 3 days after the last treatment dose

Trenkwalder et al. *JNNP* '04

Ropinirole for PLMS

- N = 59
- Mean dose = 1.8 mg/d
- 54% < 5 PLMS/hr
- Improved sleep time
- RLS rating score not different



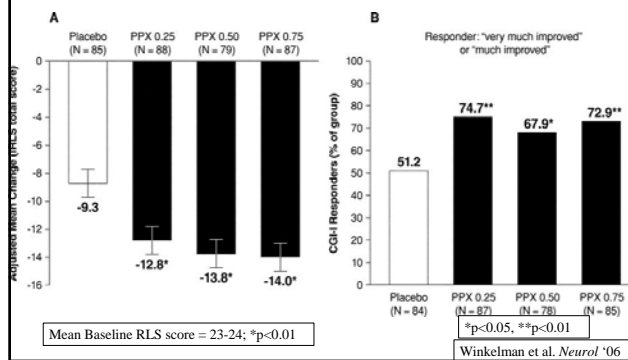
Allen et al. *Sleep* '04

Pramipexole for RLS

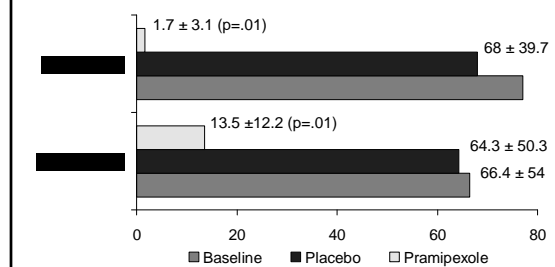
- On-label¹⁻³ and double-blind trials^{4,6,7}
- Improves RLS and PLMS
- Doses of 0.375 to 0.75 mg/d single or divided doses
- Main SE: nausea, orthostasis, sleepiness, insomnia
- Augmentation does occur (33% pts in retrospective studies)^{3,5}

¹Lin et al. *Mayo Clin Proc* '98; ²Becker et al. *Neurol* '98; ³Silber et al. *Sleep* '03; ⁴Montplaisir et al. *Neurol* '99; ⁵Winkelman & Johnston. *Sleep Med* '04; ⁶Winkelman et al. *Neurol* '06; ⁷Oertel et al. *Mov Dis* '07

Pramipexole 12 week study



Pramipexole for PLMS



Montplaisir et al. *Neurol* '99

Potential Side Effects with Dopamine Agonists

- Nausea and vomiting
- Augmentation
- Rebound
- Impulse Control Disorders

Anticonvulsants for RLS

- Gabapentin^{1,2}
 - 100 mg qHS up to 600 mg qid
 - Works in hemodialysis patients³
 - Nausea, dizziness, somnolence
- Carbamazepine⁴
 - 200 mg qHS up to 200 mg tid
 - Nausea, dizziness, somnolence, liver toxicity

¹Adler, *Clin Neuropharm* '97; ²Garcia-Borreguero et al, *Neuro* '02; ³Thorp et al, *Am J Kid Dis* '01; ⁴Zucconi et al, *Functional Neuro* '89

Gabapentin for RLS

	Gabapentin (n=22)	Placebo (n=22)	P value
RLS rating scale ¹	9.5 (1.3)	17.9 (1.3)	<.001
CGI-C ²	1.8 (0.3)	2.9 (0.3)	<.01

¹Baseline RLS score = 20/40; ²CGI-C is 1-7 scale w/4 being no change

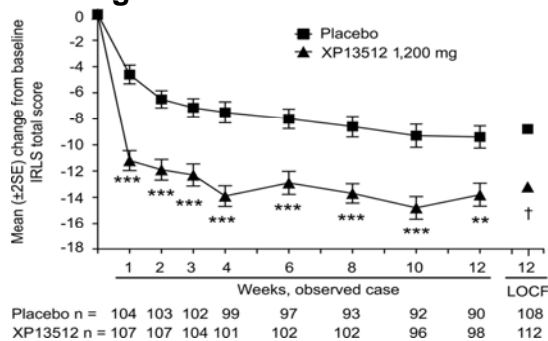
Garcia-Borreguero et al, *Neuro* '02

Gabapentin Pro-drug

- Gabapentin absorption varies in patients
- XP13512/GSK1838262 is a gabapentin pro-drug rapidly converted to gabapentin
- Placebo (n=108) vs. XP 1,200 mg/d (n=113) for 12 wks
- Primary outcome measure is IRLS Rating Scale. Baseline: placebo = 22.6, XP=23.1

Kushida et al, *Neuro* '09

Change from baseline RLS score



Kushida et al, *Neuro* '09

Side Effects

- Somnolence: XP 27%, placebo 7%
- Dizziness: XP 20%, placebo 5%
- Fatigue: XP 9%, placebo 2%
- Headache: XP 14%, placebo 11%

Kushida et al, *Neuro* '09

Opioids/Narcotics

- Open-label and placebo-controlled studies show benefit for RLS and PLMS¹⁻³
- No clear advantage of one over another
- SE: nausea, dizziness, constipation, sedation, sleep apnea
- Tolerance, addiction are minimal problems
- Can be used prn

¹Hening et al. *Neurol* '96; ²Walters et al. *Sleep* '93; ³Walters et al. *Mov Dis* '01; ⁴Jakobsson et al. *Acta Anesthes Scand* '02; Ondo et al. *Mov Dis* '05

Benzodiazepines

- Limited studies with only modest improvement of RLS or PLMS
- Clonazepam (0.25-4 mg/d) is most commonly prescribed but no clear advantage
- Can be used prn
- Side effects: somnolence, confusion, tolerance, dependence, withdrawal syndrome
- Main use is at night to help with insomnia

Horiguchi et al. *Japan J Psych Neurol Neurol* '92; Vignatelli et al. *Eur J Neurol* '06

Other Medications for RLS

- Non-benzodiazepines
- Clonidine
- Baclofen
- Amantadine
- Tramadol- narcotic w/ non-opioid mechanism of action
- Ropinirole XL

¹Bezerra, Martinez, *Eur Neurol* '02; Evidente et al. *Mov Disorders* '00; Lauerma & Markkula *J Clin Psych* '99

Evidence Based Medicine Review: Trenkwalder et al. *Mov Dis* '08

Class	Efficacious	Likely efficacious	Investigational	Non-efficacious
Non-ergot dopaminergic	Levodopa Ropinirole Pramipexole	Rotigotine patch		
Ergot dopaminergic	Pergolide	Bromocriptine	DHE Transderm lisuride	
Opioids		Oxycodone	Methadone Tramadol	
Benzodiazepines			Clonazepam	
Non-benzo			Zolpidem	
Anticonvulsants	Gabapentin	Carbamazepine Valproic acid	Topiramate	
Iron		IV in renal dis	Oral in iron deficiency IV in non-renal dis	Oral in non-iron deficient
Other		Clonidine	Amantadine Folic acid, Mg	

Treatment of Augmentation

- Reduce the dose of the provocative medication
- Switch to an alternate dopaminergic medication (dopamine agonist for levodopa) or different class (opioid or anticonvulsant)
- Combine agents

Treatment of Rebound

- Add a middle of the night dose
- Switch to a longer lasting medication (e.g. controlled release levodopa or a dopamine agonist)

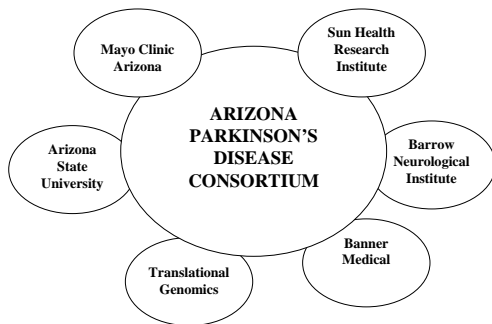
RLS Conclusions

- Must be sure to ask about RLS
- Not all cases need to be treated but all should be diagnosed
- Treatment is trial and error with multiple medication options in multiple drug categories
- Treat based on subjective response
- Watch for augmentation and rebound
- Participate in research

Brain Donation Program: Sun Health Research Institute

- Established in 1987 in Sun City, AZ
- Neuroscientists interested in studying Alzheimer's disease and Parkinson's Disease
- Individuals from the community enroll to donate their brains upon death. Undergo standardized antemortem evaluations
- Neuropathology report sent to the family and physicians

AZ PD Consortium: 1996-Present



Arizona Parkinson's Disease Consortium

- Longitudinal clinical assessments
- Find biomarkers for development of PD
- Find biomarkers for development of dementia in PD
- Clinicopathologic correlation studies of PD and other movement disorders (PSP, ET, RLS, etc)

Whole Body Donation Program

- Started in late 2005
- Currently ~1,000 subjects enrolled
- Target is 1,000 living subjects (500 "normal" elderly and 500 with targeted disorders)
- ~75 autopsies performed each year
- Mean postmortem interval = 3 hours

Current Clinical Core Methods

- **Annual evaluations:** Movement disorder exam and neuropsych test battery on all subjects; general neurological exam/medical evaluation on affecteds; sleep, autonomic, bowel movement questionnaires
- **Every other year:** General neurological exam/medical evaluation on controls; electrophysiological testing on a subset of cases
- **Every 3rd year:** Smell test (UPSIT-40)

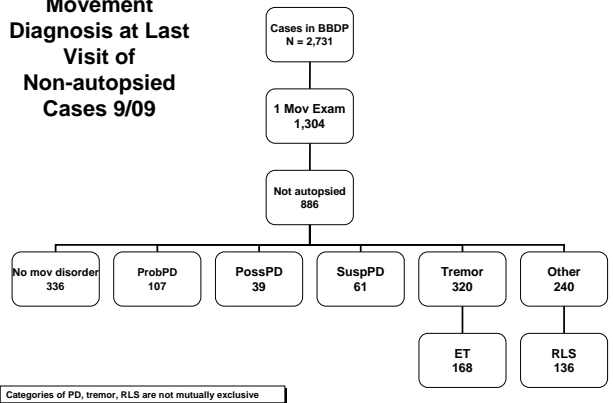
Current Movement Battery

- UPDRS- all 4 sections
- Hoehn & Yahr staging
- Timed tap test
- Purdue pegboard test
- Tremor ratings
- Evaluate for RLS (RLS rating scale), dystonia, myoclonus (lateral flicker), chorea, square wave jerks, vertical gaze palsy

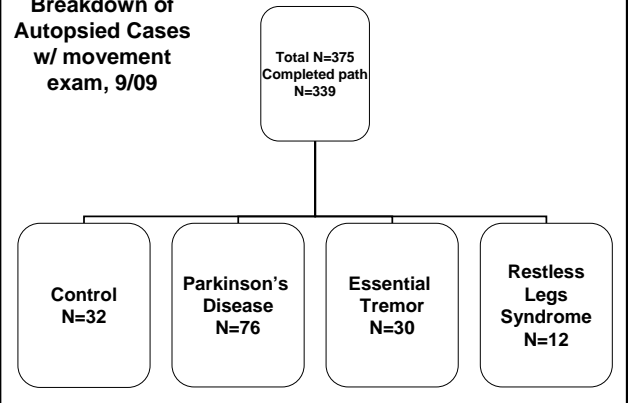
Current Cognitive Battery

- Global Functioning: Folstein MMSE
- Attention domain: Digits Forward and Backward
- Memory domain: Auditory Verbal Learning Test (AVLT)
- Language domain: COWA and Category Fluency
- Visuospatial domain: Clock Drawing and JLO
- Frontal Executive Domain: Trails Part A/B and STROOP
- Depression: Geriatric and Hamilton

Movement Diagnosis at Last Visit of Non-autopsied Cases 9/09



Breakdown of Autopsied Cases w/ movement exam, 9/09

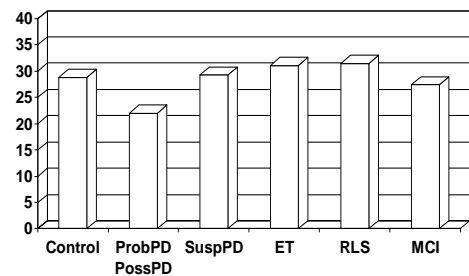


Smell Test Study

- To date we have performed UPSIT on 733 subjects and 155 subjects have had >1 UPSIT
- Cross-sectional analysis was last performed March, 2008
- N = 365
- Paper in press in International Journal of Neuroscience



UPSIT adjusting for age, sex, smoking



RLS and Cognitive Function

- Compared 26 RLS with 208 Controls
- Mean age 78
- Mean duration of RLS= 11 yrs, score = 11
- No difference in cognitive scores
- No difference in depression scores
- Currently analyzing data to determine whether RLS patients have an increased likelihood for developing cognitive impairment

Driver-Dunckley et al. *Mov Disorders* '09

RLS and Impulse Control Disorders

- Survey sent to 261 RLS patients, 99 responded, 77 on a dopamine agonist
- 70 answered gambling questions, 4 (6%) had an increase on DA
- 3/77 (4%) had increased sexual desire on DA

Driver-Dunckley et al. *Clin Neuropharmacol* '07

Brain and Body Donation Program: RLS studies

- **How can we learn more about RLS?**
- **Antemortem studies**
 - Serum for biomarkers
- **Autopsy studies**
 - 12 RLS brains: 10 Cog NL, 2 MCI
 - 36 RLS brains: with associated ET, PD and dementia