

Restless Leg Syndrome and Parkinson's Disease: Dopamine Deficient States

Scott J. Sherman MD, PhD
Associate Professor of Neurology
The University of Arizona

Restless Leg Syndrome

- Urge to move legs
 - With or without unpleasant sensations
- Worsened with rest
- Improved with activity
- Worsening in the evening or night
- Supportive factors
 - Family Hx
 - Presence of PLMS

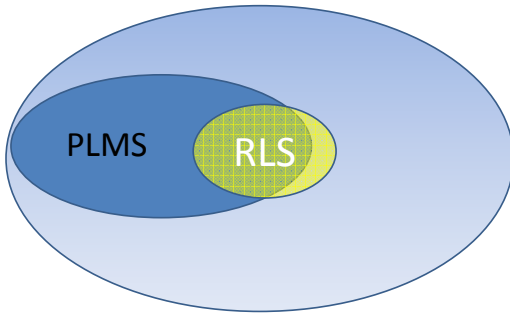
Sensory Phenomenon

- Need to move
- Crawling
- Tingling
- Restless
- Cramping
- Creeping
- Pulling
- Painful
- Tension
- Discomfort

Periodic Limb Movements

- Repetitive, stereotyped
- Video
- Movements occur during sleep

Overlap of clinical syndromes



Pathophysiology

- Reduced concentrations of brain iron stores
- Alterations in brain dopamine systems
- Multiple links between Fe and Dopamine
 - Tyrosine Hydroxylase
 - Thy-1 Adhesion molecule
 - Dopamine-2 receptor
- NO LOSS OF DOPAMINE PRODUCING NEURONS

Secondary RLS

- Renal Failure
 - (20-57% in HD patients)
 - Iron Deficiency
 - Neuropathy
 - Pregnancy (26%)
 - Other CNS conditions
 - Parkinson Disease
 - Reflects “wearing off” of dopamine replacent meds
- Is Akithesia related to RLS?
 - Fits with dopamine hypothesis

Treatment of RLS

- Dopamine Agonists
 - Ropinerole (™Requip)
 - Pramipexole (™Mirapex)
 - Rotigotine (™Neupro)
 - transdermal
- Anti-epileptics
 - ($\alpha_2\delta$ -blockers of calcium channels)
 - Gabapentin
 - Pregabalin (™Lyrica)
- Opioids
- Benzodiazepines
- Iron
 - Oral
 - IV iron dextran

Drug	Amount Per Dose (mg)	Duration of Effect (h)	Comment
<i>Dopaminergic: immediate effect, consider first line therapy</i>			
L-dopa	100-250	2-6	Approved in Europe, fast onset, can use as needed, highest augmentation rates
Pramipexole	0.125-1	5-12	Approved, commonly used, slower onset but longer duration
Ropinerole	0.25-4	4-8	Approved, slow release preparations available
Pergolide	0.125-1	6-14	Well studied but seldom used because of the risk for cardiac valve fibrosis and other possible ergot AEs
Cabergoline	0.25-2	>24	Long acting but may have same AEs as other ergot DAs
Rotigotine	0.5-6	24	Patch preparation, well studied and effective in RLS
Bismocriptine	5-20	4-6	Rarely used in RLS
<i>Opioids: numerous opioids are used</i>			
Methadone	2-15	8-12	Latency to benefit
Hydrocodone	5-10	4-10	Faster acting, shorter duration
<i>Alpha 2 delta blockers</i>			
Gabapentin	300-1200	4-8	May help painful component of RLS
Pregabalin	50-200	6-12	trials underway but almost no published data
Gabapentin	600-12,000	8-16	Gabapentin prodrug with better absorption and pk profile. Well studied and effective
<i>Benzodiazepines: more beneficial for sleep than RLS, can be used in combination with other RLS medications. Clonazepam (0.5-2.0 mg) is traditionally used.</i>			
Oral iron	>50	?	No specific iron salt is superior, titrate up as tolerated. Ferritin will only modestly increase
IV iron dextran	1 g	?	Usually not repeated before 3 months, several day latency to benefit, long term safety unknown, patients with “normal” serum ferritin equally responsive

William G . Ondo
Neurol Clin 27 (2009)
9779-799

Treatment Complications

- Augmentation (48%)
 - Phase shift
 - Dose escalation
- Drug Side Effects
- Dopamine agonists
 - Nausea
 - Rare but must monitor
 - Compulsive behaviors
 - “Sleep attacks”

Diagnosis of RLS

- Differential Diagnosis
 - Peripheral Neuropathy
 - Akathisia
 - Nocturnal Leg Cramps
 - Secondary RLS
 - “painful legs and moving toes” syndrome
- Ferritin and iron studies
- Electrolytes
- Optional Studies
 - (particularly when there is NO family hx)
 - NCV/EMG to r/o neuropathy
 - Polysomnography

PD: Clinical Features/Cardinal Signs

- 1817: James Parkinson “An Essay on the Shaking Palsy”
- Onset
 - mean PS 61.6 years; PD 62.4 years
 - rare before age 30; 4-10% cases before age 40
- Affect 1% of the population over 60 years of age

Early Signs and Symptoms

- Cardinal Characteristics
 - Resting tremor
 - Bradykinesia
 - Rigidity
 - Postural instability
- Other
 - Micrographia
 - Masked face
 - Stooped, shuffling gait
 - Decreased arm swing when walking

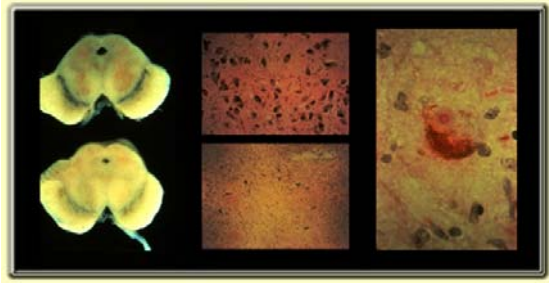
Additional Signs and Symptoms

- Difficulty arising from a chair
- Difficulty turning in bed
- Hypophonic speech
- Sialorrhea
- Loss of the sense of smell
- Foot dystonia

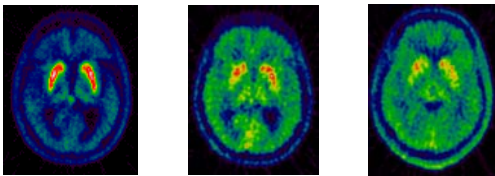
Criteria for Diagnosis

- At least two of three: rest tremor, bradykinesia, rigidity
- Absence of a secondary cause—drugs, metabolic, etc.
- Definitive diagnosis can only be made by autopsy
- Pragmatic approach: response to dopamine replacement therapy
 - May want to avoid early use of levodopa in younger patients

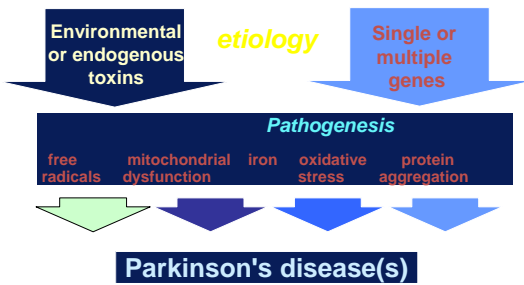
Pathology of Parkinson's Disease



^{18}F -DOPA PET scans



Etiology of Parkinson's disease

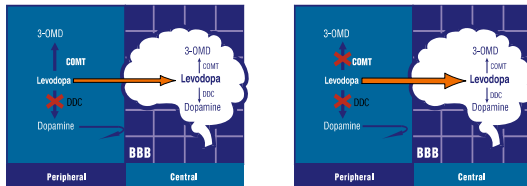


Drug Classes in PD

- Dopaminergic agents
 - Dopamine agonists
 - Levodopa
 - COMT inhibitors
- MAO-B inhibitors
- Anticholinergics
- Amantadine

Reducing the Peripheral Metabolism of Levodopa

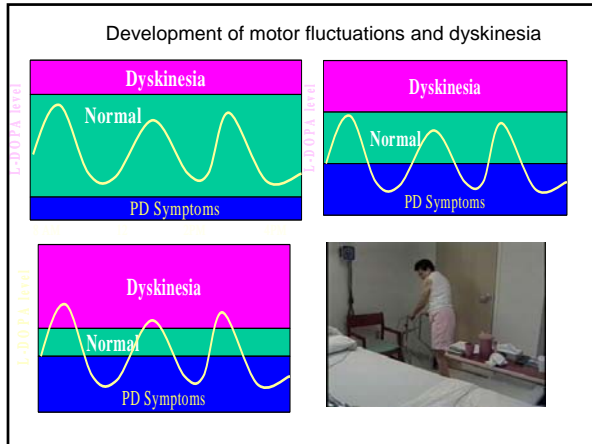
Addition of a COMT Inhibitor Decreases Conversion of Levodopa to 3-OMD in the Periphery



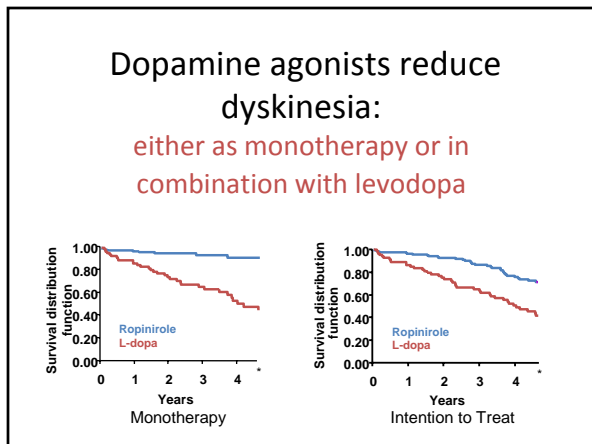
DDC = dopa decarboxylase; 3-OMD = 3-O-methyldopa; BBB = blood-brain barrier; COMT = catechol-O-methyltransferase.

Levodopa/Carbidopa Formulations

	Onset	Duration
Immediate Release 10/100, 25/100, 25/250	20-40 min	2-4 hr
Controlled Release 25/100, 50/200	30-60 min	3-6 hr
TM Stalevo 50, 75, 100, 125, 150 Triple combination Carbidopa/levodopa/entacapone	20-40 min	3-5 hr



- ### Benefits of Dopamine Agonists
- Direct receptor stimulation
 - does not require conversion to dopamine
 - does not add additional oxidative stress to remaining nigral neurons
 - Delay onset of dyskinesia
 - Decrease pulsatile stimulation
 - May have a neuroprotective effect



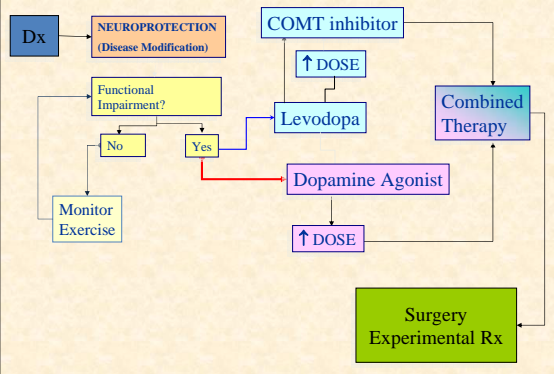
Dopaminergic Drugs

Drug	Dosing interval	PD dose	RLS dose
Ropinirole	TID (for PD)	6-24 mg/day	0.5-3 mg/night
Requip XL	qd	same	same (?)
Pramipexole	TID (for PD)	0.75-4.5 mg/day	0.125-1 mg/night
Mirapex ER	QD	same	Same (?)
Rotigotine	QD, transdermal	2-8 mg/day	Not approved (?)
Levodopa	TID- q2hr (PD)	300-1200 mg/day	100-250mg/night

DAs: Common Adverse Effects

- Nausea, vomiting
- Dizziness, postural hypotension, peripheral edema
- Drowsiness & somnolence, SLEEP ATTACKS
- Confusion, hallucinations
- COPULSIVE BEHAVIOR
 - Gambling, sexual addiction, compulsive eating

TREATMENT ALGORITHM FOR PARKINSON'S DISEASE



Comparison of RLS vs PD

	Parkinson Disease	Restless Leg
Dopamine dysregulation	+++	+++
Iron Dysregulation	? +	++
Dopaminergic cell loss	+++	-
Dopamine agonist response	++	+++
Levodopa response	+++	++
Family history/genetic component	+/-	+++
Primarily Clinical Dx	+++	+++
