Diagnosis and Treatment of Parkinson’s Disease

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Parkinson’s Disease

• 2nd most common neurodegenerative disorder
  – lifetime risk: 1 in 40-100
• Age of onset
  – Common after 60 y/o
  – Young onset (20-50 y/o) 10-15%
• Men get it more often than women
• 5% Inherited
• 95% likely caused by genetic predisposition and environmental influences
Parkinsonism

- Tremor (rest)
- Rigidity
- Bradykinesia/akinesia
- Decreased facial expression
- Stooped posture
- Micrographia/hypophonia
- Postural instability
Not all Parkinsonians have Parkinson’s Disease

**Neurodegenerative Disorders**
- Idiopathic Parkinson’s Disease
- Multiple System Atrophy
- Progressive Supranuclear Palsy/CBGD
- Diffuse Lewy Body Disease

**Secondary Parkinsonism**
- Vascular
- Neuroleptics
- Normal Pressure Hydrocephalus
Differential Diagnosis

**Parkinsonism**  
- Multiple System Atrophy  
  - Shy-Drager  
  - Striatal nigral degeneration  
  - OPCA  
- Progressive Supranuclear Palsy  
- Diffuse Lewy Body Disease  
- Corticobasal Degeneration

**Plus**  
- Postural instability  
- Dysautonomia  
- Non dopa-responsive  
- Cerebellar dysfunction  
- Gaze paresis  
- Dementia  
- Dystonia, apraxia

Most do not respond to L-dopa and have early loss of postural reflexes
MRI and MSA
$^{18}\text{F}-\text{Dopa PET}$

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

Pavese and Brooks, 2008
Think Parkinson’s Disease

With:
- Asymmetric onset
- L-dopa responsive
- Rest tremor

Without:
- Cerebellar signs
- Long-tract signs
- Early dementia
- Early dysautonomia
- Early falls
Initiation of Treatment

• General Considerations
  – Age
    • Young onset
      – neuroprotection
      – motor fluctuations
    • Older patients
      – cognitive issues
      – comorbidities
  – Disability
  – Cost
Early Parkinson’s Disease Treatment Guidelines*

Pharmacologic therapy/functional impairment

No treatment has been shown to be neuroprotective²

MAO-B Inhibitors (SEL) very mild symptomatic benefit¹

Dopamine Agonists¹

Levodopa†

Combined treatment (+/- COMT inhibitor)

Nonpharmacologic therapy

Education

Support Services

Exercise²

Nutrition

* AAN guidelines last updated in 2006 (2)
MAO-B Inhibition
Selegiline and Rasagiline

• Both have small symptomatic effect.
• Both might slow disease down a little.
• Rasagiline and SL selegiline have been shown to help wearing off (PO selegiline not well studied).
Rasagiline: The TEMPO Trial

Levodopa

• Efficacy
  – Most efficacious medication for control of PD symptoms.
  – Improves UPDRS motor scores by approx 50% in advanced patients.
  – Short half-life
  – Significant protein effect

• Side-effects
  – Long-term risk of motor fluctuations
Clinically, Levodopa Slows Ds Progression

Figure 2. Changes in Total Scores on the Unified Parkinson’s Disease Rating Scale (UPDRS) from Baseline through Evaluation at Week 42.
FIG. 8.2. Levodopa plasma levels following a standard oral dose of 125 mg given on an empty stomach (dark symbols) or with a 60-mg milk protein drink (open symbols). Note delayed plasma peak and reduced area under the curve when the drug was taken with protein.
Dopamine Agonists

• Efficacy
  – Less efficacious than levodopa
  – Have long half-lives
  – Less likely to cause motor fluctuations
  – Absorption without transporter (no protein effect)
  – Potential alternate routes of administration (e.g. patch, injection)

• Side-effects
  – Relatively more common than for levodopa especially in the elderly
  – Include sedation, hallucinations, impulse control, nausea
CALM-PD: Pramipexole vs Levodopa

Total UPDRS Score

Mean Score

$P < .002$ for each 3 month interval.

Weeks From Randomization

Pramipexole

Levodopa
5 Yr Ropinirole vs. Levodopa

Fig. 1. Dyskinesias in MPTP monkeys. Frequency of dyskinesia in 1-methyl-4-phenyl-1,2,3,6-

(a) Survival distribution function

(b) Survival distribution function

P < 0.0001

Ropinirole (n = 179)
L-dopa (n = 89)

Rascol 2000
Initiating Therapy

Disabled

Yes

-MAO-B I
-agonist (young)
-Sinemet CR

No

-educate
-exercise
-MAO-B I?

inadequate response

-reg sinemet
-question Dx
-COMT-I
-anticholinergic
Advancing Parkinson’s Disease

• Motor fluctuations (young)
  – Wearing off
  – Dyskinesias
  – On-off phenomenon

• Non-Motor Problems
  – Medication-induced psychosis
  – Cognitive decline
  – Postural instability
  – Urinary problems
  – Sleep problems
Principles of Managing Fluctuations

• Decrease fluctuations of L-dopa blood levels
  • Use smaller more frequent dosing.
  • Use combination of regular and CR Sinemet.
  • Add COMT inhibitor
  • Add MAO-B inhibitor

• Add DA agonist and reduce L-dopa
• Add amantadine for dyskinesias
• Surgery
Levodopa Biochemistry

L-dopa → dopamine

carbidopa

L-dopa

dopamine

Entacapone/tolcapone

3-OMD

BBB

dopamine

MAO

COMT

tolcapone

3-OMD
Effect of COMT-I on Plasma Levels

L-DOPA

with COMT-I

without COMT-I

Time

Sinemet
Advancing Parkinson’s Ds

- Hallucinations
  - D/C selegiline, anticholinergics, amantadine
  - lower dopaminergic medications (agonist 1st)
  - clozapine, quetiapine, cholinesterase-I

- Falls
  - optimize therapy
  - R/O orthostatic hypotension
  - physical therapy for training and assistive devices.
Advancing Parkinson’s Ds (cont.)

- **Depression**
  - serotonin uptake inhibitor (e.g. Paxil, Celexa), nortriptyline, NA/Serotoninergic uptake inhibitors, Wellbutrin

- **Dementia**
  - R/o other causes (metabolic, structural etc.)
  - Reduce medications as much as possible
  - Consider cholinesterase-I, memenatine
Advancing Parkinson’s Ds (cont.)

- Sleep Problems
  - sleep hygiene
  - optimize DA therapy
  - treat depression
  - Consider sleep study (apnea, RSB)
  - Sleep initiation: short acting benzo (Ambien, Sonata), Rozerem.
  - Sleep maintenance: Lunesta, Ambien CR, tricyclic antidepressant (nortriptyline, trazadone), Remeron, Benadryl
Summary

• Motor fluctuations are treatable but can require time and persistence
• Identify and treat non-motor problems, they can be very disabling
• When in doubt, call or refer to the National VA Parkinson’s Disease Consortium

http://www.vapdconsortium.org