Parkinson’s Disease: initial diagnosis, initial treatment & non-motor features

J. Timothy Greenamyre, MD, PhD
“Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported with a propensity to bend the trunk forwards and to pass from a walking to a running pace: the senses and intellect being uninjured.”
Clinical Signs and Symptoms

**Cardinal Features**
- Resting tremor*
- Bradykinesia*
- Rigidity*
- Postural instability*

**Other Motor Symptoms**
- Micrographia*
- Masked face*
- Slowing of ADLs*
- Stooped posture*
- Shuffling gait*
- Decreased arm swing when walking*
- Difficulty arising from a chair*
- Difficulty turning over in bed
- Sialorrhea*
- Hypophonic speech*

*noted by James Parkinson
How do we make a clinical diagnosis of PD?

• Insidious, unilateral onset
• 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
Differential Diagnosis

• **Drugs:**
  – Antiemetics: prochlorperazine (Compazine), metaclopramamide (Reglan)
  – Dopamine depleting agents: tetrabenazine, reserpine
  – Neuroleptics: including newer ‘atypical’ agents
  – Valproate
  – SSRIs
  – Many other drugs cause tremor
Differential Diagnosis

- **Vascular parkinsonism**: small vessel ischemic changes
  - typically lower body parkinsonism (gait disorder)
  - ± tremor, speech changes, bradykinesia, cognitive changes
Differential Diagnosis

• **Normal Pressure Hydrocephalus:**
  – Urinary incontinence, gait disorder, cognitive changes

• **HIV:**
  – Bradykinesia, rigidity, cognitive changes

• **Parkinson-plus syndromes:**
  – Corticobasal degeneration, Multiple system atrophy, Progressive supranuclear palsy, Spinocerebellar atrophy
How do we make a clinical diagnosis of PD?

**TABLE 1. UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria**

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<th>Supportive criteria</th>
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<td>And at least one of the following:</td>
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UK, United Kingdom; PD, Parkinson’s disease; CT, computed tomography.

Litvan et al, Movement Disorders, 2003
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<td>And at least one of the following:</td>
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<td>Muscular rigidity</td>
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<td>Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction</td>
<td>Neuroleptic treatment at onset of symptoms</td>
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<td>More than one affected relative</td>
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<td>Presence of cerebral tumour or communicating hydrocephalus on CT scan</td>
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<td>Negative response to large doses of levodopa (if malabsorption excluded)</td>
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<td>Progressive disorder</td>
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<td>Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction</td>
<td>Neuroleptic treatment at onset of symptoms</td>
<td>Persistent asymmetry affecting side of onset most</td>
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<td>More than one affected relative</td>
<td>Excellent response (70–100%) to levodopa</td>
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<td>Sustained remission</td>
<td>Severe levodopa-induced chorea</td>
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<td>Strictly unilateral features after 3 yr</td>
<td>Levodopa response for 5 yr or more</td>
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<td>Supranuclear gaze palsy</td>
<td>Clinical course of 10 yr or more</td>
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<td>Cerebellar signs</td>
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“Non-motor” Signs and Symptoms

- Anosmia
- Sleep disorders (REM Sleep Behavior Disorder)
- Constipation
- Depression
- Anxiety
- Erectile dysfunction
- Cardiac sympathetic denervation
- Orthostasis
- Memory problems & dementia
- Psychosis

*may precede motor symptoms by years*
How do we diagnose PD on a daily basis?

• Insidious, **unilateral** onset
• Bradykinesia, rigidity
• **Rest** tremor present
• Slowly progressive, but asymmetry is maintained
• Excellent response to levodopa

**Supportive data:**

• History of anosmia, constipation and/or REM sleep behavior disorder (RBD)
• No potential causes of 2° parkinsonism
Red Flags

• Rapid or sudden onset
• Symmetric presentation
• Rapid progression
• Lack of response to levodopa (or minimal/transient response)
• Early falls
• Early cognitive impairment
• Early, severe autonomic symptoms (orthostasis, ED, incontinence)
Ioflupane – $^{123}$I-labeled ligand for dopamine transporter found on dopaminergic terminals in striatum

- $^{123}$I is a gamma-emitting isotope that can be imaged with a gamma camera
- Loss of the striatal DATscan signal is indicative of degeneration of dopaminergic terminals
- FDA approved to assist in evaluation of adult patients with suspected Parkinsonism, Jan 2011
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*Diagnostic accuracy increases with disease duration and with assessment by movement disorders specialists*
Initial Treatment of Parkinson’s Disease
General Principles

The decision of when treatment is needed is a collaboration between patient and provider. (think functional impairment)

In terms of duration of drug efficacy or disease progression, there is no disadvantage to early vs. late treatment initiation. (*Myth: “Levodopa’s beneficial effects last only X years…”*)

Non-dopaminergic drugs (amantadine, selegiline, rasagiline) generally have minimal to mild symptomatic benefits. The exception is anticholinergic agents (e.g., trihexyphenidyl) for rest tremor.

The choice of dopaminergic drug (levodopa vs. dopamine agonist) to start with must be individualized.
Starting dopaminergic therapy

Levodopa is more efficacious for motor symptoms, and easier/faster to start and titrate to therapeutic doses than dopamine agonists, but it is associated with earlier development of motor fluctuations: wearing off, peak-dose dyskinesias, unpredictable “off” periods.

Dopamine agonists are associated with fewer motor fluctuations but must be started and titrated VERY slowly and are associated with more frequent side effects, including hallucinations, somnolence, edema and impulse control disorders. (Generally, do not start DAs in individuals over age 70)

As a general rule for all dopaminergic drugs, “start low and go slow”.
Starting dopaminergic therapy

When aiming for 3 times a day dosing, think TID rather than Q8h – need therapeutic levels in waking hours – less so over night until late in disease.

Despite package inserts to the contrary, it is often most practical (easily remembered) to take levodopa with meals. (Functionally important protein interference with LD absorption is not common in early-mid disease.)

Sustained-release levodopa preparations may be absorbed erratically leading to less predictable effects.

Anecdotal evidence suggests sustained release or patch formulations of dopamine agonists may be somewhat better tolerated than immediate release formulations.
Management of Nonmotor Symptoms in Parkinson’s Disease
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- Anxiety
- Erectile dysfunction
- Cardiac sympathetic denervation
- Orthostasis
- Memory problems & dementia
- Psychosis
AAN recommendation levels

- **A** = *Established* as effective, ineffective or harmful.
- **B** = *Probably* effective, ineffective or harmful.
- **C** = *Possibly* effective, ineffective or harmful.
- **U** = Data inadequate or conflicting; given current knowledge, treatment is *unproven*. 
REM Sleep Behavior Disorder

• There is insufficient evidence to support or refute the treatment of RBD (Level U)

• In practice, melatonin (3 – 10 mg hs) may be effective for many patients.
• Clonazepam (0.25 – 2 mg hs) is often used to treat RBD.
• Antidepressants (SSRIs & TCAs) may exacerbate.
Contipation

• Polyethylene glycol may be considered to treat constipation in PD (*Level C*)

• Increased water and dietary fiber intake have shown clinical benefit.
• Stool softeners may be useful.
• There is no information on linaclotide in PD.
• PD drugs may cause or exacerbate constipation.
Urinary Incontinence

• There is insufficient evidence to support or refute the treatment of urinary incontinence in PD (Level U)

• Although RCTs of anticholinergic agents in patients with PD are lacking, their widespread use is consistent with clinical benefit.

• Anticholinergics can cause confusion in PD.
Orthostatic Hypotension

• There is insufficient evidence to support or refute the treatment of orthostatic hypotension in PD (Level U)

• NaCl tablets (tid-qid) and increased water intake may be beneficial.
• Midodrine and droxidopa are likely beneficial in PD, but often cause supine hypertension.
• PD medications may cause or exacerbate OH.
Sialorrhea (drooling)

• Botulinum toxin should be considered for sialorrhea in PD (**Level B**)

• In practice, PD drugs may cause dry mouth, which can be equally bothersome.
Erectile Dysfunction

• Sildenafil may be considered in patients with ED associated with PD (Level C)

• Other treatable causes of ED, including drug side effects should be ruled out.

• Other drugs in this class (e.g., tadalafil, vardenafil) may also be beneficial.
Excessive Daytime Sleepiness

• Modafinil should be considered to improve subjective perception of EDS in PD (Level A)

• Insufficient evidence of a safety benefit (Level U) for PD patients who engage in activities where sleepiness poses a danger.

• May experience an improvement in sleepiness perception without improvement in objective sleep measures.
Fatigue

• Methylphenidate may be considered in PD patients with fatigue (Level C)

• In practice, a scheduled 30 minute nap in the afternoon is often very beneficial.

• Methylphenidate has potential for abuse.
Anxiety

- There is insufficient evidence to support or refute the treatment of anxiety in PD (*Level U*)

- Although RCTs are lacking, antianxiety drugs may have benefit in PD.

- Antianxiety drugs may increase risk of ataxia, falls and confusion/cognitive impairment.
Depression

• Amitriptyline may be considered for treatment of depression in PD (Level C)

• Although the highest level of evidence is for amitriptyline, it may not be the first choice.
• Insufficient evidence (Level U) for other treatments of depression in PD.
• Absence of evidence of efficacy does not imply lack of efficacy.
Psychosis

• Clozapine should be considered for psychosis in PD (Level B)

• Quetiapine may be considered for psychosis in PD (Level C).

• Clozapine is associated with agranulocytosis which may be fatal.

• Olanzapine should NOT be routinely considered for psychosis in PD (Level B).

• Pimavanserin (Nuplazid) recently approved for PD psychosis – specialty pharmacy
Dementia

• Donepezil should be considered for treatment of dementia in PD (Level B)
• Rivastigmine should be considered for treatment of dementia in PD (Level B).

• PD medications, especially those with anticholinergic properties, may cause or exacerbate cognitive impairment.