Parkinson’s Disease Initial Clinical and Diagnostic Evaluation

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

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*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), metaclopramide (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?

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UK, United Kingdom; PD, Parkinson’s disease; CT, computed tomography.

Litvan et al, Movement Disorders, 2003
# 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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<td>Persistent asymmetry affecting side of onset most</td>
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<td>Excellent response (70–100%) to levodopa</td>
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<td>Severe levodopa-induced chorea</td>
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<td>Levodopa response for 5 yr or more</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)
DATscan

- 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
Management of Nonmotor Symptoms in Parkinson’s Disease

J. Timothy Greenamyre, MD, PhD
Clinical Signs and Symptoms

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

**Other Motor Symptoms**
- Micrographia*
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- Slowing of ADLs*
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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 \textbf{(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).
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.