Parkinson's Disease (PD) Epidemiology

- Uncommon before age 50 years\(^1\)
- Annual incidence (all ages): 8.6 to 19.0/100,000\(^2\)
- Incidence increases dramatically with age: approximately 100/100,000 over age 70 years\(^3\)
- Prevalence in individuals older than 65 years: approximately 1%\(^4\)
- More common in men\(^5\)


Motor Features of PD

Cardinal features
- Rest tremor
- Rigidity
- Bradykinesia
- Postural instability

Other motor features
- Masked face
- Shuffling gait
- Freezing
- Micrographia
- Dystonia
- Cramps
Non-Motor Features of PD

- Autonomic
  - Constipation
  - Hyperhidrosis
  - Urinary dysfunction
  - Sexual dysfunction
  - Sialorrhea

- Psychiatric disorders
  - Depression/Anxiety
  - Apathy
  - Fatigue

- Sleep disorders
  - Insomnia
  - REM behavior disorder

- Cognitive
  - Dementia
  - Psychosis

Differential Diagnosis of PD

Key:
- Vascular
- Drugs
- Secondary
- Toxins
- Encephalitis
- Other
- Alzheimer’s Disease
- Lewy Body Disease
- Corticobasal Degeneration
- Parkinson-plus
- Multi-System Atrophy
- Progressive Supranuclear Palsy
- Essential Tremor
- Idiopathic Parkinson’s Disease
- Neurodegenerative parkinsonism (ALL)
- Essential tremor
- Vascular parkinsonism
- Drug-induced parkinsonism
- Psychogenic

Clinical Features that May Suggest a Diagnosis Other than PD

- Poor response to adequate dosages of levodopa
- Early onset of postural instability
- Axial more than appendicular rigidity
- Early dementia
- Supranuclear gaze palsy
- Profound autonomic dysfunction
- Significant limb dystonia prior to levodopa exposure

Dopamine Transport Imaging (DaTscan™)

Dopamine transport imaging differentiates between parkinsonian disorders with and without dopamine deficiency

Treatment Goals

• Slowing disease progression
• Controlling symptoms
• Preserving quality of life

Agents Recently or Currently Being Tested for Disease-Modifying Properties

No
• Coenzyme Q10
• Pramipexole

Results Pending
• Creatine
• Inosine
• Isradipine
• Exercise

Maybe
• Rasagiline

Can Exercise Slow PD Progression?
Exercise Therapy Is Effective in Improving Activities of Daily Living


Sites of Action of PD Drugs

Adapted from www.wemove.org

*Massachusetts Medical Society. Used with permission.
Considerations in the Initial Management of PD

• Control of disability
• Favorable side-effect profile
• Optimal long-term strategy
• Cost

Case Example 1

• A 37-year-old male presents to your office with tremor of right hand for 4 to 5 years.
• He also has decreased manual dexterity on right and right foot cramping.
• He has a family history that is positive for essential tremor.
• His past medical history is unremarkable.

Case Example 1 (Cont’d)

• Examination reveals increased tone bilaterally, right greater than left; a rest tremor on the right; and bradykinesia in some tasks on the right.
• Right arm swing is depressed while walking.
• MRI normal, DaTscan-decreased uptake in the corpus striatum, especially on the left side.

How would you treat this patient?

Levodopa Clearly Beneficial as a Treatment of PD

Change in total unified PD rating scale by dose of levodopa

Levodopa Associated With Risk of Motor Complications

- Dyskinesia
  - Peak dose
  - End of dose
- Motor fluctuations
  - End-of-dose wearing off
  - Unpredictable “on-off”
  - “Yo-yo-ing”

Results from a multi-center study of 3000 patients

- ICDs were identified in 13.6% of PD patients overall:
  - 17.1% of patients taking a dopamine agonist (DA) alone
  - 6.9% of patients on levodopa, and not taking a DA
- Types of ICDs
  - 5.7% compulsive buying
  - 5.0% problem/pathologic gambling
  - 4.3% binge eating disorder
  - 3.5% compulsive sexual behavior

MAO-B Inhibitors for Early PD

- Indications: monotherapy in early PD; add on to levodopa
- Available dosage: 1 mg tablet daily
- Benefits: mild symptomatic improvement; well tolerated
- Side effects: minimal; potential drug interactions

Symptomatic treatment effect of rasagiline on total UPDRS at 6 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean change from baseline in total UPDRS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.0</td>
</tr>
<tr>
<td>Rasagiline 1 mg</td>
<td>-0.13</td>
</tr>
<tr>
<td>Rasagiline 2 mg</td>
<td>0.51</td>
</tr>
<tr>
<td>Rasagiline 2 mg</td>
<td>4.07</td>
</tr>
</tbody>
</table>

P < .001

UPDRS: Unified Parkinson's Disease Rating Scale


Advanced Parkinson’s Disease

Treatment-Emergent Adverse Events With Rasagiline Monotherapy*

- Placebo
- Rasagiline 1 mg/d

*Adverse-event incidence >5%; between-group differences not statistically significant


AAN Practice Guidelines for Treatment of Early PD

- When symptomatic therapy is required:
  - MAO-B inhibitors may be used.
  - Either dopamine agonists or levodopa may be used when dopaminergic therapy is required.
    - Levodopa provides better immediate symptomatic relief.
    - Agonists have lower risk of motor complications, particularly dyskinesias.
    - Agonists may carry a higher side effect profile.


Issues in Advanced PD

- Reduced quality of life¹
- Functional impairment
- Higher risk of depression and cognitive impairment²
- Higher risk for comorbidities²
- Increased medical expenses²
- Caregiver burden and risk of early nursing home placement²,³

Problems in Advanced PD

• Motor
• Neuropsychiatric
• Autonomic

Motor Problems

• Fluctuations
• Dyskinesias
• Freezing of gait
• Falls

Causes of Falls

• Postural instability
• Freezing
• Dyskinesia
• Hypotension
• Other neurological problems
• Environmental

Schematic of Possible Changes in Clinical Effect in Patients as PD Progresses

Adapted with permission from:
Definition of Terms

- “On” state – relatively good overall function and mobility corresponding to the medication working
- “Off” state – relatively poor overall function and mobility corresponding to the medication not working
- Dyskinesias – involuntary, nontremor movements
- Troublesome dyskinesias – may be painful, impair balance, or are excessive to the point of causing impairment in coordination or general function


Treatment of Dyskinesia

Peak dose or end of dose

Treatment options include:
- Amantadine
- Clozapine (rarely used)
- Experimental therapy
- Deep Brain Stimulation (DBS)

Amantadine

- Mechanism: NMDA receptor antagonist, dopamine releasing agent
- Indications: Early PD, dyskinesias, fatigue
- Benefits: Mild symptomatic benefit, effective for dyskinesias
- Side effects: Leg swelling, livedo reticularis, neuropsychiatric, interacts with anticholinergics


Amantadine vs placebo for levodopa-induced dyskinesias

<table>
<thead>
<tr>
<th></th>
<th>Amantadine*</th>
<th>Placebo*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dyskinesia</td>
<td>22.0 (13.2)</td>
<td>29.0 (12.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Maximal dyskinesia</td>
<td>5.2 (2.6)</td>
<td>6.3 (2.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>UPDRS IV dyskinesia</td>
<td>3.2 (1.6)</td>
<td>4.3 (1.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>UPDRS III motor off</td>
<td>38.4 (14.8)</td>
<td>41.7 (13.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>UPDRS III motor on</td>
<td>22.3 (12.1)</td>
<td>23.4 (9.0)</td>
<td>0.44 NS</td>
</tr>
</tbody>
</table>

*Mean score (SD)
†Wilcoxon signed-rank test

Case Example 2

- A 65-year-old female with PD for 4 years is taking carbidopa/levodopa 25/100 QID.
- She is experiencing regular and predictable wearing off of the effect, 1½ hours prior to each dose.
- With this wearing off she gets painful foot dystonia and shortness of breath, as well as a return of her PD symptoms.

How would you manage this patient?

Examples of Other “Off” Symptoms

- Slowness of thinking
- Irritability
- Fatigue
- Drenching sweats
- Constipation
- Urinary urgency
- Abdominal bloating
- Pain

Wearing Off

- Definition: Re-emergence of features of Parkinson's disease at end of dose
- May be motor or non-motor

Case Example 2: Wearing Off Treatment Options

- Extended-release levodopa
- More frequent dosing of levodopa
- COMT inhibitors: entacapone or tolcapone
- Dopamine agonists
- MAO-B inhibitors
- Anticholinergics
- Botulinum toxin injection
### Agents Commonly Used in the Management of PD

- **Levodopa**
- **COMT Inhibitors**
  - Tolcapone
  - Entacapone
- **MAO-B Inhibitors**
  - Selegiline
  - Zydus selegiline
  - Rasagiline
- **Dopamine Agonists**
  - Pramipexole
  - Ropinirole
  - Bromocriptine
  - Apomorphine
  - Rotigotine
- **Other**
  - Amantadine
  - Anticholinergics

### Incidence of Non-Motor Symptoms of PD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfactory dysfunction*</td>
<td>90%</td>
</tr>
<tr>
<td>ANS dysfunction</td>
<td>80%</td>
</tr>
<tr>
<td>Dementia</td>
<td>78%</td>
</tr>
<tr>
<td>Sleep disorders *</td>
<td>66%</td>
</tr>
<tr>
<td>Urogenital dysfunction</td>
<td>57-83%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms *</td>
<td>50-95%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>50%</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>50%</td>
</tr>
<tr>
<td>Depression *</td>
<td>40-50%</td>
</tr>
<tr>
<td>Pain</td>
<td>40-50%</td>
</tr>
<tr>
<td>Impulse control disorders</td>
<td>7-14%</td>
</tr>
</tbody>
</table>

*Identified as possible pre-motor symptoms

AAN Recommendations for Treatment of Non-motor Symptoms of PD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recommendation</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>Donepezil† should be considered</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Rivastigmine should be considered</td>
<td>B</td>
</tr>
<tr>
<td>Depression</td>
<td>Amantripine may be considered</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insufficient evidence for other treatments</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Methyphenidate† may be considered</td>
<td>C</td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>Sildenafil citrate (50 mg) may be efficacious</td>
<td>C</td>
</tr>
<tr>
<td>Constipation</td>
<td>Polyethylene glycol may be considered</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Insufficient evidence to support/refute the use of botulinum toxin</td>
<td>U</td>
</tr>
</tbody>
</table>

*Evidence level was based on the AAN’s classification scheme
†: Off-label use

AAN Recommendations for Treatment of Non-motor Symptoms of PD (cont’d)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recommendation</th>
<th>Evidence Level*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic Hypotension</td>
<td>Insufficient evidence to support/refute treatment in PD</td>
<td>U</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td>Insufficient evidence to support/refute treatment in PD</td>
<td>U</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Insufficient evidence to support/refute the treatment of anxiety with levodopa</td>
<td>U</td>
</tr>
<tr>
<td>REM Behavior Disorder (RBD)</td>
<td>Insufficient evidence to support/refute the treatment of RBD</td>
<td>U</td>
</tr>
<tr>
<td></td>
<td>Clonazepam† and melatonin are often used in the general population</td>
<td>U</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Insufficient evidence to support/refute the benefit of levodopa/carbidopa on objective sleep parameters that are not affected by motor status</td>
<td>U</td>
</tr>
<tr>
<td></td>
<td>Insufficient evidence to support/refute the benefit of melatonin on the treatment of poor sleep quality</td>
<td>U</td>
</tr>
</tbody>
</table>

*Evidence level was based on the AAN's classification scheme
†: Off-label use

Case Example 3

A 75-year-old male retired physician comes to your office with PD and hallucinations.
- He is seeing deceased relatives in his house and accusing his wife of having an affair.
- His medications for PD include carbidopa/levodopa 25/100 QID.
- He continues to suffer from slowness and some disability.

How would you manage this patient?

Neuropsychiatric

- Cognitive impairment and dementia
- Psychosis
- Compulsive disorders
- Depression
- Apathy
- Anxiety

Management of Psychotic Symptoms

- Rule out causes of mental status changes
  - Infection
  - Electrolyte imbalance
  - Medications
- Modify PD regimen
  - Reduce PD medications to minimum tolerable, yet effective dose
  - Discontinue, if necessary
- Evaluate risk/benefit of atypical antipsychotic

Priority of modification

- Anticholinergics
- Amantadine
- MAO-B inhibitors
- Dopamine agonists
- COMT inhibitors
- Levodopa/carbidopa
Therapy for Cognitive Impairment in PD

- Cholinesterase inhibitors
- Memantine?
- Avoid anticholinergics
- Atypical neuroleptics
- Caregiver support


© Massachusetts Medical Society. Used with permission.

Case Example 3 (Cont’d)

- He is likely to have mild underlying dementia.
- He cannot lower his levodopa because he is quite impaired from the PD.
- His wife should get counseling.
- He should be treated with a cholinesterase inhibitor and an atypical antipsychotic (quetiapine and clozapine ONLY).

Depression

- Severe depression is unusual.
- Suicide is unusual.
- Weight loss, fatigue, insomnia can be due to PD or depression.
- Difficult to differentiate.

Treatment of Depression in PD

- Very few studies have been conducted.
- Most antidepressants work, but very few randomized clinical trials exist.
- Caution with the side effects of antidepressants (low blood pressure, dry mouth, confusion and sedation with the tricyclics, and increased tremor and impotence with the SSRIs).
Summary of PD Depression Double-Blind Studies

Citalopram or desipramine vs placebo

- Citalopram and desipramine both more effective than placebo, but significant short-term effect (at 14 days) only with desipramine

Nortriptyline or paroxetine CR vs placebo

- Nortriptyline was superior to placebo; paroxetine was not


Sleep Disorders

- Insomnia and sleep fragmentation
- Nightmares, hallucinations
- REM behavior disorder
- Sleep apnea
- Excess daytime sleepiness and sleep attacks
- Frequent urination
- PD immobility

SAD-PD: Efficacy

SAD-PD: Study of Antidepressants in PD

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Effect</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine vs Placebo</td>
<td>-6.2</td>
<td>(-9.7, -2.7)</td>
<td>.0007</td>
</tr>
<tr>
<td>Venlafaxine vs Placebo</td>
<td>-4.2</td>
<td>(-7.8, -0.6)</td>
<td>.02</td>
</tr>
</tbody>
</table>


Autonomic Dysfunction

- Constipation
- Urinary problems
- Sexual problems
- Orthostatic hypotension
- Sweating
- Pain
- Dysphagia
- Seborrhea
**Orthostatic Hypotension**

- Eliminate blood pressure medications.
- Try to stop PD medications (ie, dopamine agonists):
  - Fludrocortisone
  - Midodrine
  - Pyridostigmine
  - Domperidone (outside of US)

**Other Autonomic Problems**

**Gastrointestinal (GI) Problems**

- Drooling
- Dysphagia
- Weight loss
- Gastroparesis
- Constipation

**Genitourinary (GU) Problems**

- Urinary anticholinergics may cause confusion and hallucinations
- Alpha adrenergic blocking agents may cause hypotension

**When to Consider DBS**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mild Symptoms, No Disability</th>
<th>Symptoms with Some Disability</th>
<th>Worsening Symptoms</th>
<th>Need for Levodopa ± Adjunctive Therapy</th>
<th>Beginning of Complications from Disease and Treatment</th>
<th>Increasing Disability Despite Therapy</th>
<th>Complications of Disease and Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Does not yet need treatment</td>
<td>May need treatment but not yet levodopa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Future Directions in PD Treatment

- Treat or restore function in advanced disease.
- Treat dyskinesia.
- Prevent development of motor complications.
- Treat “nondopaminergic” features.
- Neuroprotective treatments?

### Adverse Events from DBS

40% of patients in study receiving DBS had a serious adverse event, including:

- **Up to 3 months following DBS**
  - Fall ($P = .02$)
  - Pain ($P = .04$)
  - Confusional state ($P < .001$)
  - Speech disorder ($P = .004$)
  - Headache ($P < .001$)

- **4-6 months following DBS**
  - Dystonia ($P = .02$)
  - Fall ($P = .03$)

---

### Patient Motor Diary Outcomes

<table>
<thead>
<tr>
<th>Time</th>
<th>BMT change from baseline to 6 mos (n=134)</th>
<th>DBS change from baseline to 6 mos (n=121)</th>
<th>Mean difference between BMT vs DBS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On without troublesome dyskinesia</td>
<td>0.1</td>
<td>4.6</td>
<td>-4.5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>On with troublesome dyskinesia</td>
<td>-0.3</td>
<td>-2.6</td>
<td>2.3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Off</td>
<td>0.1</td>
<td>-2.4</td>
<td>2.5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Asleep</td>
<td>0.3</td>
<td>0.4</td>
<td>-0.1</td>
<td>.66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question 2</th>
<th>Question 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can deep brain stimulation (DBS) be considered in older patients?</td>
<td>In male patients with Parkinson’s disease, if they suffer from postural hypotension is there an alternative to sildenafil for erectile dysfunction?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question 3</th>
<th>Question 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there effective treatments available for sialorrhea in patients with Parkinson’s disease?</td>
<td>Why are only quetiapine and clozapine recommended for the treatment of psychosis in patients with Parkinson’s disease?</td>
</tr>
<tr>
<td>For these drugs, what are the starting doses?</td>
<td></td>
</tr>
</tbody>
</table>
Question 6
What are the best ways to assess and manage dysphagia in patients with Parkinson’s disease?

Question 7
Is there a maximum/ceiling dose of:
Carbidopa/levodopa in patients with end-stage Parkinson’s disease?
Quetiapine in managing psychosis in Parkinson’s disease?

Question 8
What are the indications for botulinum toxins in Parkinson’s disease?

Question 9
Is the rotigotine patch a viable option for early Parkinson’s disease?
Is it an alternative to levodopa in those with advanced disease?
Question 10
How do you define a “poor response” to levodopa?

Question 11
Is there a hereditary component to Parkinson’s disease?

Question 12
Does DBS necessitate changes in prior medical therapy?

STN: subthalamic nucleus
GPI: Globus Pallidus Pars Interna