Parkinson’s Disease for the Primary Care Physician

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Objectives

To recognize criteria for the diagnosis of PD

To understand choices in the treatment of motor symptoms of PD
  - Initial therapy
  - Later management

To appreciate non-motor symptoms of PD and options for their management
PD is a clinical diagnosis
- No lab biomarkers
- Findings on routine CT and MRI are unremarkable

Clinical diagnosis requires the presence of 2 of 3 cardinal signs
- Resting tremor
- Rigidity
- Bradykinesia
Initial Motor Symptoms of PD

- Tremor at rest
- Subtle decrease in dexterity; micrographia
- Decreased arm swing on the first-involved side
- Slower, shuffling gait, or slight dragging of one leg
- Stooped posture
- Soft voice
- Decreased facial expression
Early Non-motor Symptoms of PD

- Sleep disturbances
  - Rapid eye movement (REM) behavior disorder (RBD; a loss of normal atonia during REM sleep)
- Hyposmia
- Symptoms of autonomic dysfunction
  - constipation, bladder or sexual dysfunction
- Depression or anxiety
The Parkinson’s Complex

Adapted with permission from Langston JW. The Parkinson’s complex: Parkinsonism is just the tip of the iceberg. *Ann Neurol.* 2006;59(4):591-596.
Importance of Recognizing Non-Motor Symptoms in Early PD

- Non-motor symptoms are common in early PD
- Recognition of the combination of motor and non-motor symptoms can:
  - Promote early diagnosis
  - Enable early intervention
  - Result in a better quality of life
PD – Goal of Management

To provide control of signs and symptoms, both motor and non-motor, for as long as possible, while minimizing adverse effects.
Individualized Management Considerations

- **Patient-related considerations:**
  - Age
  - Lifestyle
  - Employment status
  - Comorbidities
  - Cognitive/psychiatric profile
  - Caregiver status

- **Treatment-related considerations:**
  - Efficacy
  - Tolerability and side-effect profile
  - Timing of treatment initiation
When to Start Drug Treatment?

- Earlier is better than later

  - Data from longitudinal observational studies of self-reported health status of patients with early PD
  - Data from early vs delayed initiation of drug therapy with rasagiline in patients with early PD
Quality-of-Life Health Status Remains Stable in Treated Parkinson’s Patients and Deteriorates in Untreated Patients Over 18 Months

Horizontal line within box = median value; box edges = lower and upper quartiles; whiskers display range.
Treatment Options

Pharmacologic therapy
- Levodopa
- MAO-B inhibitors
- COMT inhibitors
- Dopamine agonists
- Anticholinergics
- Amantadine

Nonpharmacologic therapy
- Education
- Exercise
- Nutrition
- Support services

Surgical therapy
- Deep brain stimulation
## Nonpharmacologic Considerations

<table>
<thead>
<tr>
<th>Nonpharmacologic Considerations</th>
<th>Details</th>
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</table>
| **Physical therapy** | - Goals:  
  - Improve motor function  
  - Increase range of motion  
  - Build endurance  
- Techniques: counting steps, marching, visual fixation, balance training  
- Can be helpful for symptoms such as stooped posture, shuffling and other gait disturbances, difficulty rising from chairs |
| **Occupational therapy** | - Concentrates on fine finger and hand movements  
- Techniques: adaptive equipment, energy conservation, range of motion |
| **Speech therapy** | - Concentrates on speech impairments and swallowing difficulties  
- Techniques: voice projection and vocal exercises |
| **Diet** | - Patients should maintain a well-balanced diet  
- Meals rich in protein may reduce absorption of levodopa |
Exercise: Benefits in PD Studies

- Helps maintain function
- Improves mood, energy level, and sleep,
- Can improve gait, grip strength, and motor coordination
- Treadmill training produces sustained motor benefits
- Tai Chi improves balance
- Animal studies:
  - Exercise reverses motor deficits in chronic PD animals
  - Treadmill reduces dopamine loss
Forced Exercise Improves Motor Function in PD Patients

- Forced exercise with trainer on tandem bike vs. voluntary exercise on stationary bike at own pace
- 1-hour sessions 3 days a week for 8 weeks
- After forced exercise:
  - 35% improvement in UPDRS
  - 35% improvement in bimanual dexterity task
  - Results sustained for 4 weeks
  - No similar changes in voluntary exercise group
- fMRI: increase in cortical activation in 2 motor areas — SMA and primary motor cortex — similar to L-dopa effects
- Conclusion: Forced exercise leads to shift in motor control strategy, and may alter central motor control processes
The Theracycle
Sites of Action of PD Drugs

Periphery  Blood-brain barrier  Neuron  Brain

COMT inhibitors  3-OMD  LD  CD  DA  DA  DA  DA

LD  AADC  DA  COMT inhibitor*

MAO-B inhibitors  DOPAC  DA  COMT inhibitor*  Dopamine agonists  3-MT

Dopamine receptors

*Only tolcapone inhibits COMT in brain.
COMT indicates catechol-O-methyltransferase; CD, indicates carbidopa; LD, levodopa; 3-OMD, 3-O-methyldopa; DA, dopamine; AADC, aromatic acid decarboxylase; DOPAC, dihydroxyphenylacetic acid; 3-MT, 3-methoxytyramine.
## Treatment Options in Early PD: Pros and Cons

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>MAO-B inhibitors</td>
<td>Effective Potential disease modification AE profile similar to placebo</td>
<td>Potential drug interactions</td>
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<tr>
<td>Carbidopa/levodopa</td>
<td>Highly effective Rapid onset of action</td>
<td>Motor fluctuations and dyskinesia common with long-term use</td>
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<tr>
<td>Carbidopa/levodopa / entacapone</td>
<td>Highly effective Rapid onset of action</td>
<td>Even earlier risk of dyskinesia than with levodopa</td>
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<tr>
<td>Dopamine agonists</td>
<td>Effective Low risk of motor complications</td>
<td>Neuropsychiatric AEs Somnolence warning Impulse disorders</td>
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<tr>
<td>Amantadine</td>
<td>Beneficial for tremor Anti-parkinsonian effects</td>
<td>Cognitive AEs Anticholinergic AEs Withdrawal effects</td>
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</table>
Management Strategy

Diagnosis of PD
- Nonpharmacologic management
- Pharmacologic management
  - Significant functional impairment
    - Yes: Dopaminergic therapy
      - Dopamine agonist
        - < 70 years of age
      - Levodopa
        - > 70 years of age
        - Cognitive issues
        - Comorbidities
    - No: Selegiline or rasagiline

Response to Levodopa and Progression of Parkinson’s Disease

- **Early PD**
  - Long duration motor response
  - Low incidence of dyskinesias

- **Moderate PD**
  - Shorter duration motor response
  - Increased incidence of dyskinesias

- **Advanced PD**
  - Short duration motor response
  - “On” time consistently associated with dyskinesias

Surgical Management of PD

Deep brain stimulation (STN vs GPi)

Consider for more advanced PD patients with levodopa-responsive PD and intact cognitive function, with significant off-time and/or troublesome dyskinesias despite best medical therapy; age is not necessarily a contra-indication!

- Improvement in “off” function
- More functional “on” time
- Reduced dyskinesia
- Lower medication doses
Deep Brain Stimulation for Parkinson’s Disease
Motor symptoms

Cognitive symptoms and dementia

Neuropsychiatric symptoms

Sleep disturbances

Autonomic dysfunction

Multidisciplinary Treatment of Motor and Nonmotor Symptoms
# Nonmotor Symptoms

| Neuropsychiatric symptoms                  | Depression*, anxiety, apathy |
|                                         | Hallucinations, illusions, delusions |
|                                         | Dementia, cognitive impairment |
|                                         | Compulsive and impulsive behaviors |
| Sleep disorders                          | Insomnia |
|                                         | Sleep fragmentation |
|                                         | Excess daytime somnolence |
|                                         | Restless legs syndrome |
|                                         | REM (rapid eye movement) sleep behavior disorder* |
|                                         | Vivid dreaming |
| Sensory disorders                        | Pain, paresthesia |
|                                         | Impaired olfaction* |

* Premotor symptom.
### Nonmotor Symptoms (Cont’d)

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td><strong>Autonomic disorders</strong></td>
<td>Bladder disturbance: nocturia, urgency, frequency</td>
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<td>Heat or cold intolerance</td>
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<td>Excess sweating</td>
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<td>Orthostatic hypotension</td>
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<td></td>
<td>Sexual dysfunction</td>
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<tr>
<td></td>
<td>Drooling of saliva</td>
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<tr>
<td><strong>Gastrointestinal disorders (overlap with autonomic)</strong></td>
<td>Dysphagia</td>
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<tr>
<td></td>
<td>Ageusia (absence of taste)</td>
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<td></td>
<td>Constipation or incomplete emptying of bowel*</td>
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<tr>
<td><strong>Other symptoms</strong></td>
<td>Fatigue</td>
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<td></td>
<td>Diplopia</td>
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<td></td>
<td>Seborrhea</td>
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<td></td>
<td>Weight loss</td>
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* Premotor symptom.
Parkinson’s Complex

- Depression
  - Psychosis/Dementia
- Sleep Disorder
- Constipation
- Parkinsonism
- Anosmia
- Autonomic dysfunction
Sialorrhea: Management

- Chewing gum or sucking sugar-free candy
- Oral medications
  - Consider adjustment of anti-Parkinson medications
  - Glycopyrrolate
  - Atropine (1%) eye drops to tongue
    - Monitor closely for systemic anticholinergic effects
- Intra-parotid Botox
  - Frequently very effective (Level B evidence, AAN QSS)
  - Needs to be repeated approx. q 3 months
Constipation: Treatments

- High fiber diet - 5-25 grams per day
- Plenty of fluids - 8+ glasses per day
- Exercise
- Stool softener (Docusate sodium)
- Osmotic macrogel - Polyethylene glycol (MiraLAX) (Level C evidence, AAN QSS)
- Lactulose
- Bisacodyl (Dulcolax)
- Milk of magnesia
- Enema if needed
Urinary Symptoms

- Impaired bladder emptying or storage (due to impaired relaxation or bradykinesia of the external urethral sphincter)
  - Usually require intermittent catheterization

- Symptoms of detrusor overactivity:
  - Frequency and nocturia
  - Urgency ± urge incontinence
Detrusor Overactivity: Management

Consider urological evaluation

Practical strategies

- Reducing evening fluid intake, emptying bladder before going to bed; bedside commode/urinal or diapers

Anticholinergic options:

- Older medications (e.g. oxybutynin, tolterodine XL), although effective, have more side effects
- The newer non-selective anticholinergic tropsium chloride (Sanctura) does not cross the BBB and has a more favorable side-effect profile
- Newer M3-receptor (bladder-) specific agonists have superior tolerability but are more expensive: Solifenacin (Vesicare), Darifenacin (Enablex)
Orthostatic Hypotension: General recommendations

Avoid situations/activities that will make it worse

- Warm environments
  - Hot tubs, sauna, hot showers
  - Hot humid weather
- Alcohol
- Large meals (post-prandial hypotension)
Orthostatic Hypotension: Treatments

- Remove any offending medications
- Monitor salt and fluid intake (they may need to be increased)
  - Salt rich fluids: tomato juice, chicken broth, bullion
  - Salt tablets
  - Drink 2 liters of fluid per day
- Thigh-high surgical stockings
- Medications to raise the blood pressure
  - Fludrocortisone (Florinef)
  - Midodrine (Proamatine)
REM Sleep Behavior Disorder

- “Acting out dreams”
- Loss of normal REM paralysis
- Dream content changes - more violent
- Can occur very early
- May be worsened by serotonergic medications

Management

- Safety considerations to self and bed partner
- Clonazepam, melatonin
Sleep Disorders: Therapeutic Guidelines

- Reinforce normal light-dark cycle
- Maximize daytime activity and interactions
- Decrease medications that aggravate symptoms
- Evaluate irregular breathing patterns
- Address pain, mood, motivation, medical issues
- Consider medications for day-time sleepiness
  - Modafinil (Provigil) (Level A evidence, AAN QSS)
  - Armodafinil (Nuvigil)
Management of Depression

- Lifestyle changes
  - Exercise
  - Social activities (worship, support groups, friends, family)

- Counseling

- Cognitive-Behavioral therapy (CBT)

- Medication
  - SSRIs, SNRIs, tricyclics – both paroxetine and venlafaxine effective in a controlled trial
  - ? Buproprion; +/- adjunctive pramipexole

- Consider ECT if severe or refractory
Management of Cognitive Symptoms

- Minimizing other medications that may worsen cognition (e.g. anticholinergics, amantadine, dopamine receptor agonists, antihistamines, benzodiazepines, opioids)
- Improving sleep to help daytime alertness
- Treating depression and anxiety

Medication:
- Acetylcholinesterase Inhibitors
  - Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (Razadyne)
- Memantine (Namenda)
Psychosis

- Hallucinations and paranoia in up to 30% of PD patients
- Tends to accompany cognitive dysfunction
- Look for infections, offending medications
  - If possible reduce meds (especially anticholinergics, amantadine and dopamine agonists)
- Use Seroquel (quetiapine fumarate) - Level C evidence, AAN QSS
- Clozapine is effective (Level B evidence) but need to monitor neutrophil count weekly
- Consider “memory” medications like rivastigmine (Exelon) donepezil (Aricept), galantamine (Razadyne)
- Pimavanserin likely available in 2015
Long-term Management of PD: Key Points

- Individualize therapy according to age, cognitive status, symptoms, and response to treatment
- Initiate pharmacologic and non-pharmacologic care early
- Monitor functional impairment
- Introduce dopaminergic agents in response to individual symptomatic needs
- Address non-motor symptoms *(role for PCP!)*
- Evaluate response and modify treatment if necessary
- Consider DBS for appropriate candidates
Typical Progression and Clinical Course

- Preclinical Phase
- Motor Complication Period
- Resistant Symptoms
- Cognitive Decline

-2 to -6 0 3 8 15 20

Years

Onset Therapy Diagnosis