Treatment of Parkinson’s Disease

- Objectives:
  1. Discuss treatment options for the motor symptoms of Parkinson’s Disease.
  2. Describe different treatment strategies that can differ based on age at presentation.
  3. Relate the best-evidence treatment options for the non-motor symptoms of Parkinson’s.

Background

- 2nd most common neurodegenerative disorder
- Loss of dopaminergic neurons
- Defined by
  1. Bradykinesia (slowness)
  2. Rigidity (stiffness)
  3. Tremor (resting tremor)
  4. Postural instability (impaired balance)
- Symptoms often asymmetric, progressive
- Many associated non-motor symptoms

Treatment: motor symptoms

- Carbidopa/Levodopa
- Monoamine Oxidase-B Inhibitors (MAO-B)
- Dopamine Agonists
- Catechol O-methyltransferase Inhibitors (COMT)
- Anticholinergics
- Late disease agents
Treatment: *motor symptoms*

- **Mainstay: Carbidopa/Levodopa**
  - **Mechanism:**
    - Levodopa converted to dopamine by neurons
      - These neurons are degenerating – results in ↓response/↑ predictability over time
    - Carbidopa blocks peripheral metabolism of levodopa

Treatment: *motor symptoms*

- **Carbidopa/Levodopa**
  - **Dosing:**
    - IR: 10/100, 25/100, 25/250 (3-4 times daily)
    - CR: 25/100, 50/200 (twice daily)
    - ODT: (Parcopa™) bioequivalent to IR formulations
  - **Dosing Considerations:**
    - Start at ½ tab daily and ↑ by ½ tab every week
    - lessens nausea

Treatment: *motor symptoms*

- **Carbidopa/Levodopa**
  - **Short-term Adverse Effects:**
    - Nausea/vomiting, drowsiness, dizziness, hypotension
  - **Long-term Adverse Effects:**
    - Motor fluctuations
      - “wearing off” – no longer lasts between doses
    - Dyskinesias
      - Choreiform movements occurring at “peak dose”

Treatment: *motor symptoms*

- **MAO-B Inhibitors**
  - **Mechanism:**
    - ↑half-life of dopamine by blocking its breakdown
  - **Agents:**
    - Selegiline
      - 5mg twice daily
    - Rasagiline (Azilect™)
      - 0.5 – 1.0 mg once daily
Treatment: motor symptoms

- MAO-B Inhibitors
  - Use:
    - monotherapy early
    - adjunct (treat motor fluctuations)
    - When “off-time” becomes impairing
      - Can increase dyskinesias
  - Adverse Effects:
    - Potentiate the dopaminergic side effects
    - Risk of Serotonin Syndrome

- Dopamine Agonists
  - Use:
    - Monotherapy early
      - Can delay initiation of Carbidopa/Levodopa
    - Adjunct late
      - Decrease motor fluctuations
  - Adverse Effects:
    - Sleepiness, hallucinations, peripheral edema,
    - Impulse control disorders:
      - Hypersexuality, pathological gambling

Treatment: motor symptoms

- COMT Inhibitors
  - Mechanism:
    - Blocks metabolism of levodopa (to an inactive compound), ↑ plasma and brain levels
  - Agents:
    - Entacapone
      - 200mg with each dose of carbidopa/levodopa
      - Stalevo™ is carbidopa/levodopa/entacapone
    - Tolcapone
      - 100-200mg TID
      - Black Box Warning
### Treatment: Motor Symptoms

**COMT Inhibitors**
- **Uses:**
  - Adjunct therapy to ↓ motor fluctuations/off time
- **Adverse Effects:**
  - Diarrhea, orange discoloration of the bodily fluids
  - Potentiation of dopaminergic side effects
  - Tolcapone – hepatic failure
    - Greatly limits use (most severe patients only)

**Anticholinergics**
- **Uses:**
  - Reduce tremor
- **Agents:**
  - Trihexyphenidyl, Benztropine, Diphenhydramine
  - Low doses, 1–3 times daily
- **Adverse Effects:**
  - Constipation, urinary dysfunction, blurry vision, dry mouth, cognitive dysfunction, hallucinations, tachycardia
  - Usually used in patients under 60 yrs of age and without any existing cognitive dysfunction

**Options in Late Disease:**
- **Amantadine**
  - 100mg twice to four times daily
  - Exact mechanism unknown
  - Reduces peak dose dyskinesias
  - Wean slowly, d/c associated with pronounced worsening of PD symptoms
  - Side effects similar to dopamine agonists, including hallucinations
    - livedo reticularis

**Apomorphine**
- Nonergot dopamine agonist given by sub-q injection
- Rescue medication for acute, severe hypomobility
- Onset of action 10–15 minutes, lasts about 60–120 min
- Pronounced nausea, given with antiemetic
- Dose must be carefully determined in office by trained physicians.
Treatment: *motor symptoms*

- Options in Late Disease:
  - **Deep Brain Stimulation**
    - Approved for medically refractory symptoms
    - Does not cure or alter progression
    - Improves LEVODOPA-RESPONSIVE symptoms
      - Tremor, motor fluctuations, dyskinesias
    - Patient characteristics
      - Younger, without dementia, depression, or psychosis

- Alternative Therapies
  - There is no good evidence to support the use of any herbal medications or supplements
  - There is no known drug that provides *neuroprotection* or slows progression
  - There is sufficient evidence to recommend AGAINST Vitamin E
    - Studies have shown it does NOT slow disease progression

**Treatment Considerations**

- Initiation
  - AAN recommends starting therapy when patients develop *functional disability*
  - Carbidopa/Levodopa, Dopamine Agonists, and MAO-B Inhibitors are all appropriate first line, monotherapy agents

- Levodopa eventually produces motor fluctuations and dyskinesias
  - Initially:
    - Neurons convert Levodopa to dopamine
    - Neurons can store the dopamine and release it more smoothly/appropriately
  - Late:
    - More neurons degenerate
      - Converting and storing capacity is decreased, variable, and unpredictable
Treatment Considerations

- Dopamine Agonists and MAO-B Inhibitors
  - Less effective than Carbidopa/Levodopa at treating bradykinesia, rigidity, imbalance
  - Less incidence of motor fluctuations and dyskinesias

- In early disease/mild impairment
  - Consider initiating a dopamine agonist or MAO-B inhibitor, particularly in younger patients (<65-70)
  - Generally MAO-B inhibitors preferred as they have lesser side effect profile.
  - This can delay the need for carbidopa/levodopa
    - Which could delay the onset of dyskinesias and motor fluctuations

Case 1

53yo right-handed man with 6 months of left-handed tremor and stiffness. Works as an accountant. Exam shows slight bradykinesia, mild rigidity and intermittent left upper extremity tremor. Symptoms are not particularly bothersome.

What would you do?

6 month follow-up:
His symptoms have progressed. Increased tremor and stiffness. Can still work but more bothered by his symptoms.

What would you do?
Case 1

1 year later
Was seen q 4 months without medication change. Good response for 9. Over last 3 months worsened tremor and pain in left arm. Right arm more stiff and difficult to write. Occasionally in the A.M. he has painful cramping and curling of the toes.

What now?

Case 2

65 yo woman with 7 year h/o Parkinson’s. Currently on Carbidopa/Levodopa IR 25/100 4 times a day (every 4 hours). Also takes Pramipexole 1.0 mg on same schedule. Symptoms are worsening and meds are wearing off after about 3 hours.

What changes can you make?

Case 3

68 yo male with an 8 year history of Parkinson’s. Presents today with involuntary twisting and turning movements of his trunk, extremities, and neck. These occur about 1 hour after each carbidopa/levodopa dose. He take IR 25/100, 2 tablets 4 times daily, entacapone (COMT) 200mg 4 times daily, and ropinirole (DA) 3 mg 4 times daily. He does not have bothersome off time but the movements are very embarrassing.

What do you do?

Treatment: NON-motor symptoms

• Non-motor symptoms are extremely common – Significantly ↓ quality of life
• As control of motor symptoms has improved, treatment of the non-motor symptoms has gained more attention
Treatment: **NON-motor symptoms**

- Common non-motor symptoms:
  - Behavioral Disorders
    - Dementia, Depression, Psychosis
  - Sleep Disorders
    - Restless Leg, Periodic Limb Movements of Sleep, and REM Sleep Behavior Disorder
  - Autonomic Dysfunction
    - Constipation, Urinary Incontinence, Hypotension, Sexual Dysfunction

Treatment: **NON-motor symptoms**

- Dementia
  - Consider stopping dopaminergic medications, anticholinergics
  - Agents:
    - Donepezil (Aricept™), Level B
    - Rivastigmine (Exelon™), Level B

Treatment: **NON-motor symptoms**

- Depression
  - Best evidence is for amitriptyline (level C)
    - Anticholinergic side effect can be limiting
  - SSRI’s used routinely in practice, evidence lacking
  - Studies for other drugs have been inconclusive
- Anxiety
  - Not studied systematically in Parkinson’s
  - low dose SSRI or lorazepam twice daily anecdotally helpful

Treatment: **NON-motor symptoms**

- Psychosis
  - Clozapine, Level B
    - Close monitoring of ANC mandatory
  - Quetiapine (Seroquel™), Level C
  - Olanzapine (Zyprexa™) should NOT be considered, Level B
Treatment: **NON-motor symptoms**

- REM Sleep Behavior Disorder
  - Limited data, but low dose clonazepam appears to be effective
- Restless Leg and Periodic Limb Movements
  - 20% of patients with Parkinson’s experience these
  - Limited data, but a bedtime dose of carbidopa/levodopa appears better than the DA’s

Treatment: **NON-motor symptoms**

- Excessive Daytime Sleepiness
  - Results from the disease as well as side effects of treatment
  - Affects 50% of patients with Parkinson’s
  - Modafinil (Provigil™) is Level A recommendation
  - Methylphenidate also effective

Treatment: **NON-motor symptoms**

- Autonomic Dysfunction
  - Insufficient evidence:
    - Orthostatic hypotension, urinary incontinence
  - Level C evidence:
    - Constipation – Polyethylene glycol
    - Erectile Dysfunction - Sildenafil

What’s new...

- **Rytary™**
  - New extended release formulation of oral carbidopa/levodopa
  - Most effective at decreasing off-time and extends interval between doses
- **Duopa™**
  - Dopamine pump – continuous dopamine infusion in gel form, via a percutaneous gastrojejunalostomy tube
  - Already in use in 43 countries
What could be coming...

- Immunotherapies
  - Aimed at alpha-synuclein protein
    - Build up in the brain parallels progression of PD
  - Goal: stimulate an immune response against this protein
    - Protein gets cleared, Parkinson’s disease progression could be slowed
  - Vaccine and Monoclonal Antibodies both in investigation

Summary

- Begin treatment when functional disability occurs
- Carbidopa/Levodopa, DA’s, MAO-B inhibitors all first-line, monotherapy options
  - Consider starting with something other than levodopa in those <70 years
- Add on agents as response, side effects, and comorbidities allow
- Once Carbidopa/Levodopa is started, then dosing is increased in amount and frequency until desired response or undesirable side effects

Summary

- Multiple non-motor symptoms occur in Parkinson’s disease and ↓ quality of life
  - Some are unavoidable side effects of treatment
  - Treating them can improve quality of life, even if they don’t improve motor symptoms
- Newest approved drugs are new ways to administer dopamine
  - There is no known agent that alters disease progression, though immunotherapies are currently being researched

Questions?
References
www.Parkinson.org