Overview

- Epidemiology
  - 1-2% of the total population
  - Parkinson's disease (PD) affects approximately 1 million individuals in the United States.
  - Prevalence increases exponentially with age between 65 and 90

- 5 - 10% of Parkinson's patients have symptoms before age 40

- Parkinson's disease is the 2nd most prevalent neurodegenerative disease next to Alzheimer's
Burden of Parkinson’s Disease

- Reduced quality of life
- Higher susceptibility to depression and cognitive impairment
- Increases risk for co-morbidities such as pneumonia
- Increases medical expenses (physician and emergency care)
- Caregiver burden and risk of early nursing home placement

Cardinal Motor Manifestations

Mnemonic - PART:

- Postural imbalance
- Akinesia/Bradykinesia
- Rigidity
- Tremor at rest

Physical Examination

- Observation
  - Gait disturbances
  - Reduced Arm Swing
  - Postural instability
  - Reduced Strength
  - Rigidity
  - Lack of Manual Dexterity
- Objective Measures
  - Mild orthostatic hypotension
  - Labs generally not useful
  - CT/MRI normal early on, may show cortical atrophy in later stages

Continuum of Parkinsonism

Idiopathic Parkinson's Disease
- Essential Tremor
- Progressive Supranuclear Palsy
- Multi-System Atrophy
- Drug-related
- Essential Tremor
- Secondary Parkinson’s Disease
- Alzheimer's Disease
- Lewy Body Disease
- Other Parkinson-plus
- Other

Drugs
- Vascular
- Secondary
- Other
Management of PD

- Non-Pharmacologic
- Pharmacologic
  - Managing Motor & Non-motor Symptoms
- Ongoing Education & Support
- Surgery

Goals of Therapy

- Reverse or minimize functional disability
- Prevent or minimize long term complications of PD
- Prevent or minimize long term complications associated with medications
- Delay disease progression (controversial)

Pharmacologic Management of Motor Symptoms

Note: Refer to PDF Quick Reference on PD Pharmacotherapy Motor Symptoms in addition to slides

Important Considerations...

- When should the drug therapy be started?
- What drug should be prescribed first?
- How long before we see an effect?
- What are the side effects?
- Patient-related variables..ie age, coexisting medical problems
Role of Various Neurotransmitters

- Norepinephrine
- Acetylcholine
- Glutamate
- Serotonin
- GABA
- Dopamine

Sites of Action of PD Drugs

- Substantia Nigra
- BBB
- DDC
- COMT
- Carbidopa
- Entacapone
- Selegiline, rasagiline
- Amantadine
- Dopamine agonists: bromocriptine, pramipexole, ropinirole, rotigotine, apomorphine
- Trihexyphenidyl, benztropine

Progression of Pharmacotherapy

- Polytherapy
- Monotherapy

- Early Stages of PD
- Advanced Stages

Levodopa

- Mechanism of Action:
  - decarboxylated in the brain to form dopamine
- Advantages:
  - “Gold Standard”
  - Improves:
    - rigidity, tremor, bradykinesia, gait, hypomimia, micrographia
- Disadvantages:
  - Motor Complications
  - Side effects:
    - e.g. nausea, vomiting, hallucinations, orthostatic hypotension
Clinical Use of Carbidopa

- Blocks peripheral dopa decarboxylase
- Optimal daily dose 75 to 100mg
- Increases the amount of levodopa entering the brain
- Decrease peripheral adverse effects:
  - nausea
  - vomiting
  - cardiac irritability
  - orthostasis

Sinemet® (carbidopa/levodopa)

- Regular Sinemet®:
  - onset of effect 15-30 minutes, duration of effect lasts 2-5 hours (peaks and troughs)
  - Absorption better on empty stomach
- CR Sinemet®:
  - onset of effect 45-60 minutes, duration 3-8 hours. (smoother response)
  - Absorption better with food
  - Need to give 30% more of the CR because of reduced absorption.

Food/Drug Interactions:
- High protein meals can interfere with absorption of levodopa across GI endothelium and across blood brain barrier. Timing of meals may be clinically important as disease progresses

Interventions to delay use or optimize Levodopa

- Monoamine Oxidase (MAO)-B Inhibitors
  - eg. selegiline, rasagline
- Amantadine
- Dopamine Agonists
  - eg. pramipexole, ropinirole, bromocriptine, apomorphine
- Catechol-O-Methyltransferase (COMT) Inhibitors
  - eg. Entacapone, tolcapone
- Combination:
  - carbidopa/levodopa/entacapone

Advantages
- "Gold Standard" with notable improvements with use
- Improves disability and prolongs capacity to maintain employment and ADLs

Disadvantages
- Motor Disturbances
- Increasing dose may lead to increase in side effects
- Sedation
- Does not treat all features of PD
Risk vs. Benefits of Selegiline

- **Advantages**
  - requires no titration
  - increase brain dopamine levels
  - may delay need for levodopa
  - Multiple formulations (oral tablet and oral disintegrating tablet – defer to accompanying table)
  - Long term use showed improvement over placebo and levodopa in on-off fluctuations, freezing of gait and motor UPDRS yet not increased dyskinesias

- **Disadvantages**
  - Watch for drug interactions with: meperidine, antidepressants
  - Side effects: insomnia, confusion, hallucinations
  - Limited symptom improvement
  - Has amphetamine and metamphetamine metabolites

Risk vs. Benefits of Rasagiline

- **Advantages**
  - requires no titration
  - increase brain dopamine levels
  - may delay need for levodopa
  - Provides antioxidant effect (Neuroprotective)
  - RDBPC trial noted improvement with 1mg and 2mg in individuals with early stages of PD on UPDRS
  - No amphetamine metabolite

- **Disadvantages**
  - Watch for drug interactions with SSRIs yet not as much of an issue as with selegiline yet metabolized through cyp1A2
  - Side effect profile better than selegiline
  - Limited symptom improvement
  - Need long term studies re: neuroprotection

Benefits vs Risk of Amantadine

- **Advantages**
  - useful in bradykinesia, rigidity and tremor
  - useful for control of motor fluctuations and dyskinesias

- **Disadvantages**
  - Tolerance may develop
  - rebound parkinsonian sx if stopped abruptly
  - Renally eliminated
  - side effects:
    - cognitive impairment
    - hallucinations
    - livedo reticularis
    - lower extremity edema
    - insomnia

Risk vs Benefits of Dopamine Agonists

- **Advantages**
  - Monotherapy
  - direct effect on receptor
  - may delay or reduce motor fluctuations and dyskinesias
  - may be neuroprotective
  - Different preparations

- **Disadvantages**
  - Titration schedule with oral agents
  - side effects:
    - nausea, vomiting
    - insomnia
    - hallucinations
    - ophthalmologic hypotension
    - sleep attacks
    - ergot derivatives
      - vascular complications, digital vasospasm, Raynaud’s syndrome
### Dopamine Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>T1/2</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>Antagonist</td>
<td>agonist</td>
<td>agonist</td>
<td>3 hrs</td>
<td>7.5-40mg/day</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>-</td>
<td>agonist</td>
<td>Agonist (+++)</td>
<td>8-12 hours</td>
<td>0.75-3 mg/day</td>
</tr>
<tr>
<td>Ropinerole</td>
<td>-</td>
<td>agonist</td>
<td>agonist</td>
<td>6 hours</td>
<td>9–24 mg/day</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>Agonist</td>
<td>Agonist</td>
<td>Agonist</td>
<td>5-7 hrs</td>
<td>4–6 mg/day</td>
</tr>
</tbody>
</table>

### Comparison of DA to Levodopa

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pramipexole</th>
<th>Cabergoline</th>
<th>Ropinerole</th>
</tr>
</thead>
<tbody>
<tr>
<td># of pts yrs</td>
<td>301/2</td>
<td>412/3-5</td>
<td>268/5</td>
</tr>
<tr>
<td>Efficacy (%)</td>
<td>MOTOR 7.3</td>
<td>ADL 5.4</td>
<td>MOTOR 4.8</td>
</tr>
<tr>
<td>LD Agonist</td>
<td>51/28</td>
<td>31/10</td>
<td>40/14</td>
</tr>
<tr>
<td>MOTOR</td>
<td>30/22</td>
<td>34/22</td>
<td>45/20</td>
</tr>
<tr>
<td>ADL</td>
<td>14/6</td>
<td>16/33</td>
<td>22/0</td>
</tr>
<tr>
<td>Wearing Off</td>
<td>34/23</td>
<td>34/22</td>
<td>35/33</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>6/19</td>
<td>16/33</td>
<td>20/0</td>
</tr>
</tbody>
</table>

### Advantages of Apomorphine
- First approved agent for treating acute intermittent hypomobility attacks
- Lessens duration of acute "off" episodes for advanced PD
- Allows patients to perform ADL
- Does not affect levodopa pharmacokinetics
- Speed of onset (CSF in 15 min)
- Reduce "crisis" visit to hospitals → reduce cost

### Disadvantages of Apomorphine
- Needs to be taken with antiemetic for 6 weeks
- Cardiovascular events
  - MI, angina, cardiac arrest
- Fails due to decreased BP and dyskinesia
- Intensive monitoring for testing dose
- Monitoring for hepatic and renal function
- Time for patient and caregiver education
- Purchase issues
- Abuse potential

### Risks vs. Benefits of COMT Inhibitors
- **Advantages**
  - Improve motor function
  - Increase "on" and decrease "off" time
  - Constant dopaminergic stimulation
  - Ease of initiation and effect seen immediately
  - Available in a combination with levodopa/carbidopa
- **Disadvantages**
  - Not monotherapy must be given same time as levodopa
  - Side effects
    - Levodopa induced dyskinesias
    - Hypotension
    - GI nausea and diarrhea
    - Hepatotoxicity with tolcapone
    - Urine discoloration
Tremor Predominant PD Patients

- Anticholinergics
- Mechanism of Action:
  - Restore balance of Ach/DA by blocking acetylcholine in basal ganglia
  - address tremor yet not bradykinesia or rigidity

Clinical Use of Anticholinergics

- Benztropine (Cogentin®) 0.5, 1 and 2 mg tablets, 1mg/ml inj
  - give 0.5mg at hs and increase to TDD 4-6mg/day
- Trihexyphenidyl (Artane®) 2 and 5mg tablets, 5 mg sustained release capsule, 2mg/5ml elixir
  - give 1-2 mg/day and increase to 6-10mg/day in divided doses. Increase doses in 2mg increments every 3-5 days

Note: side effects limit use in our elderly

Simplified Guidance on Pharmacologic Management

Add anticholinergic or amantadine
Add amantadine, Dopamine agonist or Sinemet

OTCs and Nutraceuticals

Add amantadine
Add amantadine, Dopamine agonist, or Sinemet

Adapted from Pharmacotherapy 27(12), December 2007
Risks vs Benefits of Coenzyme Q10 (Ubiquinone)

**Advantages:**
- Endogenous antioxidant (Heart, liver and kidneys)
- RDBPC showed improvement at the 1200mg/day (p = 0.04) with greatest effect noted in ADLs
- Well tolerated

**Disadvantages:**
- Cost
- Still not sure of the best dose and when to initiate
- Interactions:
  - Do not use if:
    - You are taking WARFARIN
    - You have DIABETES

Vitamins

- **Vitamin E**
  - Multiple clinical trials in PD patients looking at neuroprotection—however available studies have mixed results and recent Guideline does not advise its use
- **Vitamin C**
  - Can increase levels of levodopa yet small studies and not recommended
- **Folic acid**
  - No clinical benefit noted in small studies and not recommended

Additional Nutraceuticals

- **Vicia faba** (fava beans):
  - L-DOPA in the seedlings, pods, and beans of the broad bean. May also provide symptomatic relief especially early in the disease.
- **Mucuna pruriens** (cowhage or velvet beans):
  - Seed powder of the leguminous plant has long been used in traditional Ayurvedic Indian medicine for diseases including parkinsonism. Evidence to support its potential role in PD (Journal of Neurology Neurosurgery and Psychiatry 2004;65:1672-1677)

Pharmacologic Management of Non Motor Symptoms
Complications of PD Treatment

- **Dopamine excess**
  - Dyskinesias
  - Hallucinations
  - Delusions

- **Dopamine deficiency**
  - Worsening PD symptoms

Non Motor Symptoms Overview

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Respond to dopaminergic treatment</th>
<th>Worsened by Dopaminergic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychiatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hallucinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panic Attacks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excess, Day Sleepiness</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>RLS and periodic limb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urgency/Nocturia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin Syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sensory SxS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain related to PD</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Management of Non Motor Symptoms

**Hallucinations**

- Occurs in approximately 20% of patients
- Evaluate etiology
- Is it distressing to the patient?
- Treatment options:
  - Typical vs. Atypical Antipsychotics
    - clozapine (Clozaril)
    - quetiapine (Seroquel)
    - olanzapine (Zyprexa)
    - risperidone (Risperdal)

Management of Non Motor Symptoms

- **Cognitive Impairment and Dementia**
  - Dementia occurs in approximately 30% of PD patients
  - Evaluate etiology
  - Formal testing as well as caregiver interviewer may be needed
  - Treatment:
    - Evaluate non-PD meds
    - Evaluate PD meds esp. Anticholinergics, TCAs, Amantadine, selegiline and dopamine agonist
    - If possible- may reduce levodopa/carbidopa
    - Trial of cholinesterase inhibitor (e.g. rivastigmine)
Management of Non Motor Symptoms

Depression
- Occurs in approximately 50% of patients
- Identification often delayed
- Treatment:
  • Optimize PD treatment
  • Antidepressants
  • Pramipexole

Sleep Disturbances
- Etiology:
  • Secondary to Motor Complications ("wearing off")
  • Excessive daytime sleepiness/Medication Related
  • REM Sleep Disorder (RBD)
  • Hallucinations
- Potential Treatments:
  • Depends on underlying etiology
    - Optimizing regimens
    - Modafinil (Provigil)

Management of Non Motor Symptoms

• Autonomic Dysfunction
  - Constipation
    • Increase movement and fiber
    • Increase fluids
    • Txs: stool softeners & Senna
  - Sialorrhea
    • Treatment: Atropine SL drops twice daily

• Orthostatic Hypotension
  - Eliminate antihypertensives
  - Non-drug
    - Drug: fludrocortisone, midodrine
• Sexual Dysfunction
• Urinary Incontinence
Conclusion

As pharmacists it is important to:

- Individually assess stage of illness, & target symptoms (motor and non-motor)
- Educate patients and families on various pharmacologic choices in regards to benefits and adversities &
- Ensure ongoing monitoring with medications and progression of PD.

Education and Resources

Books & Journals
Guidelines: American Academy of Neurology 2006
visit: www.aan.com

Websites
- www.parkinson.org
- www.mpd.org
- www.parkinson.org/education
- http://medweb.bham.ac.uk/depts/clin_neuro/teaching/tutorials/parkinsons/parkinsons1.html

Resources

- New Drug Development Resources:
  - Parkinson Pipeline Project (Parkinson’s Disease Foundation)
    - http://www.pdpipeline.org
    - 710 West 168th Street, New York, NY 10032-9982
    - Phone: (800) 457-6676
  - The National Parkinson’s Foundation
    - http://www.parkinson.org
    - 1501 N.W. 9th Avenue (Bob Hope Road), Miami, Florida 33136-1494
    - Phone: (800) 327-4545

QUESTIONS?