TOPIC REVIEW

PARKINSON DISEASE IN THE ELDERLY: MANAGEMENT
INTRODUCTION

- Described by James Parkinson in 1817
- Chronic, progressive neurodegenerative disorder
- Cardinal signs:
  - Rest tremor
  - Rigidity
  - Bradykinesia
  - Gait disturbance
Parkinson Disease: Pathogenesis
Pathogenesis

- Loss of neurons in the caudal and anterolateral parts of the substantia nigra
- Reactive gliosis and formation of Lewy bodies
Pathophysiology

- **Direct pathway**
  - Decreased striatal inhibition of the GPi
  - Inhibitory influence of the GPi on the thalamus
  - Reduced activity in the thalamocortical projection

- **Indirect pathway**
  - Lack of dopamine neurotransmission in the striatum
  - Increase in striatal activity, functional disinhibition STN
Blue arrows indicate inhibitory connections
White arrows indicate excitatory connections.
The thickness of the arrows indicates the amount of activity.
**DIAGNOSIS**

- “Gold standard” for diagnosis
  - Neuropathologic examination
- Diagnosis of idiopathic PD
  - 2 of 3 cardinal manifestations
    - Tremor
    - Bradykinesia
    - Rigidity

DIFFERENTIAL DIAGNOSIS

- Essential tremor
- Dementia with Lewy bodies
- Corticobasal degeneration
- Multiple system atrophy
- Progressive supranuclear palsy
- Secondary parkinsonism Drug-induced parkinsonism
Clinical manifestation

- Cardinal Manifestations
  - Tremor
  - Bradykinesia
  - Rigidity

- Affect the craniofacial musculature
  - Masklike facies
  - Defective mouth closure, reduced blinking, drooling
  - Hypophonia, hoarse, poorly enunciated, and dysarthrophonia
Postural changes
- Stooped posture, a mildly flexed and adducted posture of the arms
- Postural instability

Gait disturbances
- Small-stepped gait, with reduced arm swing
- Difficulty initiating gait
- Impairment of fine motor control
- Pill-rolling tremor
- Cogwheel rigidity
- Dystonia
○ Behavioral Changes
  • Depression
  • Anxiety
  • Dementia
  • Hallucinations

○ Autonomic Dysfunction
  • Hypotension
  • Constipation
  • Polyuria, urinary urgency, and urinary incontinence
  • Sleep disorders
  • Sexual dysfunction
  • Hyperhidrosis
TREATMENT

- Goal of treatment
  - Improvement of the motor, autonomic, and cognitive symptoms of the disease
- Pharmacotherapy
  - Neuroprotective therapy
  - Symptomatic therapy
- Nonpharmacological therapy
Figure 1. Loss of Dopamine-Synthesizing Neurons in the Brain Stem of a Patient with Parkinson's Disease.
A schematic comparison of coronal brain slices from a control subject (left) and a patient with Parkinson's disease (right) illustrates the major neurodegenerative loss of dopamine-synthesizing neurons in the substantia nigra pars compacta in the brain stem, projecting to striatal nuclei (caudate and putamen) in the cerebrum. Exogenous levodopa administered for treatment of Parkinson's disease is transported to the brain, where it enhances striatal dopaminergic neurotransmission.
Figure 2. Pathways of Levodopa and Dopamine Metabolism, Showing Sites of Action by Inhibitory Drugs Used with Levodopa.

AAAD denotes aromatic L-amino acid decarboxylase, ALDH aldehyde dehydrogenase, COMT catechol-O-methyltransferase, and MAO-B monoamine oxidase type B.
Levodopa
- levodopa is possibly neuroprotective for at least 9 months and does not accelerate disease progression

Neurotoxic versus neuroprotective effects
- Prolonged use of levodopa may directly hasten the degeneration of dopamine neurons in the substantia nigra
- Free radicals and oxidative stress
- The evidence is not strong

Symptomatic therapy

- Levodopa
- MAOB inhibitors
- Dopamine agonists
- COMT inhibitors
- Anticholinergic agents
- Glutamate antagonists; Amantadine
<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Usual starting dose</th>
<th>Usual maintenance dose</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trihexyphenidyl</td>
<td>Artane</td>
<td>1 mg BID</td>
<td>2 mg BID-TID</td>
<td>Anticholinergic</td>
</tr>
<tr>
<td>Benztrapine</td>
<td>Cogentin</td>
<td>0.5 mg BID</td>
<td>1 to 2 mg BID-TID</td>
<td>Anticholinergic</td>
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<tr>
<td>Amantadine</td>
<td>Symmetrel</td>
<td>100 mg BID</td>
<td>100 mg BID-TID</td>
<td>?</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Eldepryl</td>
<td>5 mg</td>
<td>5 mg qam</td>
<td>MAO B inhibitor</td>
</tr>
<tr>
<td>Carbidopa/levodopa</td>
<td>Sinemet</td>
<td>25/100 mg TID</td>
<td>25/250 mg TID-QID</td>
<td>Dopamine precursor</td>
</tr>
<tr>
<td>Carbidopa/levodopa</td>
<td>Sinemet CR</td>
<td>25/100 mg TID</td>
<td>50/200 mg TID</td>
<td>Dopamine precursor</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Apokyn</td>
<td>2 mg SC test dose</td>
<td>2 to 10 mg SC TID</td>
<td>Dopamine agonist</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Parlodel</td>
<td>2.5 mg daily</td>
<td>5 to 10 mg QID</td>
<td>Dopamine agonist</td>
</tr>
<tr>
<td>Pergolide</td>
<td>Permax</td>
<td>0.05 mg daily</td>
<td>0.5 to 1.0 mg TID</td>
<td>Dopamine agonist</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>Mirapex</td>
<td>0.125 mg TID</td>
<td>1.5 mg TID</td>
<td>Dopamine agonist</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Requip</td>
<td>0.25 mg TID</td>
<td>1.0 mg TID</td>
<td>Dopamine agonist</td>
</tr>
<tr>
<td>Entacapone</td>
<td>Comtan</td>
<td>200 mg with L-dopa</td>
<td>600 to 800 mg a day</td>
<td>COMT inhibitor</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>Tasmara</td>
<td>100 mg TID</td>
<td>100 to 200 mg TID</td>
<td>COMT inhibitor</td>
</tr>
</tbody>
</table>
Decision to initiate symptomatic therapy

- The effect of disease on the dominant hand
- The degree to which the disease interferes with work, activities of daily living, or social and leisure function
- The presence of significant bradykinesia or gait disturbance
- Personal philosophy regarding the use of drugs
LEVODOPA: FORMULATIONS

- Levodopa + peripheral decarboxylase inhibitor
- Carbidopa/levodopa
  - Immediate-release
    - Sinemet; 10/100, 25/100, and 25/250 mg
    - Parcopa; dissolves on the tongue
  - Controlled-release
    - Sinemet CR and Madopar HBS
- Benserazide/levodopa
  - 25/100 and 50/200 mg

LEVODOPA: DOSE

- Sinemet 25/100 mg,
  - 1/2 tab 2-3 times daily with meals
  - titrated over several weeks 1 tab 3 times daily
- The first time should take each dose with a meal to avoid nausea, a common early side effect.
- Levodopa is more effective if taken on an empty stomach 1 hour before or after meals
**LEVODOPA: SIDE EFFECT**

- **Common side effects**
  - Nausea, somnolence, dizziness, and headache

- **Serious adverse reactions**
  - Confusion, hallucinations, delusions, agitation, and psychosis
  - Mainly in the elderly
**LEVODOPA: SIDE EFFECT**

- Longterm side effect
  - Motor fluctuations (the wearing-off phenomenon)
    - Dyskinesia
    - Dystonia
  - After 5 to 10 years of treatment
    - At least 50 %
  - DATATOP study
    - Motor complications
    - 30 % after only 2 years of treatment

NEUROTOXIC VERSUS NEUROPROTECTIVE

A consensus conference:

- There is no evidence that levodopa causes neuronal death in animal models of parkinsonism.
- The relevance of in vitro studies of levodopa toxicity to clinical use of levodopa is highly uncertain.
- There is no evidence that chronic administration of levodopa exacerbates the degenerative process in PD.
- Late motor complications arise due to the combination of progressive degeneration of dopamine neurons and the reversible effects of levodopa administration.

MAO B INHIBITORS

- Selegiline (Eldepryl)
  - Monotherapy does not produce a functionally significant benefit
  - RCT (2006)
    - Combined selegiline and levodopa compare with placebo and levodopa
- Rasagiline
  - Initial monotherapy in patients with early PD
  - Adjunct treatment in moderate to advanced PD

MAO B INHIBITORS: DOSE

- Selegiline
  - Initial dose 5 mg once a day in the morning
  - 5 mg twice daily
    - Second dose given at noon to avoid insomnia
  - >10 mg daily; no additional benefit
MAO B INHIBITORS: SIDE EFFECT

- Selegilene
  - Nausea and headache
  - Insomnia; Amphetamine metabolites of selegilene
  - Confusion in the elderly patients

- Selegilene; Drug interaction
  - Levodopa
    - Increase levodopa-induced side effects such as dyskinesia
  - TCA or SSRI's
DOPAMINE AGONISTS

- Bromocriptine
- Pramipexole
- Ropinirole
- Rotigotine
- Injectable apomorphine
- Pergolide
DOPAMINE AGONISTS: EFFECTIVENESS

- Bromocriptine, pergolide, pramipexole, and ropinirole
  - Effective in patients with advanced PD

- Pramipexole, ropinirole, transdermal rotigotine
  - Effective as monotherapy in patients with early disease

Systematic review published in 2008

- Compared DA therapy (with or without levodopa) versus placebo and/or levodopa
- 29 eligible trials involving 5247 subjects
- DA treatment were less likely to develop dyskinesia, dystonia or motor fluctuations than levodopa
- Symptomatic control of PD appeared to be better with levodopa than with DAs

DOPAMINE AGONISTS: DOSE

- Bromocriptine
  - Initial 1.25 mg twice a day
  - Increased at 2-4 week intervals by 2.5 mg a day
  - 20 to 40 mg daily in three to four divided doses
  - Maximum dose; 90 mg/d

- Pramipexole
  - Initial 0.125 mg three times a day
  - Increased 0.125 mg per dose every 5-7 days
  - Total daily doses of 1.5 to 4.5 mg
DOPAMINE AGONISTS: DOSE

- **Ropinirole**
  - Started at 0.25 mg 3 times/d
  - Increased 0.25 mg per dose each week for 4 wk
  - After 4 week; Increased weekly by 1.5 mg/d
  - Benefit; 12 -16 mg/d
  - Maximum 24 mg/d

- **Transdermal rotigotine**
  - Started at 2 mg/24 hr
  - Titrated weekly 2 mg/24 hr -> 6 mg/24 hr
DOPAMINE AGONISTS: APOMORPHINE

- Apomorphine
  - 2 mg SC
  - Monitoring BP before and after the injection
  - Increased by 1 mg per dose every 2-4 days to a maximum of 6 mg per dose. Maximum 20 mg/d
  - Antiemetic therapy (e.g., with trimethobenzamide)
  - Prochlorperazine and metoclopramide
    - Reduce the effectiveness of apomorphine
  - C/I
    - Ondansetron and other serotonin receptor agonists
    - Severe hypotension and loss of consciousness
DOPAMINE AGONISTS: SIDE EFFECT

- Nausea, vomiting, sleepiness, orthostatic hypotension, confusion, and hallucinations
- Chronic use; Common - Peripheral edema
- Psychiatric side effects
  - **Dopaminergic dysregulation syndrome**
    - Impulse control disorders; Pathologic gambling, compulsive sexual behavior or compulsive buying
    - Elderly and demented patients
- C/I; Breast feeding

DOPAMINE AGONISTS: SIDE EFFECT

- **Pramipexole**
  - Dose above 1.5 mg/day "sleep attacks"

- **Apomorphine**
  - Cutaneous reactions
  - Neuropsychiatric problems
  - Chest pain, angina, and orthostatic hypotension

- **Pergolide and cabergoline**
  - Potential risk of heart valve damage

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COMT INHIBITORS

- Catechol-O-methyl transferase inhibitors
  - Tolcapone
  - Entacapone

- Action
  - Inhibition of COMT reduces the peripheral (entacapone) and central (tolcapone) methylation of levodopa and dopamine
  - Increases the plasma half-life of levodopa

COMT INHIBITORS

- Use of COMT inhibitors
  - Monotherapy is not used
  - Reduce total daily levodopa dose by as much as 30%
  - Increased levodopa effect

- Tolcapone
  - Start 100 mg 3 times daily

- Entacapone
  - 200 mg tab with each dose of levodopa
  - Maximum of 8 doses per day
COMT INHIBITORS: SIDE EFFECT

- **Most common side effects**
  - Dyskinesia, hallucinations, confusion, nausea, and orthostatic hypotension
  - Diarrhea
  - An orange discoloration of the urine

- **Rare**
  - Elevations in liver enzymes
  - Tolcapone; liver function monitoring

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ANTICHOLINERGICS

- Trihexyphenidyl and benztropine

- Action
  - Benztropine
    - Increase the effect of dopamine by inhibiting its presynaptic reuptake

- Anticholinergic drugs are most useful as monotherapy in patients age < 70 with disturbing tremor who don’t have akinesia or gait disturbance
ANTICHOLINERGICS : DOSE

- Trihexyphenidyl
  - Start 0.5-1 mg twice daily
  - Increase to 2 mg 3 times daily

- Benztropine
  - 0.5 - 2 mg twice daily
ANTICHOLINERGICS: SIDE EFFECT

- **Elderly and cognitively impaired patients**
  - Memory impairment, confusion, and hallucinations

- **Peripheral antimuscarinic side effects**
  - Dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, and tachycardia

- **Withdrawal symptoms**
  - Acute parkinsonism
GLUTAMATE ANTAGONISTS

- Amantadine
  - Antiviral agent, N-methyl-D-aspartate (NMDA) receptor antagonist properties
  - Action
    - Increase dopamine release, inhibit dopamine reuptake, stimulate dopamine receptors
  - Short-term monotherapy; mild disease
  - Little benefit when added to levodopa
GLUTAMATE ANTAGONISTS

- Amantadine
  - Dose in early PD; 200-300 mg/d
  - Side effect;
    - Confusion, hallucinations, and nightmares
      - Combine with antiparkinsonian drugs in older patients
    - Peripheral side effects
      - Livedo reticularis and ankle edema
NONPHARMACOLOGICAL THERAPY

- Stereotactic Neurosurgical Procedures, Deep Brain Stimulation
- Transplant Surgery
- Education
- Support; psychological support patient and family
- Exercise
- Speech therapy
- Nutrition
SUMMARY

- PD is chronic, progressive neurodegenerative disorder, loss of neurons in the substantia nigra
- Lewy bodies are pathologic hallmark of PD
- Cardinal features of PD: tremor, bradykinesia, rigidity, postural instability
- Levodopa combined with a peripheral decarboxylase inhibitor is the most effective symptomatic therapy for PD
SUMMARY

- Levodopa should be introduced when the patient and physician jointly decide that quality of life, particularly related to job performance, self care.
- Initial therapy with a DA in younger patients (age <65) with PD, and with levodopa in elderly patients (age >65).
- Anticholinergic drugs should be avoid in older or dementia.