END STAGE PARKINSON’S DISEASE

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OBJECTIVES

- Understand the pathogenesis of Parkinson’s Disease (PD)
- Identify the clinical presentation of PD
- Understand the prognosis of PD
- Identify pharmacological treatment options
- Discuss management of autonomic disturbances

WHAT IS PARKINSON’S?

- Chronic and progressive neurodegenerative disorder
- Death of vital nerve cells called neurons
- Affects dopamine-producing neurons in the substantia nigra
- Dopamine: controls movement & coordination
- Decrease
- Motor symptoms
- Presence of Lewy Bodies (LB)
- Protein deposits in nerve cells of brain
- Poor regulation of body functions (autonomic nervous system)
- Non-motor symptoms

EPIDEMIOLOGY

- 1% of individuals older than 60 years
- Common in men than women
- One of the most common neurologic disorders
- 4 to 21 cases per 100,000 population per year
- Incidence
- PD affects about 1 million people in the U.S
- More than 10 million people worldwide
- Parkinson’s Disease Foundation
- NHPCO statistics
- CDC
- 1% of annual hospice admissions

PARKINSON’S DISEASE

Prognosis
- Rapid/slow rate of progression
- Age
- Primary symptom presentation
- Presence of comorbidities
- No cure
- Life expectancy of 15 to 20 years from time of diagnosis
- Pneumonia may be the cause of death in about 45% patients with PD
- Estimated Healthcare Costs Related to PD in the U.S
- $13 billion per year in U.S. alone
- Medications alone cost an average of $2,500 a year
PARKINSON'S DISEASE: SIGNS & SYMPTOMS

- Motor symptoms
  - tremor
  - bradykinesia
  - rigidity
  - dystonia
  - shuffling gait
- Nonmotor symptoms
  - sensory
  - deep
  - mood disorders
  - autonomic dysfunction

HOERNH AND YAHRI STAGING OF PARKINSON'S DISEASE

- Stage 1 - unilateral symptoms
  - tremors on one side of the body
- Stage 2 - bilateral symptoms
  - tremors on both sides of the body
- Stage 3 - mild to moderate bilateral symptoms
  - impaired balance
- Stage 4 - severe disability
  - able to walk/stand unassisted
- Stage 5 - advanced stage
  - bedridden or wheelchair bound

EARLY STAGE TREATMENT

- Patients with PD <5 years
- No motor complication from levodopa use
- Mild symptoms may be treated with
  - Levodopa-carbidopa
  - Dopamine agonists
  - MAO-B inhibitors
  - Anticholinergics
  - Amantadine

American Academy of Neurology
- Recommends Levodopa or Dopamine agonist
- Improve motor disability
- Levodopa
- Decrease motor complication
- Dopamine agonist

**Most patients will always need levodopa or a dopamine agonist**

PHARMACOLOGICAL AGENTS

- Levodopa
  - Most effective pharmacological agent
  - Primary treatment
  - Controls bradykinesia and rigidity
  - Always combined with carbidopa
  - Decrease in peripheral adverse effects
  - Increase in cerebral levodopa
  - Available formulations:
    - Immediate release
      - Sinemet, Carbidopa-levodopa
    - Controlled release
      - Sinemet CR, Carbidopa-levodopa ER, Rytary
    - Carbidopa-levodopa ODT
    - Duopa Enteral
    - Suspension

LIMITATIONS OF LEVODOPA

- Does not prevent the neurodegeneration of disease
- Efficacy tends to decrease as the disease progresses
- Adverse effects:
  - nausea
  - orthostatic hypotension
  - Hallucinations
  - Chronic treatment - advanced disease
  - Motor fluctuations
  - Dyskinesia

LIMITATIONS OF LEVODOPA: MOTOR FLUCTUATIONS

- Alternations between "on" and "off" periods
  - "On" period
    - Time period when patient has a good response to the medication
  - "Off" period
    - Time period when patient's response to medication wears off and PD symptoms return (rigidity, freezing gait)

"On" period increases, "off" period decreases

"On-off" phenomenon, "wear-off" phenomenon
- May be accompanied by painful dystonic muscle cramping
**LEVODOPA-INDUCED DYSKINESIA**

- What are dyskinesias?
  - Involuntary movements that include chorea and dystonia
  - Related to dopaminergic medication dosing peaks
- Occurs at maximal clinical benefit
- Peak plasma concentration
- Peak dose dyskinesia
- As disease progresses, the therapeutic window narrows

**PHARMACOLOGICAL AGENTS**

- **Dopamine Agonists**
  - Pramipexole (Mirapex), Ropinirole (Requip), Rotigotine (Neupro), Apomorphine
  - Directly stimulate dopamine receptors
  - Early and advanced PD
- Adverse effects:
  - Nausea
  - Orthostatic hypotension
  - Hallucinations
  - Edema
  - Sleepiness
  - Impulse control disorders

- **MAO-B Inhibitors**
  - Selegiline (Eldepryl, Zelapar), Rasagiline (Azilect)
  - MAO-B isoenzyme - predominant form in brain
  - Responsible for dopamine metabolism
  - Blocks metabolism & increases concentration
  - Early and mild PD
- Adverse effects:
  - Dizziness
  - Headache
  - Confusion
  - Arthralgia
  - Rasagiline
  - Avoid use SSRIs, SNRIs, TCAs

- **COMT Inhibitors**
  - Entacapone (Comtan), Tolcapone (Tasmar)
  - Beneficial with combination of levodopa/carbidopa
  - Prolongs availability of levodopa in plasma
  - Increase of levodopa in brain
  - Reduces off time
  - Relieves the end-of-dose wearing off effect
- Adverse effects:
  - Urine discoloration
  - Nausea
  - Orthostatic hypotension
  - Exacerbation of levodopa effects
  - Tolcapone
  - Fluid acute kidney injury
  - LFT monitoring required
  - Not recommended

**ADVANCED DISEASE-LATE STAGE TREATMENT**

- Short duration of response from levodopa/carbidopa
- Benefits last about 2 hours
- Treatment of motor fluctuations (on/off phenomenon) with end-of-dose dyskinesia
  - Increase levodopa dose
  - Dose levodopa more frequently
  - Add dopamine agonist, MAO-B inhibitor or COMT inhibitor
  - Add intermittent levodopa inhalations
  - Levodopa Oral Inhalation Powder (Inbrija)
  - FL+ for Off period symptoms – rescue therapy
  - Not appropriate for hospice patients
  - Costly $$

- Treatment of motor fluctuations with dyskinesia
  - Decrease in dopaminergic therapy
  - May increase off time
  - More PD symptoms
  - Increase in dopaminergic therapy
  - May increase peak dose dyskinesia
  - Management
    - Adjust levodopa dose and dosing schedule
    - May add COMT inhibitor (Stalevo), dopamine agonist or Amantadine
    - Manipulate dietary intake

- Amantadine
  - NMDA receptor antagonist/antiviral agent
  - Mild PD or adjunct indication
  - Gait dysfunction
  - Dyskinesia
  - Adverse effects:
    - Nausea
    - Dizziness
    - Insomnia
    - Hallucinations

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Comparison of IR and CR: Carbipoda/Lodovada in PD
- 5 year multi-center study
- Two treatment groups
- Sinemet CR 50/200mg, Sinemet 25/100mg
- Primary endpoint:
  - presence of motor fluctuations (the event)
- Results:
  - Control of PD symptoms were maintained in both groups
  - Both regimens were associated with low incidence of motor fluctuations & dyskinesias
    - 30.6% in IR group, 31.8% in CR group

Comparison of the Pharmacokinetics of Rytary with Sinemet IR, Sinemet CR, & Stalevo
- Single dose study
- 4 treatment groups
- Time to peak concentration
- Results:
  - Rytary provided an initial increase in LD concentration comparable to that with IR
  - Sustains the concentration for 1.9 to 2.5 longer than the other CD-LD formulations

**PARKINSON'S DISEASE: SYMPTOMATIC DRUG THERAPY**
- Carbidopa-Levodopa
  - all stages of disease
  - useful for motor symptoms & dyskinesia
  - adjust or maintain

**MONOAMINE OXIDASE (MAO) INHIBITORS**
- all stages of disease
- effective for motor symptoms
- adjust or maintain
- "LD" is levodopa

**COMT INHIBITORS**
- all stages of disease
- adjust or maintain

**DOPAMINE AGONISTS**
- effective for early or mild motor symptoms
- motor fluctuations
- adjunct or monotherapy

**SAME INHIBITORS**
- effective to control motor fluctuations
- adjunctive therapy with levodopa-carbidopa

**Anticholinergics**
- tremors
- high risk of adverse effects

**Medications to Avoid in Parkinson's Disease: APDA**
- Sensory
- Sleep disturbances
- Mood disorders
- Depression/hallucinations/delusions
- Autonomic dysfunction
- Excessive saliva
- Urinary urgency
- Constipation
- Orthostatic hypotension

**Hallucinations or Delusions**
- Antiparkinsonian medications should be discontinued
- N Organizations (Periactin)
  - second generation atypical antipsychotic
  - FDA approved for: hallucinations & delusions associated with Parkinson disease psychosis
  - AHR grade
  - $12/tablets
- Clozapine (Clozaril)
  - second generation atypical antipsychotic
  - effective use psychosis in Parkinson's disease
  - brisk reflexes are required for antipsychotic
- Sertraline (Zoloft)
  - second generation atypical antipsychotic
  - effective use psychosis in Parkinson's disease
  - 150 mg in 3 divided doses (50-250 mg)
  - efficacy not confirmed

**Medication Management of Autonomic Disturbances**
- Gastrointestinal Dysfunction
  - Carbopoli
  - Sedohep (Bulbul)
  - Drug resistant angina
  - Dysphagia (dry mouth)
  - Anticholinergics
  - Hydration
  - Increase physical activity
  - Medications to avoid
  - Anticholinergics
- Orthostatic Hypotension
  - Nicotine (Nicorette)
  - Hydrocortisone
  - Medications to avoid
  - Antihypertensives
  - Metoclopramide (Reglan)
  - Avoid high-fat foods and large portions
  - Increase fluid and salt intake
  - Elevate head of the bed
  - Wear compression stockings
  - Avoid alcohol intake
  - Slow postural changes

**Non-motor Symptoms**
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MEDICATION MANAGEMENT OF AUTONOMIC DISTURBANCES

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Medications that may improve symptoms</th>
<th>Non-pharmacological options</th>
<th>Medications to avoid</th>
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</thead>
<tbody>
<tr>
<td>Salivation</td>
<td>Hyoscyamine (Levsin)</td>
<td>Chew food slowly</td>
<td>Trihexyphenidyl (Artane)</td>
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<tr>
<td></td>
<td>Glycopyrrolate (Robinul)</td>
<td></td>
<td>Benztropine (Cogentin)</td>
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<td></td>
<td>Atropine (Isopto)</td>
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<td>Diphenhydramine (Benadryl)</td>
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<td></td>
<td>Scopolamine patch (Transderm-Scop)</td>
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<td></td>
<td>Chewing gum can increase swallowing reflex</td>
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Urinary Difficulties

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<tr>
<td>Overactive bladder:</td>
<td>Oxybutynin (Oxytrol)</td>
<td>Schedule voiding</td>
<td>Trihexyphenidyl (Artane)</td>
</tr>
<tr>
<td></td>
<td>Tolterodine (Detrol)</td>
<td></td>
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CLINICAL PEARLS

- Nausea most common SE of dopaminergic therapy
- Avoid dopamine antagonists for nausea
- Haldol and Reglan
- Consider low dose of promethazine (2.5 mg)
- Consider reduction in dose of dopaminergic medications prior to initiating any antipsychotic medication
- Taper antiparkinsonian medications
- Allerges to dopamine can cause symptoms of parkinsonism-hyperpyrexia syndrome
- Hyperkinesias, akathisia, rigidity

QUESTIONS?

REFERENCES

- https://www.epic-parkinson.com/australia/epic-parkinson/
- https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7019?cesid=a46A5ZCFMsW&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dhaldol%26t%3Dname%26va%3Dhaldol#phase
- https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7598?cesid=3Xev253aIUe&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3DSEROquel%26t%3Dname%26va%3Dseroq#fee