PHARMACOLOGICAL MANAGEMENT OF PARKINSON’S DISEASE

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OUTLINE

• Principles of pharmacologic treatment
• Initiating pharmacologic treatment
• Levodopa: use and side effects
• Dopamine agonists: use and side effects
• Other drug treatments
• Early versus Late/Advancing PD
• Pharmacologic treatment of non-motor symptoms
• Neuroprotection
Principles of pharmacologic treatment

• Mainstay: aimed at correcting dopamine insufficiency
• Tailored to individual needs
• Current tx: symptomatic relief without effect on slowing disease progression.
• Progressive disease: long term treatment requiring follow up, dose adjustments and drug manipulation
• Drug choices: depend on evidence of efficacy, side effects, cost, individual needs
Initiating pharmacologic therapy

- Tailored to disease severity at presentation
- Discuss drug treatment options with the patient/family
- Allow adequate time interval to assess drug responsiveness
- Dose escalation to reasonable dose before dismissing
- Consider cost and availability/access to drugs
Initiating pharmacologic treatment

- Typically begin treatment in early PD with **EITHER** levodopa or a dopamine agonist

- **Levodopa**: more significant motor improvement but greater risk of later complications (fluctuations and dyskinesias)

- **Dopamine agonist**: less marked motor response, but lower risk of motor complications. However, other complications occur.

*Practice Parameter: American Academy of Neurology; Recommendations EFNS 2013*
LEVODOPA

• Most effective medication to improve motor features

• Reduces bradykinesia and rigidity, variable on tremor

• Fixed dose combination with peripheral dopa decarboxylase inhibitor (PDI) carbidopa or benserazide

• Available in 1:4 (preferred) and 1:10 ratios (LD to PDI)

• Immediate release or controlled release (CR)
LEVODOPA ii

• Start at low dose

• Escalate to tolerable dose with minimal side effects

• Starting low reduces nausea and increases compliance: ½ tablet daily increasing weekly by ½ tablet to initial target 100/25 q8hrs or 6 hrs

• Common side effects:
  – Short term: nausea, vomiting, dizziness, hypotension
  – Long-term use – motor complications (motor fluctuations and dyskinesias)
LEVODOPA: Motor fluctuations

- Risk factors: young age, increased severity, long PD duration, high LD dose

- 4 clinical patterns
  - Wearing off; Delayed on; Random On/Off; No on

- Why?
  - Fluctuating plasma levels, intermittent delivery of LD to brain, pulsatile striatal dopamine stimulation
  - disease progression (insufficient LD dose), impaired or erratic absorption

- Treatment: depends on type: e.g. Wearing off: increase dose or reduce dose interval, or add COMT, MAO-B or DA.
LEVDOPA: Dyskinesias

• Manifests as wriggling, writhing, choreiform movements or dystonia in any body part.

• Often not bothersome to patients

• Types (based on timing of occurrence)
  – Peak dose
  – Diphasic
  – Off-state

• Treatment: depends on type. E.g. Peak dose: reduce dose of LD. Off state: increase LD dose
DOPAMINE AGONISTS

- Recommended as initial therapy in early PD

- Types:
  - ergot derived: bromocriptine, pergolide, cabergoline, lisuride
  - non-ergot derived: apomorphine, piribedil, pramipexole, ropinirole, rotigotine

- All oral except apomorphine (subcut) and rotigotine (transdermal patch)
**DOPAMINE AGONISTS: S/E**

- **Ergot derived:**
  - Moderate or severe cardiac valvulopathy
  - Serosal fibrosis (pleural, pericardial, retroperitoneal)
  - Caution: avoid; screening required

- **All:**
  - Impulse control disorders (pathologic gambling, binge eating, hypersexuality). Risk ↑ in young men, OCD, alcohol abuse.
  - Daytime somnolence
  - Peripheral edema
  - Others: nausea, dizziness, hallucinations, constipation
OTHER TREATMENTS

• MONOAMINE OXIDASE B INHIBITORS
  – E.g. Selegilene, Rasagiline
  – May be used as monotherapy in early PD

• ANTICHOLINERGICS
  – Should not be used as first line treatment in PD
  – Increased frequency of neuropsychiatric and cognitive adverse side effects (especially in elderly)
OTHER TREATMENTS ii

• AMANTADINE
  – Weak antiparkinsonian effect
  – Useful in treating levodopa-induced dyskinesias

• CATECHOL-O-METHYL TRANSFERASE INHIBITOR (ENTACAPONE)
  – Added to levodopa/carbidopa to prolong effect (reduce ‘off’ time) by about 1.5 hours/day
  – Prevents peripheral levodopa and central dopamine metab.
<table>
<thead>
<tr>
<th>Early (Mild) PD</th>
<th>Moderate PD/functional impairment/Severe PD</th>
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<tbody>
<tr>
<td>• Monotherapy with Dopamine agonist</td>
<td>• Add or start Levodopa</td>
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<tr>
<td>• Levodopa</td>
<td>• Add COMT if indicated</td>
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<tr>
<td>• MAO-Inhibitor</td>
<td>• Add any drug from other choices when indicated</td>
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<tr>
<td>• Anticholinergics may be added for tremor-dominant PD (also propranolol)</td>
<td>• Adjust dosage/dosing interval when indicated</td>
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<tr>
<td>• Adjust DA or LD dose to improve response</td>
<td>• Withdraw anticholinergics if S/E intolerable</td>
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# PHARMACOLOGIC TX: NON-MOTOR SYMPTOMS

<table>
<thead>
<tr>
<th>CONSTIPATION</th>
<th>ORTHOSTATIC HYPOTENSION</th>
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<tbody>
<tr>
<td>• Fibre supplements (e.g. methylcellulose)</td>
<td>• Review medications</td>
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<tr>
<td>• Osmotic laxatives (e.g. lactulose)</td>
<td>• Fludrocortisone 0.1mg</td>
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<tr>
<td>• Short-term irritant laxatives</td>
<td>• Midodrine</td>
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## PHARMACOLOGIC TX: NON-MOTOR SYMPTOMS ii

<table>
<thead>
<tr>
<th>DAYTIME SOMNOLENCE</th>
<th>URINARY DISTURBANCE</th>
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<tr>
<td>• Reduce any sedative drugs</td>
<td>• Screen for and treat any UTI</td>
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<tr>
<td>• Decrease dopaminergic drugs (esp agonists)</td>
<td>• Anticholinergics may be used e.g oxybutinin</td>
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<tr>
<td>• Add wake-promoting drugs</td>
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<td>e.g methylphenidate</td>
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PHARMACOLOGIC TX:
NON-MOTOR SYMPTOMS

ANXIETY
- Benzodiazepines (diazepam, lorazepam, clonazepam); SSRIs (fluoxetine, sertraline, paroxetine, etc. Start at low doses.)

REM-SLEEP BEHAVIOURAL DISORDER
- Benzodiazepines (clonazepam, with caution)

HYPERSALIVATION (SIALORRHEA)
- Atropine drops (1% drops 1-2 drops at night or b.d. under the tongue may be useful)
PHARMACOLOGIC TX: NON-MOTOR SYMPTOMS iv

• DEMENTIA
  – Discontinue potential aggravating drugs: anticholinergics, amantadine, TCAs
  – Add cholinesterase inhibitors: rivastigmine, donepezil, or galantamine

• PSYCHOSIS
  – Reduce polypharmacy
  – Add atypical antipsychotics: quetiapine, clozapine
  – Typical antipsychotics, olanzapine, risperidone, aripripazole worsen parkinsonism.
NEUROPROTECTION

• Insufficient evidence to recommend treatment with coenzyme Q10 for early PD

• Tocopherol: not recommended.
  – No evidence of any beneficial effect of vitamin E (tocopherol) 2000 iu/day in either slowing functional decline or ameliorating the clinical features of PD