Pharmacological Treatments in Parkinson’s Disease

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Goals

1) Review basic principles of pharmacological treatments specific to motor symptoms in Parkinson’s Disease

2) Provide examples of treatment options
Dopaminergic Neurons

Cut section of the midbrain where a portion of the substantia nigra is visible.

Substantia nigra

Diminished substantia nigra as seen in Parkinson’s disease.
Dopaminergic Pathways
Theoretical treatment options

• Replace dopamine

• Prevent breakdown of dopamine

• Protect dopaminergic neurons from dying

• Regrow dopaminergic neurons

• Modify neuronal circuitry
Treatment Examples

• Replace dopamine
  – Levodopa
  – Dopamine agonists (Pramipexole, Ropinirole, Rotigotine, Apomorphine)

• Prevent breakdown of dopamine
  – AADC inhibitors (Carbidopa, Benserazide)
  – COMT inhibitors (Entacapone, Tolcapone)
  – MAO-B inhibitors (Rasagiline, Selegiline)

• Protect dopaminergic neurons from dying

• Regrow dopaminergic neurons

• Modify neuronal circuitry
  – DBS
Why can’t I just take dopamine?
Levodopa

Periphery

Blood-brain barrier

Neuron

Brain

L-DOPA

Carbidopa

DA

AADC

DA

Dopamine receptors

*Only tolcapone inhibits COMT in brain.

L-DOPA = levodopa
3-OMD = 3-O-methylldopa
DA = dopamine

AADC = aromatic acid decarboxylase
DOPAC = dihydroxyphenylacetic acid
3-MT = 3-methoxytyramine
Levodopa
Levodopa Formulations

- Immediate release (IR) – Sinemet
- Controlled release (CR) – Sinemet CR
- Stalevo (Combined with entacapone)
- Rytary
1. Patient questions?

• Why do I need to make medication adjustments?
2. Patient questions?

- If I miss a dose, I don’t even realize it. So do I really have Parkinson’s disease?
3. Patient questions?

- Can levodopa cause dyskinesias?
Dopamine Agonists

- Ropinirole, Pramipexole and Rotigotine
- Can be used at any time in the course
- Side effects
  - Low blood pressure, sleepiness, leg swelling,
  - Impulse control disorder
Long Acting Dopamine Agonists

<table>
<thead>
<tr>
<th>Immediate-Release Ropinirole</th>
<th>REQUIP XL</th>
<th>Rx</th>
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</thead>
<tbody>
<tr>
<td>0.75 - 2.25 mg</td>
<td>2 mg</td>
<td>1 x 2 mg</td>
</tr>
<tr>
<td>3 - 4.5 mg</td>
<td>4 mg</td>
<td>1 x 4 mg</td>
</tr>
<tr>
<td>6 mg</td>
<td>6 mg</td>
<td>1 x 6 mg</td>
</tr>
<tr>
<td>7.5 - 9 mg</td>
<td>8 mg</td>
<td>1 x 8 mg</td>
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<tr>
<td>12 mg</td>
<td>12 mg</td>
<td>1 x 12 mg</td>
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<tr>
<td>15 mg</td>
<td>16 mg</td>
<td>2 x 8 mg</td>
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<tr>
<td>18 mg</td>
<td>18 mg</td>
<td>3 x 6 mg</td>
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<tr>
<td>21 mg</td>
<td>20 mg</td>
<td>5 x 4 mg</td>
</tr>
<tr>
<td>24 mg</td>
<td>24 mg</td>
<td>2 x 12 mg</td>
</tr>
</tbody>
</table>

- **ReQuip XL 2,4,6,8 and 12 mg**

- **Mirapex ER 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, 4.5 mg.**
Apomorphine (Apokyn)

- D1/D2 agonist
- Subcutaneous, pen system
- Rapid “off” period rescue
- Treatment of unpredictable, frequent motor fluctuations
- Adverse effects: nausea, vomiting, hypotension
  - Trimethobenzamide
Inhibitors of Dopamine Breakdown

*Only tolcapone inhibits COMT in brain.

L-DOPA = levodopa
3-OMD = 3-O-methyldopa
DA = dopamine
AADC = aromatic acid decarboxylase
DOPAC = dihydroxyphenylacetic acid
3-MT = 3-methoxytyramine
Other treatments for motor symptoms

• Dyskinesia
  – Amantadine
  – Clozapine

• Tremor
  – Anticholinergics

• Dystonia
  – Botulinum Toxin injections
## Treatments for other symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug class</th>
<th>Drug name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive impairment</strong></td>
<td></td>
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</tr>
<tr>
<td>Dementia</td>
<td>Acetylcholinesterase inhibitor</td>
<td>Rivastigmine</td>
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<tr>
<td><strong>Psychiatric symptoms</strong></td>
<td></td>
<td></td>
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<tr>
<td>Depression</td>
<td>Dopamine agonist</td>
<td>Pramipexole</td>
</tr>
<tr>
<td></td>
<td>Serotonin reuptake inhibitor</td>
<td>Citalopram, escitalopram, fluoxetine, paroxetine, sertraline</td>
</tr>
<tr>
<td></td>
<td>Serotonin and norepinephrine reuptake inhibitor</td>
<td>Venlafaxine extended release, Desipramine, nortriptyline</td>
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<tr>
<td></td>
<td>Tricyclic antidepressant</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>Atypical antipsychotic</td>
<td>Clozapine, quetiapine</td>
</tr>
<tr>
<td></td>
<td>Acetylcholinesterase inhibitor</td>
<td>Rivastigmine</td>
</tr>
<tr>
<td><strong>Sleep disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REM sleep behaviour disorder</td>
<td>Benzodiazepine</td>
<td>Clonazepam</td>
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<tr>
<td></td>
<td>Hormone</td>
<td>Melatonin</td>
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<tr>
<td><strong>Autonomic dysfunction</strong></td>
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<tr>
<td>Constipation</td>
<td>Osmotic laxative</td>
<td>Polyethylene glycol</td>
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<td></td>
<td>Chloride channel activator</td>
<td>Lubiprostone</td>
</tr>
<tr>
<td>Gastrointestinal motility</td>
<td>Peripheral dopamine antagonist</td>
<td>Domperidone</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Peripheral dopamine antagonist</td>
<td>Domperidone</td>
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<tr>
<td></td>
<td>Mineralocorticoid</td>
<td>Fludrocortisone</td>
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<tr>
<td></td>
<td>Vasopressor</td>
<td>Midodrine</td>
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<tr>
<td></td>
<td>Acetylcholinesterase inhibitor</td>
<td>Pyridostigmine</td>
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<tr>
<td></td>
<td>Norepinephrine prodrug</td>
<td>Droxidopa</td>
</tr>
<tr>
<td>Sialorrhoea</td>
<td>Anticholinergic</td>
<td>Atropine drops, glycopyrrolate</td>
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<tr>
<td></td>
<td>Neurotoxin</td>
<td>Botulinum toxin A, botulinum toxin B</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Stimulant</td>
<td>Methylphenidate, modafinil</td>
</tr>
</tbody>
</table>

REM=rapid eye movement.

*Table 3: Pharmacological treatments for non-motor symptoms*
How to select which treatment?

Patient with Parkinson disease

- Identify source of greatest disability

  - Tremor
  - Bradykinesia with slowness and impaired dexterity
  - Postural instability and/or gait impairment

  See Figure 3
  See Figure 4

- Age <60y
  - Initial treatment: Anticholinergic drug or β-blocker
    - Benefit? Yes: Monitor
      - None or suboptimal benefit: Add or change to dopamine agonist
        - Benefit? Yes: If excellent tremor control, discontinue anticholinergic drug or β-blocker
          - None or suboptimal benefit: Add or change to levodopa
            - Benefit? Yes: Add clozapine
              - None or suboptimal benefit: Consider surgery to treat refractory tremor
    - Benefit? No: Add clozapine
      - None or suboptimal benefit: Consider surgery to treat refractory tremor

- Age ≥60y
  - Initial treatment: Dopamine agonist
    - Benefit? Yes: Add or change to levodopa, anticholinergic drug, or β-blocker
      - Benefit? Yes: Add dopamine agonists or COMT-I or MOAB
        - Benefit? Yes: Add clozapine
          - None or suboptimal benefit: Consider surgery to treat refractory tremor
    - Benefit? No: Add dopamine agonists or COMT-I or MOAB
      - Benefit? No: Monitor
        - None or suboptimal benefit: Add dopamine agonists or COMT-I or MOAB
          - Benefit? Yes: Add clozapine
            - None or suboptimal benefit: Consider surgery to treat refractory tremor

Connolly & Lang, 2014
A potential disaster
“Billy and I are playing doctor. So far, I’ve kept him waiting three hours.”