On current treatments of Parkinson’s disease

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Parkinson's disease

- Blank facial expression
- Slow, monotonous, slurred speech
- Forward tilt to posture
- Reduced arm swinging
- Rigidity and tremor of extremities and head
- Short, shuffling gait

Over 7 Million People

Parkinson's disease is the second most common neurodegenerative disease in the world, second only to Alzheimer's disease.
Disease hallmarks in Parkinson’s disease

1. Loss of dopamine neurons

2. Accumulation of Lewy bodies
Reduction of dopamine neurons in PD

Fazio et al., 2016
Dopamine replacement as therapy in PD

L-dopa

Carlsson et al Nature 1957; 180: 1200
Metabolism of L-DOPA and dopamine

AADC: L-aromatic amino acid decarboxylase, Peripheral inhibitors: Carbidopa (Sinemet), Benserazide (Madopark)
COMT: Catechol-O-methyltransferas inhibitors: Entacapone, Tolcapone
MAO-B: Monoamine oxidase B inhibitors: Selegiline, Rasagiline, Safinamide
Dopamine receptor agonists

L-dopa

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**Table 1: Pharmacological properties of the dopamine agonists**

<table>
<thead>
<tr>
<th></th>
<th>D2/D3 receptor affinity</th>
<th>D1 receptor affinity</th>
<th>NE receptor affinity</th>
<th>5-HT&lt;sub&gt;2A&lt;/sub&gt; receptor affinity</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ergot agonists</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>D2</td>
<td>−</td>
<td>+</td>
<td>+/-</td>
<td>3–6</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>D3&gt;D2</td>
<td>−</td>
<td>+</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>Dihydroergocriptine</td>
<td>D2</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>12–16</td>
</tr>
<tr>
<td>Lisuride</td>
<td>D2</td>
<td>−</td>
<td>+</td>
<td>+*</td>
<td>2–3</td>
</tr>
<tr>
<td>Pergolide</td>
<td>D3&gt;D2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>15–20</td>
</tr>
<tr>
<td><strong>Non-ergot agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Apomorphine</td>
<td>D3&gt;D2</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>0.5</td>
</tr>
<tr>
<td>Piribedil</td>
<td>D3&gt;D2</td>
<td>−</td>
<td>+/-</td>
<td>−</td>
<td>20</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>D3&gt;D2</td>
<td>−</td>
<td>+/-</td>
<td>−</td>
<td>10</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>D3&gt;D2</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>6</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>D3&gt;D2</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>5–7†</td>
</tr>
</tbody>
</table>

|=no affinity. +=high affinity. +/-=moderate affinity. NE=norepinephrine. *Antagonist. †After transdermal application.
L-DOPA vs Dopamine Agonists

Efficacy

Side effects

Dyskinesia
Motor fluctuations
Dopamine dysregulation syndrome
Oedema
Somnolence
Impulse control disorders
Hallucinations
Nausea
Fibrosis*

Higher risk with levodopa
Higher risk with dopamine agonists


Early disease
- Long duration of clinical benefit
- Low incidence of dyskinesias

Mid-stage disease
- Diminished duration of clinical benefit
- Increased incidence of dyskinesias

Advanced disease
- Clinical response mirrors levodopa plasma pharmacokinetic profile
- ‘On’ time is associated with dyskinesias

Continuous delivery of levodopa-carbidopa with an intestinal gel

Continuous delivery of apomorphine

A

Change from baseline to week 12 (h per day)

-4 -3 -2 -1 0 1 2 3 4 5

Off time (LOCF) On time without troublesome dyskinesia On time without dyskinesia On time with non-troublesome dyskinesia On time with troublesome dyskinesia

Prespecified endpoints Post-hoc analysis

Katzenschlager Lancet Neurol. 2018 Sep;17(9):749-759.
Deep brain stimulation

Non-motor symptoms in PD

Some examples of Therapies

Pimavanserin against PD psychosis

Rivastigmine against PD dementia

Summary

- Many approved symptomatic therapies against motor symptoms PD

Unmet medical therapy needs in PD

- Therapies against side effects to L-DOPA, primarily wearing off fluctuations and dyskinesias
- Therapies against many non-motor symptoms
- Therapy that slows down disease progression
- Restorative therapies
- Precision medicine therapies
Thank you for your attention