How to start therapy in early PD

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Learning Objectives

After the lecture, the audience will be able to

• Describe when to start treatment of early PD
• Describe the benefit and risk of L-dopa therapy
• Describe the benefit and risk of L-dopa sparing therapy
Parkinson’s disease (PD) is a neurodegenerative disease which is characterized by dopaminergic neuronal death and abnormal aggregation of α-synuclein (α-syn) proteins, called Lewy body.
History of drug therapy for PD

1817
Belladonna Alkaloid

1860
Anti-cholinergics

1950
L-dopa therapy has a huge impact on PD prognosis!

1950
L-dopa

1967

1975

1989

2002~
-making agonist

MAO-B inhibitor

DBS, LCIG, etc.

L-dopa therapy has a huge impact on PD prognosis!
Sites of action of drug therapies for PD

- **Dopamine agonist**
  - Bromocriptine
  - Cabergoline
  - Ropinirole
  - Pramipexole
  - Rotigotine
  - Apomorphine

- **Dopaminergic neuron**
  - DA receptor
  - A2a
  - AchR

- **MAO-B inhibitor**
  - Selegiline
  - Rsagiline

- **Anticholinergics**
  - Trihexyphenidyl

- **L-dopa**
  - Tyrosine
  - L-DOPA
  - blood-brain barrier

- **COMT inhibitor**
  - Entacapone

- **A2a-R blocker**
  - Istradefylline

- **MAO-B**
  - Metabolism

- **Stimulates release of DA**
  - Amantadine

- **Noradrenaline**
  - Droxidopa

- **Multiple effect?**
  - Zonisamide

- **Peripheral nerve**
  - L-DOPA
  - Metabolism

- **Noradrenergic neuron**
  - NA
  - L-DOPA
  - Tyrosine
First-line treatment
Offer L-dopa for the early stage PD patients with moderate to severe motor symptoms.

DA or MAO-B inhibitor for the early stages PD patients with mild to moderate motor symptoms.

Potential benefits and harms of dopamine agonists, Levodopa and MAO-B inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Levodopa</th>
<th>Dopamine agonists</th>
<th>MAO-B inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor symptoms</td>
<td>More improvement in motor</td>
<td>Less improvement in motor</td>
<td>Less improvement in motor symptoms</td>
</tr>
<tr>
<td></td>
<td>symptoms</td>
<td>symptoms</td>
<td></td>
</tr>
<tr>
<td>Activities of daily</td>
<td>More improvement in activities</td>
<td>Less improvement in activities</td>
<td>Less improvement in activities of daily living</td>
</tr>
<tr>
<td>living</td>
<td>of daily living</td>
<td>of daily living</td>
<td></td>
</tr>
<tr>
<td>Motor complications</td>
<td>More motor complications</td>
<td>Fewer motor complications</td>
<td>Fewer motor complications</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Fewer specified adverse events*</td>
<td>More specified adverse events*</td>
<td>Fewer specified adverse events*</td>
</tr>
</tbody>
</table>

Abbreviation: MAO-B, monoamine oxidase B.

* Excessive sleepiness, hallucinations and impulse control disorders.
L-dopa vs other therapy

**UPDRS-Part III**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>LD Mean</th>
<th>SD</th>
<th>Total</th>
<th>LD sparing Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holloway 2004</td>
<td>-3.4</td>
<td>12.3</td>
<td>150</td>
<td>1.3</td>
<td>13.3</td>
<td>151</td>
<td>18.2%</td>
<td>-4.70 [-7.59, -1.81]</td>
</tr>
<tr>
<td>Oertel20006PELMOPET</td>
<td>-2.8</td>
<td>7.8</td>
<td>146</td>
<td>2.8</td>
<td>9.8</td>
<td>148</td>
<td>22.5%</td>
<td>-5.60 [-7.62, -3.58]</td>
</tr>
<tr>
<td>Rascol 2000 FK056study</td>
<td>-4.8</td>
<td>8.3</td>
<td>89</td>
<td>-0.8</td>
<td>10.1</td>
<td>179</td>
<td>21.2%</td>
<td>-4.00 [-6.27, -1.73]</td>
</tr>
<tr>
<td>Storch 2013</td>
<td>-7.2</td>
<td>7.2</td>
<td>18</td>
<td>-6.5</td>
<td>8.3</td>
<td>17</td>
<td>10.1%</td>
<td>-0.70 [-5.86, 4.46]</td>
</tr>
<tr>
<td>USA Olamow 1995</td>
<td>3.3</td>
<td>1</td>
<td>21</td>
<td>5</td>
<td>1</td>
<td>19</td>
<td>28.1%</td>
<td>-1.70 [-2.35, -1.05]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>424</td>
<td></td>
<td>514</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td>-3.51 [-5.53, -1.48]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 3.69; Chi² = 18.61, df = 4 (P = 0.0009); I² = 79%
Test for overall effect: Z = 3.40 (P = 0.0007)

**Psychotic symptom**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>LD Events</th>
<th>Total</th>
<th>DA Events</th>
<th>Total</th>
<th>Weight</th>
<th>M–H, Fixed, 95% CI</th>
<th>M–H, Random, 95% CI</th>
<th>Odds Ratio</th>
<th>M–H, Fixed, 95% CI</th>
<th>M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herskovits 1988 Argentina</td>
<td>3</td>
<td>29</td>
<td>0</td>
<td>31</td>
<td>0.7%</td>
<td>8.32 [0.41, 168.45]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holloway 2004</td>
<td>4</td>
<td>150</td>
<td>4</td>
<td>151</td>
<td>6.7%</td>
<td>1.01 [0.25, 4.10]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oertel20006PELMOPET</td>
<td>0</td>
<td>146</td>
<td>5</td>
<td>147</td>
<td>9.4%</td>
<td>0.09 [0.00, 1.61]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKDS009</td>
<td>10</td>
<td>208</td>
<td>9</td>
<td>211</td>
<td>14.6%</td>
<td>1.13 [0.45, 2.85]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rascol 2000 FK056study</td>
<td>5</td>
<td>89</td>
<td>31</td>
<td>179</td>
<td>33.4%</td>
<td>0.28 [0.11, 0.76]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sydney Multiple Hely 1994</td>
<td>6</td>
<td>64</td>
<td>10</td>
<td>62</td>
<td>15.8%</td>
<td>0.54 [0.18, 1.58]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK-PDRG Lees 2001</td>
<td>0</td>
<td>249</td>
<td>10</td>
<td>262</td>
<td>17.6%</td>
<td>0.05 [0.00, 0.83]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USABromocriptine Weiner 1993</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>6</td>
<td>1.8%</td>
<td>0.63 [0.03, 12.41]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>944</td>
<td>1049</td>
<td>100.0%</td>
<td></td>
<td>0.50</td>
<td>0.32, 0.78</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Total events = 29
Heterogeneity: Chi² = 12.60, df = 7 (P = 0.08); I² = 44%
Test for overall effect: Z = 3.02 (P = 0.002)

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Guideline for treatment of Parkinson’s disease 2018 in Japan
Levodopa (L-dopa)

✓ Advantages
- L-dopa improves QOL and life expectancy.
- The most effective therapy & gold standard!
- Safety is assured.
- Inexpensive.

✗ Limitations
- Short half-life in plasma (60-90 min).
- Long term use of L-dopa causes motor fluctuations and dyskinesia.
Levels of Dopamine In synapse cleft

Therapeutic Window

Honeymoon period
Stable effect of levodopa

Unstable effect of levodopa

Levodopa treatment and Motor complications (Wearing off and dyskinesia)

Early PD
6~8 hours

Moderate PD
3~5 hours

Advanced PD
0.5~2 hours

(On-time)

The risk of developing dyskinesia increased in an L-dopa dose-dependent manner.

When should L-dopa treatment be initiated in the course of the disease?

**ELLDOPA study** prospective, randomized, double-blind study (NEJM, 2004)

Subject: Patients with PD, who had received a diagnosis of Parkinson's disease within the past two years and had no treatment for the symptom (Yahr I ~ II)

The gaps of UPDRS score (placebo vs L-dopa treated groups) had remained even after the L-dopa had washed out.

No merits in delaying the start of L-dopa treatment
There were no apparent evidence of disease modifying effect and toxicity of early levodopa treatment.

LEAP study

PD cohort with Motor Fluctuations


Summary of L-dopa therapy

- L-dopa is most effective drug and gold standard in PD therapy
- No evidence showed either toxicity or disease-modifying effect of L-dopa

- Long-term use of L-dopa increases the risk of motor fluctuation
- Motor fluctuation occurs in a L-dopa dose-dependent manner

→ Patients (≤ 70 years old) should be treated with drugs except for L-dopa, or low-dose L-dopa (less than 300-400mg)

Patients (> 70 years old) should be treated with L-dopa as a first choice to maintain their QOL
Levodopa sparing therapy avoids motor complications

PD-MED study

Initial treatment: L-dopa vs DA or MAOB-I

Levodopa 36%
Levodopa sparing 33%

Therapeutic Window

Motor fluctuation due to L-dopa is caused by long-term, non-physiological, and pulsatile dopaminergic stimulation.

Continuous Dopaminergic Stimulation (CDS)

CDS is important to reduce motor fluctuation.
Dopamine agonists

Initial treatment with dopamine agonists had a significantly lower incidence of motor complications compared with L-dopa.

**PELMO-PET study**
- Pergolide
- L-dopa
- Dyskinesia-free

**The REAL-PET study**
- Ropinirole
- L-dopa
- Dyskinesia-free

**CALM-PD study**
- Levodopa
- Pramipexole

Movements Disorders, 2006

JAMA, 2000
Comparison of the risk of adverse events associated with L-dopa vs dopamine agonists.


Common adverse effects

- Somnolence (ergot < non-ergot)
- Nausea (ergot < non-ergot)
- Hallucination
- Impulse control disorders (Pathological gambling, hypersexuality, compulsive buying)

Non-ergot dopamine agonists

- Sudden somnolence

Ergot dopamine agonists

- Increased risks of valvular heart disease, retroperitoneal fibrosis, and pulmonary fibrosis

⇒ Ergot dopamine agonists are second-line drugs. Follow up echocardiogram every half or one year!

Avoid driving, machine operation, or work at height
Treatment algorithm in the early stage of Parkinson’s disease from Japanese PD guideline

1) Discuss the person’s individual clinical symptoms, lifestyle circumstances and needs.
2) Elderly people and Dementia so on.
3) Severe motor symptoms (Hoehn & Yahr Stage 3 or more), High risk of fall so on.
4) Disease onset is less than 65 years old, so on.

Guideline for treatment of Parkinson’s disease 2018 in Japan
Other medications

- **Zonisamide**
  - Efficacious for tremor

- **Anticholinergics**
  - Efficacious for tremor
  - Inexpensive

- **Amantadine**
  - Inexpensive
  - No evidence for improving ADL or motor symptom

Consider use of zonisamide or anticholinergics for tremor dominant PD in early stage.
Key Messages

• L-dopa remains gold standard of early PD.
• L-dopa could be neither toxic nor disease-modifying.
• Use sufficient amount of L-dopa to improve patient’s QOL.
• Motor complications are L-dopa dose dependent.

• Consider dopamine agonist for young-onset PD in early stage to avoid motor complications, especially dyskinesia.
• Consider MAO-B inhibitor monotherapy for mild motor symptoms of PD.
• Consider use of zonisamide/anticholinergics for tremor dominant PD to save the amount of L-dopa therapy.
Reference

• PD Med Collaborative Group, et al. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. Lancet. 2014;384:1196-1205
• CALM-PD: Parkinson Study Group. Pramipexole vs Levodopa as Initial Treatment for Parkinson Disease A Randomized Controlled Trial. JAMA. 2000;284:1931-1938