Parkinson’s Disease (PD) Therapies

From dopamine precursors to new generations of drugs
THERAPIES FOR THE TREATMENT OF PARKINSON'S DISEASE

**Pharmacological treatments**
- Levodopa (L-Dopa) - precursor of dopamine (DA)
- Direct DA agonists with long half-lives
- COMT or MAO inhibitors (enzymes that metabolize DA)
- Anticholinergic agents
- Glutamate antagonists

**Surgical treatments**
- Deep brain stimulation (DBS)
- Pallidotomy
- Stem cell transplantation
Parkinson’s Disease Drugs

Circulation

- DDC inhibitors (peripheral)
  - Tolcapone
  - Entacapone

- COMT inhibitors (peripheral)
  - Tolcapone
  - Entacapone

- COMT inhibitors (central)
  - Tolcapone

- MAO-B inhibitors
  - Selegiline
  - Rasagiline

Blood-brain barrier

- Dopamine
  - DDC
  - L-DOPA

- L-DOPA
  - Dopamine

3-OMD

- MAO-B
  - MAO-B inhibitors

Presynaptic neuron

- Dopamine availability
  - Amantadine

Postsynaptic neuron

- Dopamine receptors

- Dopamine Agonists
  - Bromocriptine (ergot)
  - Pramipexole (non-ergot)
  - Ropinirole (non-ergot)
# Pharmacological Treatments for Parkinson’s Disease

<table>
<thead>
<tr>
<th>Drug or class</th>
<th>Indication</th>
<th>Impact on motor symptoms</th>
<th>Characteristic side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa</td>
<td>• First-line therapy</td>
<td>• Excellent</td>
<td>• Motor fluctuations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Dyskinesias</td>
</tr>
<tr>
<td>Dopamine agonist</td>
<td>• First-line therapy (younger patients)</td>
<td>• Moderate</td>
<td>• Sedation</td>
</tr>
<tr>
<td></td>
<td>• Add-on therapy</td>
<td></td>
<td>• Impulse control disorder</td>
</tr>
<tr>
<td>MAO-B inhibitor</td>
<td>• First-line therapy (mild disease, concomitant depression)</td>
<td>• Limited</td>
<td>• Generally well tolerated</td>
</tr>
<tr>
<td></td>
<td>• Add-on therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMT inhibitor</td>
<td>• Add-on therapy</td>
<td>• Improves wearing off</td>
<td>• Diarrhoea</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>• Limited use in tremor-dominant PD</td>
<td>• Limited</td>
<td>• Confusion</td>
</tr>
<tr>
<td>Amantadine</td>
<td>• Reduces dyskinesias in advanced PD</td>
<td>• Limited</td>
<td>• Dry eyes and mouth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Constipation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Urinary retention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Diarrhoea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Confusion</td>
</tr>
</tbody>
</table>

COMT = catechol-O-methyl transferase; MAO-B = monoamine oxidase type B.
Table 1 | Current drugs for Parkinson's disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa (l-dopa) + dopa decarboxylase inhibitor</td>
<td>• Probably the most potent dopaminergic drug for symptom relief</td>
<td>• Motor complications (cumulative risk 10% per annum)</td>
</tr>
<tr>
<td></td>
<td>• Generally well tolerated</td>
<td></td>
</tr>
<tr>
<td>Catechol-O-methyl transferase inhibitors, for example, entacapone, tolcapone</td>
<td>• Increase levodopa half-life</td>
<td>• Tolcapone can cause liver damage.</td>
</tr>
<tr>
<td></td>
<td>• Reduce 'off' time</td>
<td>• Diarrhoea</td>
</tr>
<tr>
<td>Ergot dopamine agonists (for example, bromocriptine, pergolide, cabergoline)</td>
<td>• Good efficacy</td>
<td>• Increased risk of somnolence, confusion, hallucinations, peripheral oedema and behavioural changes</td>
</tr>
<tr>
<td>Non-ergot dopamine agonists for example, pramipexole, ropinirole, rotigotline</td>
<td>• Delay onset of motor complications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Generally well tolerated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Once-a-day preparations available with some transdermal patch for rotigotline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Theoretical neuroprotective action</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Some antidepressant action with pramipexole</td>
<td></td>
</tr>
<tr>
<td>Monoamine oxidase B inhibitor; selegiline; rasagiline</td>
<td>• Improve motor features in early and late disease</td>
<td>• Relatively mild efficacy</td>
</tr>
<tr>
<td></td>
<td>• Easy to use, once-a-day</td>
<td>• Selegiline metabolized to amphetamines — potential cognitive effects</td>
</tr>
<tr>
<td></td>
<td>• Well tolerated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Theoretical neuroprotective effect</td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>• Mild anti-Parkinsonian effect</td>
<td>• Cognitive disturbances</td>
</tr>
<tr>
<td></td>
<td>• Improves dyskinesias</td>
<td>• Peripheral oedema</td>
</tr>
<tr>
<td></td>
<td>• Livedo reticularis</td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>• Mild anti-Parkinsonian effect</td>
<td>• Limited by side effects such as confusion</td>
</tr>
</tbody>
</table>
Levodopa Therapy for PD
Levodopa converted to dopamine & dopamine is released
Carbidopa blocks conversion of Levodopa to dopamine in periphery so Levodopa can reach the brain & be converted to dopamine
Marketed preparations:
- L-dopa + benserazide:
  Madopar 125 mg dispersible tablets (Roche)
  Madopar 125 mg tablets (Roche)
  Madopar 250 mg dispersible tablets (Roche)
  Madopar HBS 125 mg tablets (Roche) – controlled-release preparation

Posology: The average efficacious dose is 600–800 mg/day, but should be established on an individual basis. The daily dose of Madopar HBS must be about 50% higher than that of the non-delayed formulations.

- L-dopa + carbidopa:
  Sinemet 25/100 mg tablets (Bristol-Myers Squibb)
  Sinemet 25/250 mg tablets (Bristol-Myers Squibb)
  Sinemet CR 25/100 mg tablets (Bristol-Myers Squibb) – controlled-release preparation
  Sinemet CR 50/200 mg tablets (Bristol-Myers Squibb) – controlled-release preparation

Posology: The average efficacious dose is 200–600 mg/day, and the maximum dose 2000 mg/day. The average efficacious dose of Sinemet CR is 400–1000 mg/day.

- L-dopa methyl hydrochloride:
  Levomet bottles of powder + solvent: 1 ml of reconstituted solution = 251.2 mg of L-dopa (Chiesi Farmaceutici)

Posology: As adjunctive “as needed” therapy, the recommended unit dose is 1 ml of solution (251.2 mg/day of L-dopa); more than two administrations/day are not recommended.
Levodopa Therapy - Side Effects

Common Side Effects for levodopa

- Nausea
- Vomiting
- Loss of appetite
- Lightheadedness
- Lowered blood pressure
- Confusion
- Dyskinesia

Such side effects can be minimized with a low starting dose when initiating treatment with any antiparkinsonian drug and increasing the dose slowly to a satisfactory level. This is particularly helpful in elderly people with PD whose tolerance for medications is often less than in younger persons. Taking drugs with meals can also reduce the frequency and intensity of gastrointestinal side effects. For those patients who have persistent nausea or vomiting, adding extra carbidopa (Lodosyn) to each dose of carbidopa/levodopa can help.

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/Levodopa
Levodopa Therapy - Interactions

**Protein**

Some people with PD experience what is referred to as the “protein effect” in which dietary protein can interfere with absorption of levodopa. Protein and levodopa use the same transporter to cross the small intestine wall. Therefore it’s possible that dietary protein can interfere with absorption of levodopa including beef, chicken, pork, fish and eggs.

**Pyridoxine – vitamin B6**

Pyridoxine (vitamin B6) may inhibit the activity of levodopa, but only when levodopa is given alone. The vast majority of patients are on a combination of carbidopa and levodopa. With carbidopa in the system, the negative effect of pyridoxine on levodopa does not occur and there is no concern in taking vitamin B6 supplementation. People who are taking levodopa-only should avoid vitamin B6.

**Iron**

Iron supplements can bind with levodopa and thereby reduce the amount of medication that is absorbed in your system. If you require iron supplementation because of another medical condition, discuss this with your doctor so you can determine how to most effectively get the iron you need while not impacting your PD medications.

**Tyramine**

Patients who are taking medications for PD that are classified as monoamine oxidase (MAO)-B inhibitors (rasagiline, selegiline, and safinamide) are often concerned about having to adhere to a particular diet which is low in the amino acid tyramine. This is because patients who are taking non-selective MAO inhibitors (that inhibit both MAO-A and MAO-B) for reasons other than PD, such as depression, do have to be concerned about adhering to that diet (which can be difficult, as many foods contain tyramine). When MAO-A is inhibited, the body can no longer break down tyramine effectively. Elevated levels of tyramine can then cause spikes in blood pressure and other negative effects. To be clear, there are no medications indicated for PD that inhibit MAO-A. However, at high doses, MAO-B inhibitors can begin to inhibit MAO-A as well. When MAO-B inhibitors are taken at the recommended doses for PD, tyramine is broken down effectively and dangerous levels are not reached.
Complications of Levodopa Therapy for PD

L Dopa therapy

NMS accompanying Motor Fluctuations
- Cognitive
- Autonomic
- Sensory
- During Motor Off
- During Dyskinesias
- During EMQ
- Anxious – depressed Subtype of PD

Isolated NMS Fluctuations
- Psychosis
- DDS
- Metacognitions
- ICD
- Sleep, EDS, Vivid dreams

Behavioural, Sleep and Neuropsychiatric
- Punding
PD: Motor Complications with Dopamine Replacement Therapy

**Peak-dose dyskinesia**: Chorea and dystonia of neck and limbs; increases with mental and physical activity

**ON state**

**ON freezing**: Rare phenomenon (more commonly seen on OFF state)

**Predictable wearing off**: Worsening of parkinsonian symptoms before next dose of levodopa

**Diphasic dyskinesia**: Ballism or dystonia in the legs; stereotypic kicking or "funny" gait when levodopa’s levels are rising or falling

**Beginning-of-dose worsening and end-of-dose rebound**: Transient worsening of symptoms (often worsening of tremor after levodopa administration)

**Transition**

**ON - OFF - ON**

**OFF freezing**: Transient difficulties to start gait, triggered by turning, narrow spaces (e.g. doorways) and sudden stress or anxiety.

**OFF dystonia**: Painful "cramps" affecting distal leg, foot, toes with abnormal postures

**Dose failure/partial response**: Delayed onset of therapeutic effect (delayed on) or no effect or a reduced effect (dose failure)

**OFF state**

### Classification of levodopa-related motor fluctuations in PD

<table>
<thead>
<tr>
<th>Clinical pattern</th>
<th>Mechanism</th>
<th>Therapeutic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wearing-off</td>
<td>Levodopa – half-life Pre-synaptic storage</td>
<td>ON</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OFF</td>
</tr>
<tr>
<td>Delayed-on</td>
<td>Gastric emptying Intestinal absorption</td>
<td>ON</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OFF</td>
</tr>
<tr>
<td>Dose-failures (No-ON)</td>
<td>Gastric emptying Intestinal absorption Blood–brain barrier transport</td>
<td>ON</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OFF</td>
</tr>
<tr>
<td>Random ON-OFF</td>
<td>Striatal Pharmacodynamic Changes</td>
<td>ON</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OFF</td>
</tr>
</tbody>
</table>

![Graphs showing ON and OFF periods for different clinical patterns](image-url)
L-Dopa-Induced Dyskinesia – Development

Pre-motor stage of PD
Degeneration of dopaminergic neurons at SNc < 50%

Early stage of PD
Degeneration of dopaminergic neurons at SNc ≥ 50%

Approximately 3-5 years

Advanced stage of PD
Degeneration of dopaminergic neurons at SNc > 70%
Abnormal adaptation of striatal organization

L-dopa treatment
Almost complete improvement of motor symptoms

L-dopa treatment
Partial improvement of motor symptoms

L-dopa treatment
Partial improvement of motor symptoms with developing “DYSKINESIA”

PD = Parkinson’s disease; L-dopa = levodopa; SNc = Substantia nigra pars compacta
L-Dopa-Induced Dyskinesia – Development
L-Dopa-Induced Dyskinesia – Mechanisms

DA denervation
- loss of DAT
- loss of physiological DA storage and release sites

Brain surges of L-DOPA and DA

Supersensitive DAR, structural and molecular changes in striatal neurons

Altered activity patterns in basal ganglia-thalamo-cortical networks

Gliovascular mechanisms

Oral L-DOPA therapy

Serotonin neurons
- Uptake and conversion of DOPA,
- Dysregulated DA efflux

Other neuromodulators
- Noradrenaline,
- Acetylcholine,
- Opioids,
- Cannabinoids

Glutamatergic systems
- Corticostriatal pathway
- Subthalamo – pallidal pathways
## L-Dopa-Induced Dyskinesia – Management

### Table 1: Different types of levodopa-induced dyskinesia and medical management

<table>
<thead>
<tr>
<th>Types</th>
<th>Clinical description</th>
<th>Management strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak-dose dyskinesia</td>
<td>Most common type of dyskinesia (80%), which occurs at the time of peak plasma levels of levodopa, characterized by stereotypic head movements, choreiform truncal movement, and ballistic limb movement, rarely myoclonus, can be ocular, respiratory, or abdominal muscle</td>
<td>Decrease individual levodopa dosages, discontinue or reduce COMT and MAO-B inhibitors, switch to immediate release preparations and consider adding amantadine</td>
</tr>
<tr>
<td>Off-period dystonia</td>
<td>Second most common type (30%) and typically occurs in early morning, before the first dose of levodopa, usually involves leg</td>
<td>Adding long-acting formulations at bedtime for off-period symptoms during night or early morning. For off time during the day, consider adding COMT inhibitors, MAO-B inhibitors, or dopamine agonist</td>
</tr>
<tr>
<td>Diphasic dyskinesia “DID” pattern</td>
<td>Least common (20%) and starts 10-15 min after levodopa ingestion with ipsilateral leg movement and then contralateral involvement, followed by improvement of parkinsonian symptoms for several hours and then recurrence of dyskinesia, when levodopa levels decline</td>
<td>Most difficult to treat, LCIG infusion or subcutaneous infusion of apomorphine or surgical intervention, e.g., DBS</td>
</tr>
</tbody>
</table>

MAO-B = Monoamine oxidase B, COMT = Catechol-O-methyl transferase, LCIG = Levodopa/carbidopa intestinal gel, DBS = Deep brain stimulation, DID = Dyskinesia-improvement-dyskinesia
Duodopa – Drug delivery into the small intestine

Carbidopa/levodopa enteral suspension (brand name Duopa™)

Instead of taking carbidopa/levodopa in a pill form, people with PD can receive carbidopa-levodopa in a gel form infused directly into the small intestine where levodopa is known to be absorbed. This system can be useful for those with advancing PD who have motor fluctuations that are no longer controlled by oral medications alone. The system can be particularly helpful for those who have gastroparesis, or delayed gastric emptying, which is a common non-motor symptom of PD and can keep oral medications stuck in the stomach and therefore unable to be absorbed readily by the small intestine.

Avoids pulsatile stimulation of dopamine receptors

For patients with advanced PD (stage 4-5) not effectively controlled with oral therapy

# Dopamine Receptor Subtypes & Direct Acting Agonists

## Dopamine receptors

<table>
<thead>
<tr>
<th>D1-like</th>
<th>D2-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>D2</td>
</tr>
<tr>
<td>- G(\alpha)s coupled</td>
<td>- G(\alpha)/(\beta) coupled</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D5</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
</tr>
</thead>
</table>
| Substantia nigra  
Nucleus accumbens  
Olfactory bulb    | Substantia nigra  
Nucleus accumbens  
Hypothalamus  
Kidney  
Heart  
Sympathetic ganglia | Substantia nigra  
Nucleus accumbens  
Ventral tegmental area | Olfactory bulb  
Nucleus accumbens | Heart  
Blood vessels  
Substantia nigra  
Hippocampus  
Amygdala  
Gastrointestinal tract |

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**Fig. 1.** Dopamine receptors are G protein-coupled receptors, which are divided into the D\(_1\)- and D\(_2\)-like families. Some tissues of interest where these receptors are expressed are included here.

https://doi.org/10.1124/jpet.119.256818  
J Pharmacol Exp Ther 370:111–126, July 2019
<table>
<thead>
<tr>
<th></th>
<th>Bromocriptine</th>
<th>Pergolide</th>
<th>Pramipexole</th>
<th>Ropinirole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of compound</strong></td>
<td>Ergot derivate</td>
<td>Ergot derivate</td>
<td>Non-ergoline</td>
<td>Non-ergoline</td>
</tr>
<tr>
<td><strong>Receptor specificity</strong></td>
<td>$D_2, D_1$ (\alpha_1, \alpha_2, 5\text{-HT})</td>
<td>$D_2, D_1$ (\alpha_1, \alpha_2, 5\text{-HT}, \beta)</td>
<td>$D_2, D_3, D_4$ (\alpha_2)</td>
<td>$D_2, D_3, D_4$</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>8%</td>
<td>20%</td>
<td>&gt; 90%</td>
<td>55% (1\textsuperscript{st}-pass metabolism)</td>
</tr>
<tr>
<td><strong>Tmax (min)</strong></td>
<td>70 – 100</td>
<td>60 – 120</td>
<td>60 – 180</td>
<td>90</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>90 – 96%</td>
<td>90%</td>
<td>15%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Elimination route</strong></td>
<td>Metabolic (hepatic)</td>
<td>Metabolic (hepatic)</td>
<td><strong>Renal</strong></td>
<td>Metabolic (hepatic)</td>
</tr>
<tr>
<td><strong>Half-life (hr)</strong></td>
<td>3 – 8</td>
<td>27</td>
<td>8 – 12</td>
<td>6</td>
</tr>
</tbody>
</table>

\(^a\) Antagonist

*Adapted from Applied Therapeutics: The Clinical Use of Drugs, 8\textsuperscript{th} ed., 2005*
<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;2B&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>
<td></td>
<td></td>
<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>
</tr>
<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.

**Table 1:** Pharmacological properties of the dopamine agonists
Effective equivalent doses of the major dopamine receptor agonists

<table>
<thead>
<tr>
<th>DA-agonists</th>
<th>Equivalent doses (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apomorphine</td>
<td>2</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>10</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>1.5–2</td>
</tr>
<tr>
<td>Pergolide</td>
<td>1</td>
</tr>
<tr>
<td>Pramipexolo</td>
<td>1</td>
</tr>
<tr>
<td>Ropinirolo</td>
<td>5</td>
</tr>
</tbody>
</table>
Bromocriptine (D$_2$/D$_3$, D$_1$)

**Efficacy:** Efficacious in advanced disease as add-on therapy; probably efficacious in the monotherapy of early disease

**Marketed preparations:**
- Bromocriptina Dorom 5 mg tablets (Dorom)
- Bromocriptina Dorom 10 mg tablets (Dorom)
- Parlodel 2.5 mg tablets (Novartis Farma)
- Parlodel 5 mg tablets (Novartis Farma)
- Parlodel 10 mg tablets (Novartis Farma)

**Posology:** Average efficacious dose: 15–30 mg/day (or more)
Diidroergocriptine (D₂, D₁)

**Efficacy:** Probably efficacious as monotherapy and an add-on.

**Marketed preparations:**
Daverium 20 mg tablets (Monsanto)

**Posology:** 10–120 mg/day (average efficacious dose: 60 mg/day).
Cabergoline (D\textsubscript{2}/D\textsubscript{3}, alpha)

**Efficacy:** Efficacious as monotherapy in early disease, and in combination with L-dopa in advanced disease.

**Marketed preparations:**
- Cabaser 1 mg tablets (Pharmacia & Upjohn)
- Cabaser 2 mg tablets (Pharmacia & Upjohn)

**Posology:** 2–6 mg/day (average efficacious dose: 4 mg/day).
Lisuride (D<sub>2</sub>/D<sub>3</sub>/D<sub>4</sub>, alpha)

Efficacy: Probably efficacious as monotherapy; efficacious as an add-on.

Marketed preparations:
- Dopergin 0.2 mg tablets (Farmades)
- Dopergin 0.5 mg tablets (Farmades)
- Dopergin 1 mg tablets (Farmades)

Posology: 0.6–5 mg/day (average efficacious dose: 1–2 mg/day)
Pergolide (D$_2$/D$_3$, D$_1$/D$_4$, alpha)

Efficacy: Efficacious as monotherapy in early disease, and in combination with L-dopa in advanced disease.

Marketed preparations:
- Nopar 0.05 mg tablets (Eli Lilly)
- Nopar 0.25 mg tablets (Eli Lilly)
- Nopar 1 mg tablets (Eli Lilly)
- Nopar Starter (Eli Lilly)

Posology: 1.5–4.5 mg/day (average efficacious dose: 3 mg/day.)
Pramipexole ($D_3, D_2/D_4$)

**Efficacy:** Efficacious as monotherapy in early disease, and as add-on therapy in advanced disease.

**Marketed preparations:**
- Mirapexin 0.18 mg tablets (equal to 0.25 mg of pramipexole) (Pharmacia & Upjohn)
- Mirapexin 0.7 mg tablets (equal to 1 mg of pramipexole) (Pharmacia & Upjohn)

**Posology:** 1.05–3.3 mg/day (equal to 0.375–4.5 mg of pramipexole per day). Lower doses are recommended in patients with reduced renal function.
Dopamine agonists

- **Pramipexole**

The main pharmacokinetics parameters

- Peak Plasma Time: 2 hr (IR); 6 hr (ER),
- Bioavailability: >90%.
- Protein Bound: 15%/
- Vd: 500 L.
- Metabolism <10%.
- Half-Life: 8 hr (12 hr in elderly)/
- Excretion: urine 90%.
Ropinirole (D₃>D₂>D₄)

Efficacy: Efficacious as monotherapy in early disease, and in combination with L-dopa in advanced disease.

Marketed preparations:
- Requip 0.25 mg tablets (Glaxo SmithKline)
- Requip 0.5 mg tablets (Glaxo SmithKline)
- Requip 1 mg tablets (Glaxo SmithKline)
- Requip 2 mg tablets (Glaxo SmithKline)
- Requip 5 mg tablets (Glaxo SmithKline)

Posology: 3–9 mg/day; maximum dose: 24 mg/day.
Dopamine Direct Acting Agonists – Adverse Effects

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Bromocriptine</th>
<th>Lisuride</th>
<th>Pergolide</th>
<th>Piribedil</th>
<th>Cabergoline</th>
<th>Pramipexole</th>
<th>Ropinirole</th>
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<td>sedation, confusion, psychosis,</td>
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<td><strong>Other effects</strong></td>
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<td>fibrosis, retroperitoneal fibrosis</td>
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</tbody>
</table>

^a^ Mixed, central and peripheral.
**Figure:** Risk of motor complications and other adverse events with dopamine agonists versus levodopa

The length of the arrows indicates the relative extent of risk. *Ergot agonists vs levodopa (see text).*
**Fig. 1. Dyskinesias in MPTP monkeys.** Frequency of dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-marmosets treated with L-dopa versus the dopamine-receptor agonist ropinirole, and combined L-dopa plus ropinirole. Note that animals treated with L-dopa have a significantly greater frequency and shorter time to onset of dyskinesia than the agonist-treated animals. The combined treatment group has a lower frequency of dyskinesia than the L-dopa monotherapy group, but a greater frequency than the ropinirole monotherapy group. Behavioral effects were comparable in all groups. Reproduced courtesy of E. Maratos and P. Jenner.
Apomorphine ($D_1/D_2$, $D_3/D_4$, alpha)

Efficacy: Probably efficacious in advanced disease.

Marketed preparations:
- Apofin Stylo 3 ml 1% s.c. (Penject) (Chiesi Farmaceutici)
- Apofin 5 ml 1% s.c. (Chiesi Farmaceutici)

Posology: Continuous s.c. infusion: 1–7 mg/hour for 12 hours (but in any case to be individualised). Penject: additional “as needed” dose of 2–6 mg.
Apomorphine Hydrochloride Injection (APOKYN®)

Available Doses: 30 mg/3 ml vial
Typical Treatment Regimen: .2 mL during "off" periods
Side Effects*: Low blood pressure, nausea, leg swelling and discoloration, confusion, sleep attacks, compulsive behaviors like gambling. May receive antinausea medication daily for 3 days before starting medication
Indications: Adjunct therapy as needed for OFF periods. It is the only injectable, fast-acting dopaminergic drug, starts working in 10 minutes and lasts for 90 minutes

Apomorphine hydrochloride (KYNMOBI™)

Available Doses: 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg sublingual film
Typical Treatment Regimen: One 10mg film placed under the tongue as needed, up to five doses per day, separated by at least 2 hours. These films are similar in appearance to breath freshening strips. However, these are placed under the tongue rather than on top.
Side Effects*: nausea, oral/pharyngeal soft tissue swelling, oral/pharyngeal soft tissue pain and numbness, dizziness, and sleepiness. May receive antinausea medication daily for 3 days before starting medication
Indications: for the acute, intermittent treatment of "off" episodes in Parkinson’s disease. It is the only sublingual therapy approved for the on-demand treatment of Parkinson’s disease OFF episodes.
Dopamine agonists

- **Apomorphine.** Initial: 2 mg (0.2 mL) SC

The main pharmacokinetics parameters

- Peak Plasma Time: 10-60 min.
- Half-life, elimination: 30-60 min.
- Vd: 218 L.
- Metabolism: hepatic metabolism.
- Excretion: Urine (93%); feces (16%).
Dopamine agonists

• **Rotigotine**

The main pharmacokinetics parameters

• Bioavailability: 37%.
• Peak plasma time: 15-18 hr.
• Protein Bound: 92% (in vitro); 89.5% (in vivo).
• Vd: 84 L/kg.
• Metabolism: hepatic.
• Half-life, biphasic: 3 hr (initial); 5-7 hr (terminal).
• Excretion: 71% urine; 23% feces.
Rotigotine Transdermal Preparation

Problems with local crystallization of Rotigotine and local reactions, limit its use

Rotigotine Transdermal System (Neupro®)

Available Doses: 1 mg, 2 mg, 3 mg, 4 mg, 6 mg, 8 mg patch

Typical Treatment Regimen: 4–8 mg once/day

Side Effects*: Low blood pressure, nausea, leg swelling and discoloration, confusion, sleep attacks, compulsive behaviors like gambling, skin rashes

Indications: Monotherapy or combination therapy for slowness, stiffness and tremor; skin patch delivery is an advantage for some

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/Dopamine-Agonists
Non motor complications associated to DA replacement therapy in PD

DA dysregulation syndrome

Hypersexuality

Euphoria and hypomania

Punding

Pathological shopping

Pathological Gambling

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Nonmotor symptoms in PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory symptoms</td>
<td>Hyposmia</td>
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<tr>
<td>Autonomic dysfunction</td>
<td>Orthostatic hypotension</td>
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<tr>
<td>Anhedonia</td>
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<tr>
<td>Frontal executive dysfunction</td>
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<td>Dementia</td>
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<tr>
<td>Sleep disorders</td>
<td>Sleep fragmentation</td>
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<tr>
<td>Reduced sleep efficiency</td>
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<tr>
<td>Reduced slow-wave sleep</td>
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<tr>
<td>Reduced REM sleep</td>
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<tr>
<td>RBD</td>
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<tr>
<td>Excessive daytime sleepiness</td>
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<tr>
<td>Nocturnal akinesia/tremor</td>
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</tr>
<tr>
<td>REM, rapid eye movement; RBD, REM sleep behavior disorder; RLS, restless leg syndrome; PLMS, periodic limb movement disorder.</td>
<td></td>
</tr>
</tbody>
</table>

Impulse control disorders and dopamine dysregulation syndrome associated with dopamine agonist therapy in Parkinson’s disease

Sandro Fenu, Jadwiga Wardas and Micaela Morelli

Behav Pharmacol. 2009 Sep;20(5-6):363-79
Sites of Action of Various Parkinson’s Disease Therapies

Fig. 1. Schematic of various methods for PD treatment.
Anticholinergics
(tremor, muscular rigidity)

Benztropine (Cogentin®)

Available Doses: 0.5 mg, 1 mg, 2 mg
Typical Treatment Regimen: 0.5–2 mg 2-3 times/day
Side Effects: Confusion, memory issues, hallucinations, dry mouth, blurry vision, urinary retention
Indications: Monotherapy or combination therapy, predominantly for tremor and dystonia in younger people; should be avoided in elderly. Can also be helpful in reducing the amount of saliva to treat excessive drooling due to the side effect of dry mouth.

Trihexyphenidyl HCL (formerly Artane®)

Available Doses: 2 mg, 5 mg tablets, 2 mg/5 ml elixir
Typical treatment regimen: 1–2 mg 2-3 times/day
Side Effects: Confusion, memory issues, hallucinations, dry mouth, blurry vision, urinary retention
Indications: Monotherapy or combination therapy, predominantly for tremor and dystonia in younger people; should be avoided in elderly. Can also be helpful in reducing the amount of saliva to treat excessive drooling due to the side effect of dry mouth.

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/Anticholinergic-Drugs
MAO and COMT Inhibitors
MAO Inhibitors

- Selegiline
- Rasagiline
- Safinamide

- MAO-B enzymes naturally break down and block several chemicals in the brain, including dopamine
- MAO-B inhibitors prevent the break down of dopamine, making dopamine more available
- Provide modest benefit for the motor features of PD
- Usually used early in the disease as monotherapy or as an adjunct (add-on) to other medications
- When used together with other medications, MAO-B inhibitors may reduce “off” time and extend “on” time

Common Side Effects of MAO-B Inhibitors

- Mild nausea
- Dry mouth
- Lightheadedness
- Constipation
- Confusion (can occur in elderly people with PD)
- Hallucinations (can occur in elderly people with PD)

Taking some MAO-B inhibitors with the heavy consumption (greater than 150 mg/day) of foods high in tyramine carries a risk of raising blood pressure to dangerous levels. These foods are typically aged or fermented, and can include things like cheeses, dried or cured meats, fava beans, beer, sauerkraut, and soybeans. This is more of a risk with non-selective MAO-B inhibitors not used to treat Parkinson's disease.
Selegiline

Efficacy: Probably efficacious

Marketed preparations:
  - Jumex 10 mg tablets (Chiesi Farmaceutici)
  - Jumex 5 mg tablets (Chiesi Farmaceutici)

Posology: 10 mg/day
COMT Inhibitors

- Entacapone
- Opicapone
- Tolcapone *

- Only effective when used in combination with levodopa
- When taking levodopa, an enzyme in the body call catechol-O-methyl transferase (COMT) deactivates levodopa in the body before it is absorbed into the bloodstream; COMT inhibitors prevent this from happening

Common Side Effects of COMT Inhibitors

- May exaggerate some levodopa-related side effects especially dyskinesia
- Confusion
- Hallucinations
- Discoloration of urine (reddish brown or rust-colored)
- Diarrhea
Entacapone

Efficacy: Efficacious on wearing-off phenomena

Marketed preparations:
    Comtan 200 mg tablets (Novartis Farma)

Posology: 200 mg with every L-dopa administration
- Amantadine
  (NMDA-R, DA release-reuptake)
- Memantine
  (NMDA)
- Budipine
  (NMDA-R, DA release, MAO-B, M-R)
Efficacy: Probably efficacious in early and advanced disease; efficacious on L-dopa induced dyskinesias.

Marketed preparations:
Mantadan 100 mg tablets (Boehringer Ingelheim)

Posology: 200 mg/day.

Common Side Effects
- Dizziness
- Low Blood Pressure
- Nausea
- Insomnia
- Confusion
- Paranoia
- Hallucinations
- Leg discoloration

Uncommon Side Effects
- Urinary retention
- Livedo reticularis: a lacy, purplish discoloration of the skin on the legs with some leg swelling. Occurs in less than 1 percent of people with PD who take this medication.

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/Amantadine-Symmetrel
Deep Brain Stimulation (DBS) & Parkinson’s Disease

In DBS surgery, electrodes are inserted into a targeted area of the brain, using MRI (magnetic resonance imaging) and recordings of brain cell activity during the procedure. A second procedure is performed to implant an IPG, impulse generator battery (like a pacemaker). The IPG is placed under the collarbone or in the abdomen. The IPG provides an electrical impulse to a part of the brain involved in motor function. Those who undergo DBS surgery are given a controller to turn the device on or off.

DBS typically works best to **lessen motor symptoms of stiffness, slowness and tremor**. It doesn’t work as well for imbalance, freezing of gait (sudden inability to move when walking) or non-motor symptoms. As DBS may worsen thinking or memory problems, it’s not recommended for people with dementia.
Deep Brain Stimulation (DBS) & Parkinson’s Disease

How Deep Brain Stimulation Works

Exactly how DBS works is not completely understood, but many experts believe it regulates abnormal electrical signaling patterns in the brain. To control normal movement and other functions, brain cells communicate with each other using electrical signals. In Parkinson’s disease, these signals become irregular and uncoordinated, which leads to motor symptoms. DBS may interrupt the irregular signaling patterns so cells can communicate more smoothly and symptoms lessen.

https://www.michaeljfox.org/deep-brain-stimulation
Deep Brain Stimulation (DBS) & Parkinson’s Disease

Figure 3: Motor Symptoms associated with PD Progression, Response to Medication and the Therapeutic Window for DBS

**Figure 1 | History of Parkinson disease research and therapeutic advances.** \(\text{A}_{2A}\), adenosine receptor type 2A; \(\text{COMT}\), catechol-O-methyltransferase; \(\text{L-DOPA}\), levodopa; \(\text{LRRK2}\), leucine-rich repeat serine/threonine-protein kinase 2; \(\text{MAOB}\), monoamine oxidase type B; \(\text{mGlu}\), metabotropic glutamate receptor; \(\text{NAM}\), negative allosteric modulator; \(\text{PAM}\), positive allosteric modulator; \(\text{PD}\), Parkinson disease; \(\text{POC}\), proof of concept. 
Adapted from REF.\textsuperscript{239}, Springer Nature Limited.
New Therapies under development for PD

-> To modify disease
New Therapies under development for PD

-> To treat symptoms

<table>
<thead>
<tr>
<th>Compound and/or agent, company</th>
<th>Mechanism of action</th>
<th>Phase of development</th>
<th>Clinical trial number</th>
<th>Refs</th>
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</thead>
<tbody>
<tr>
<td><strong>Motor fluctuations</strong></td>
<td></td>
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<tr>
<td>Istradefylline (KW-6002), Kyowa Hakko Kirin Pharma</td>
<td>Adenosine receptor type 2A antagonist</td>
<td>* Approved in Japan</td>
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<td></td>
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<td>* Not approved by the FDA in February 2018</td>
<td>NCT02610231</td>
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<td><strong>Dyskinesia</strong></td>
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<td>Amantadine ER (ADS-5102 (Gocovri)), Adamas Pharmaceuticals</td>
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<td>Buspirone, Assistance Publique, Hôpitaux de Paris, Oregon Health and Science University and University of Rochester</td>
<td>5-HT₁₆ and α₂-adrenergic receptor agonist</td>
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<td>Foliglurax (PXT002331), Prexton Therapeutics and Lundbeck</td>
<td>mGlu4 PAM</td>
<td>Phase IIa ongoing</td>
<td>NCT03162874</td>
<td>193-194, 242,243</td>
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<td><strong>Other symptoms</strong></td>
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<td>Varenicline (gait and balance, excessive daytime sleepiness), Rush University Medical Center and VU University Medical Center</td>
<td>Partial agonist of the α₄β₂ nicotinic acetylcholine receptor</td>
<td>* Phase II ongoing for gait and balance</td>
<td>NCT01341080 NCT02473562</td>
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<td>Pimavanserin (formerly ACP-103) (psychosis), Acadia Pharmaceuticals</td>
<td>5-HT₃A receptor inverse agonist</td>
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<td>SYN120 (PD dementia), Acorda Therapeutics</td>
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5-HT, serotonin; D₂, dopamine receptor D₂; FDA, US Food and Drug Administration; mGlu, metabotropic glutamate receptor; NAM, negative allosteric modulator; NMDA, N-methyl-D-aspartate; PAM, positive allosteric modulator; PD, Parkinson disease.