Parkinson’s Disease (PD) Therapies

From dopamine precursors to new generations of drugs
Figure 1 | History of Parkinson disease research and therapeutic advances. A$_{2A}$, adenosine receptor type 2A; COMT, catechol-O-methyltransferase; l-DOPA, levodopa; LRRK2, leucine-rich repeat serine/threonine-protein kinase 2; MAOB, monoamine oxidase type B; mGlu, metabotropic glutamate receptor; NAM, negative allosteric modulator; PAM, positive allosteric modulator; PD, Parkinson disease; POC, proof of concept. Adapted from REF. 239, Springer Nature Limited.
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
<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Levodopa (L-dopa) + dopa decarboxylase inhibitor | • Probably the most potent dopaminergic drug for symptom relief  
• Generally well tolerated | • Motor complications (cumulative risk 10% per annum) |
| Catechol-O-methyl transferase inhibitors, for example, entacapone, tolcapone | • Increase levodopa half-life  
• Reduce 'off' time | • Tolcapone can cause liver damage.  
• Diarrhoea |
| Ergot dopamine agonists (for example, bromocriptine, pergolide, cabergoline)  
Non-ergot dopamine agonists for example, pramipexole, ropinirole, rotigotine | • Good efficacy  
• Delay onset of motor complications  
• Generally well tolerated  
• Once-a-day preparations available with some  
• Transdermal patch for rotigotine  
• Theoretical neuroprotective action  
• Some antidepressant action with pramipexole | • Increased risk of somnolence, confusion, hallucinations, peripheral oedema and behavioural changes  
• Cardiac valve fibrosis with ergot drugs |
| Monoamine oxidase B inhibitor; selegiline; rasagiline | • Improve motor features in early and late disease  
• Easy to use, once-a-day  
• Well tolerated  
• Theoretical neuroprotective effect | • Relatively mild efficacy  
• Selegiline metabolized to amphetamines — potential cognitive effects |
| Amantadine | • Mild anti-Parkinsonian effect  
• Improves dyskinesias | • Cognitive disturbances  
• Peripheral oedema  
• Livedo reticularis |
| Anticholinergics | • Mild anti-Parkinsonian effect | • Limited by side effects such as confusion |
# Pharmacological Treatments for Parkinson’s Disease

## Table 2. Summary of pharmacological therapy in Parkinson’s disease (PD).

<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>• Add-on therapy</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.
Carbidopa blocks conversion of Levodopa to dopamine in periphery so Levodopa can reach the brain & be converted to dopamine

https://sites.psu.edu/nicolehume/files/2013/12/definition-and-description-1dvg9b5.pdf
Levodopa (L-DOPA)
Marketed preparations:
- L-dopa + benzerazide:
  - Madopar 125 mg dispersible tablets (Roche)
  - Madopar 125 mg tablets (Roche)
  - Madopar 250 mg divisible 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

Lethargy
Euphoria, excessive day time sleepiness
Vomit
Orthostatic hypotension
Depression, delusion, delirium, Dryness, Dyskinesia
On off
Psychosis
Athetosis
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%
L-dopa treatment
Almost complete improvement of motor symptoms

Advanced stage of PD
Degeneration of dopaminergic neurons at SNC ≥ 70%
Abnormal adaptation of striatal organization
L-dopa treatment
Partial improvement of motor symptoms

PD=Parkinson’s disease; L-dopa=levodopa; SNC=Substantia nigra pars compacta
Complications of Levodopa Therapy for PD

- **Motor fluctuations**
  Wearing-off deterioration of end-of-dose response
  ‘On-off’, ‘on’ response deterioration, no ‘on’ response

- **Involuntary movements**
  peak dose or biphasic dyskinesia
  peak dose dystonia

- **Neuropsychiatric complications**
  psychosis, hallucinations, confusion, depression

- **Non-motor complications**
  autonomic dysfunctions
### 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><img src="image1" alt="Graph" /></td>
</tr>
<tr>
<td>Delayed-on</td>
<td>Gastric emptying Intestinal absorption</td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>Dose-failures (No-ON)</td>
<td>Gastric emptying Intestinal absorption Blood–brain barrier transport</td>
<td><img src="image3" alt="Graph" /></td>
</tr>
<tr>
<td>Random ON-OFF</td>
<td>Striatal Pharmacodynamic Changes</td>
<td><img src="image4" alt="Graph" /></td>
</tr>
</tbody>
</table>
L-Dopa-Induced motor fluctuations-dyskinesia – Development

![Graph showing L-Dopa concentrations over the years of disease, indicating dyskinesia and akinesia/rigidity phases.](image-url)
L-Dopa-Induced Dyskinesia – Mechanisms

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

- Glutamatergic systems
  - Corticostratial pathway
  - Subthalamo–pallidal pathways

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

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# L-Dopa-Induced Dyskinesia – 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</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

Levodopa Therapy – Nutrient 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.
Levodopa Therapy – Pharmacological Interactions

Negative interactions

- **Non-selective MAO inhibitors** (phenelzine, isocarboxazid and tranylcypromine);
- **Tricyclics** (imipramine and amitriptyline);
- **Typical antipsyhotics** (haloperidol).
DA agonists
Dopamine Receptor Subtypes & Direct Acting Agonists

<table>
<thead>
<tr>
<th>Dopamine receptors</th>
<th>D1-like</th>
<th>D2-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Gαs coupled</td>
<td>D1</td>
<td>D2</td>
</tr>
<tr>
<td><strong>Substantia nigra</strong></td>
<td>Substantia nigra</td>
<td>Substantia nigra</td>
</tr>
<tr>
<td><strong>Nucleus accumbens</strong></td>
<td>Nucleus accumbens</td>
<td>Nucleus accumbens</td>
</tr>
<tr>
<td><strong>Olfactory bulb</strong></td>
<td>Olfactory bulb</td>
<td>Olfactory bulb</td>
</tr>
<tr>
<td><strong>Lower levels:</strong></td>
<td>Lower levels:</td>
<td>Lower levels:</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Heart</td>
<td>Heart</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Blood vessels</td>
<td>Blood vessels</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Adrenal glands</td>
<td>Adrenal glands</td>
</tr>
<tr>
<td>Kidney</td>
<td>Sympathetic ganglia</td>
<td>Sympathetic ganglia</td>
</tr>
<tr>
<td><strong>D5</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>D3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>D4</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Dopamine receptors are G protein-coupled receptors, which are divided into the D₁- and D₂-like families. Some tissues of interest where these receptors are expressed are included here.
Dopamine Receptor Subtypes & Direct Acting Agonists

- **D1**
  - Cortex ++
  - Limbic system +++
  - Basal ganglia ++
  - Hypothalamus ++
  - Dopamine + apomorphine (PA)
  - Bromocriptine (PA)
  - Chlorpromazine + haloperidol ++
  - Clozapine +

- **D5**
  - Basal ganglia + hypothalamus +
  - Dopamine + apomorphine + bromocriptine +
  - Chlorpromazine + haloperidol + clozapine +

- **D2**
  - Cortex ++
  - Limbic system +++
  - Basal ganglia +++
  - Pituitary gland +++
  - Dopamine + apomorphine + bromocriptine +
  - Chlorpromazine + haloperidol + spiperone +
  - Sulpiride +
  - Risperidone ++
  - Clozapine + clozapine +
  - Chlorpromazine + haloperidol +

- **D3**
  - Limbic system + basal ganglia +
  - Dopamine + apomorphine + bromocriptine +
  - Chlorpromazine + haloperidol + spiperone +
  - Sulpiride +
  - Risperidone ++
  - Clozapine +

- **D4**
  - Limbic system +
  - Dopamine + apomorphine + bromocriptine +
  - Chlorpromazine + haloperidol + spiperone +
  - Sulpiride +
  - Risperidone ++
  - Clozapine +
<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>D₂, D₁ (\alpha_1, \alpha_2, 5\text{-HT})</td>
<td>D₂, D₁ (\alpha_1, \alpha_2, 5\text{-HT}, \beta)</td>
<td>D₂, D₃, D₄</td>
<td>D₂, D₃, D₄</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>8%</td>
<td>20%</td>
<td>&gt; 90%</td>
<td>55% (1\text{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>

\(\alpha\) Antagonist

*Adapted from Applied Therapeutics: The Clinical Use of Drugs, 8th 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 (D₂/D₃, D₁)

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 ($D_2$, $D_1$)

**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 (D₂/D₃, 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 (D₂/D₃/D₄, 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** (*D₂/D₃, D₁/D₄, 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 (D₃, D₂/D₄)

**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 pramipexolo) (Pharmacia & Upjohn)
- Mirapexin 0.7 mg tablets (equal to 1 mg of pramipexolo) (Pharmacia & Upjohn)

**Posology:** 1.05–3.3 mg/day (equal to 0.375–4.5 mg of pramipexolo 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 ($D_3 > D_2 > D_4$)

**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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopaminergic effects</strong></td>
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<tr>
<td><strong>Central</strong></td>
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<tr>
<td>Drowsiness, yawning,</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>sedation, confusion, psychosis,</td>
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<tr>
<td>hallucinations, dyskinesias,</td>
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<tr>
<td>headache</td>
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<td><strong>Peripheral</strong></td>
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<tr>
<td>Hypoprolactinaemia, nausea,</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>vomiting, orthostatic hypotension,a</td>
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<tr>
<td>cardiac arrhythmias</td>
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<tr>
<td><strong>Other effects</strong></td>
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<tr>
<td>Constipation</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Pleural effusion,</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<td>No</td>
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<td>erythromelalgia, pulmonary</td>
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<td>fibrosis, retroperitoneal fibrosis</td>
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</tbody>
</table>

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*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

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**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

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
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.
MAO and COMT Inhibitors
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.

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/MAO-B-Inhibitors
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

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Prescription-Medications/COMT-Inhibitors
Entacapone

Efficacy: Efficacious on wearing-off phenomena

Marketed preparations: Comtan 200 mg tablets (Novartis Farma)

Posology: 200 mg with every L-dopa administration
Glutamate Antagonists
Glutamate Antagonists

- **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.
New Therapies under development for PD

> To modify disease
New Therapies under development for PD

-> To treat symptoms

| Table 2: Non-dopaminergic therapies currently in development for the symptomatic treatment of PD |
| --- | --- | --- | --- | --- |
| **Compound end/or agent, company** | **Mechanism of action** | **Phase of development** | **Clinical trial number** | **Refs** |
| **Motor fluctuations** | | | | |
| Istradefylline (KW-8002), Kyowa Hakko Kirin Pharma | Adenosine receptor type 2A antagonist | *Approved in Japan*<br>• Not approved by the FDA in February 2018 | *NCT01968031*<br>*NCT02610231* | 155-159 |
| **Dyskinesia** | | | | |
| Amantadine ER (ADS-5102 (Gocovri)), Adamas Pharmaceuticals | NMDA receptor antagonist | *Approved in United States*<br>• Phase III ongoing | NCT02136914 | 103-104 |
| Dipraglurant (ADX48621), Addex Therapeutics | mGlu5 NAM | Phase III in preparation | NCT01336088 | 109-119 |
| Buspirone, Assistance Publique, Hopitaux de Paris, Oregon Health and Science University and University of Rochester | 5-HT_{1A} and a_{2A}-adrenergic receptor agonist | Phase III ongoing | *NCT02617017*<br>*NCT02803749*<br>*NCT02589340* | 108-124 |
| Eltoprazine, Amaranthus BioScience Holdings | 5-HT_{1B/2B} receptor agonist | Phase IIb in preparation | NCT02439125 | 107-130 |
| **Motor fluctuations and dyskinesia** | | | | |
| Foliglurax (PXT002331), Prexton Therapeutics and Lundbeck | mGlu4 PAM | Phase IIa ongoing | NCT03162874 | 193-194<br>194-195<br>342-343 |
| **Other symptoms** | | | | |
| Varenicline (gait and balance, excessive daytime sleepiness), Rush University Medical Center and VU University Medical Center | Partial agonist of the a_{2B} nicotinic acetylcholine receptor | • Phase II ongoing for gait and balance<br>• Phase IV ongoing for sleep | *NCT01341080*<br>*NCT02473562* | 250-254<br>242-246 |
| Pimavanserin (formerly ACP-103) (psychosis), Acadia Pharmaceuticals | 5-HT_{2A} receptor inverse agonist | Approved in United States | *NCT00550238*<br>*NCT01174004*<br>*NCT00477672* | 215<br>248-249 |
| SYN120 (PD dementia), Acorda Therapeutics | 5-HT_{5A} receptor antagonist | Phase II ongoing | NCT02258152 | 250 |

5-HT, serotonin; D_{2A}, dopamine receptor D_{2A}; 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.
Surgical treatments
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

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.

https://www.parkinson.org/Understanding-Parkinsons/Treatment/Surgical-Treatment-Options/Deep-Brain-Stimulation

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.

https://www.michaeljfox.org/deep-brain-stimulation