Parkinson's disease: from dopamine precursors to new generations of drugs
THERAPIES FOR THE TREATMENT OF PARKINSON'S DISEASE

Pharmacological treatments
- L-DOPA (precursor of dopamine)
- Direct DA agonists with long half-lives
- COMT or MAO inhibitors
- Glutamate antagonists
  - Anticholinergic

Surgical treatments
- Pallidotomy
- Deep brain stimulation
- Stem cell transplantation
<table>
<thead>
<tr>
<th>Farmaci o Classe di Farmaci</th>
<th>Mechanismo d'azione</th>
<th>Effetti Collaterali</th>
<th>Farmaci Specifici</th>
<th>Dose Giornaliera Totale Media</th>
<th>Frequenza Media di Somministrazione</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-DOPA</td>
<td>Metabolizzata in dopamina dall'enzima dopa-decarbossilasi</td>
<td>Acuti: Nausea, ipotensione, allucinazioni e psicosi. Cronici: fluttuazioni motorie, movimenti discinetici</td>
<td>L-DOPA/Carbidopa (250/25 mg) L-DOPA/Benserazide</td>
<td>400/40-800/80 mg 400/100-800/200 mg</td>
<td>3-4 volte al giorno 3-4 volte al giorno</td>
</tr>
<tr>
<td>Agonisti Dopaminergici</td>
<td>Stimolazione diretta dei recettori dopaminergici</td>
<td>Nausea, ipotensione, allucinazioni e psicosi, edema periferico, fibrilazione polmonare (per i derivati dell'ergot), improvvisi colpi di sonno</td>
<td>Derivati ergolinici* Bromocriptina Cabergolina</td>
<td>15-30 mg 2-6 mg 60-120 mg 1,5-4,5 mg 1,5-3 mg 12-84 mg 150-250 mg 1,5-4,5 mg 3-9 mg 6-8 mg</td>
<td>2-3 volte al giorno 1 volta al giorno 2 volte al giorno 2 volte al giorno 3 volte al giorno Infusione continua per 12 ore 3 volte al giorno 3 volte al giorno 3 volte al giorno 1 volta al giorno Rilascio transdermico</td>
</tr>
<tr>
<td>Anticolinergici</td>
<td>Antagonismo dei recettori colinergici</td>
<td>Secchezza delle fauci e oculari, ritenzione urinaria, peggioramento del glaucoma e deficit cognitivi</td>
<td>Biperidene Bornaprina Metixene Orfenadrina Tresilfenilide</td>
<td>1-6 mg 6-12 mg 20-60 mg 200-400 mg 6-10 mg</td>
<td>3 volte al giorno 3 volte al giorno 3 volte al giorno 3 volte al giorno 3 volte al giorno</td>
</tr>
<tr>
<td>Amantadina</td>
<td>Antagonismo dei recettori NMDA nicotinic, promozione del rilascio di dopamina</td>
<td>Disfunzioni cognitive, edema periferico e eruzioni cutanee</td>
<td>Amantadina</td>
<td>50-200 mg</td>
<td>2 volte al giorno</td>
</tr>
<tr>
<td>Inibitori delle MAO</td>
<td>Inibizione delle MAO-B e riduzione del metabolismo della dopamina</td>
<td>Disordini del sonno e deficit cognitivi, nausea, vertigini</td>
<td>Selegilina Rasagilina</td>
<td>5-10 mg 1-4 mg</td>
<td>2 volte al giorno 2 volte al giorno</td>
</tr>
<tr>
<td>Inibitori delle COMT</td>
<td>Inibizione delle COMT e aumento dei livelli della L-DOPA</td>
<td>Escacerbazione degli effetti collaterali della L-DOPA, diarrea</td>
<td>Entacapone</td>
<td>200 mg per ogni dose di L-DOPA</td>
<td>Si associa ad ogni dose di L-DOPA</td>
</tr>
</tbody>
</table>

*Derivati ergolinici: bromocriptina, cabergolina.
Levodopa
Marketed preparations:
- L-dopa + benserazide:
  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.
Side effects of levodopa

Treatment:
atypical antipsychotics (clozapine, quetiapine)
Pharmacological interactions
Prarmacological interaction with levodopa

Negative interactions

Typical antipsychotics: haloperidol

Non-selective MAO inhibitors: phenelzine and tranylcypromine or selective for MAO-A: moclobemide (foods containing tyramine)

Tricyclics potentiate the effects of anticholinergics
Complications associated with L-DOPA therapy

- **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
Dyskinesia induced by L-DOPA
- Progression of dopamine neuron degeneration
- Pulsatile stimulation of dopaminergic receptors
La proteina CREB modula la trascrizione dei geni

Proteina G che attiva l'adenilato ciclasi e produce AMPc

AMPc che attiva la PKA, la quale fosforila la proteina CREB

Proteina appena sintetizzata, ossia canale ionico o enzima modulatore

I geni codificano proteine che influenzano la trasmissione dei segnali

1. Neurotrasmettitore che si lega a un recettore
2. Esterno della cellula
3. Adenilato ciclasi
4. Canale ionico
5. Proteina appena sintetizzata, ossia canale ionico o enzima modulatore

Canale ionico

Nucleo
Terapy of dyskinesia

Adjustment of L-DOPA dose
Amantadine
Clozapine
DBS (deep brain stimulation)
Duodopa

Avoid pulsatile stimulation of dopaminergic receptors

Duodenal infusion of levodopa / carbidopa (Duodopa®)
Gel for continuous intestinal administration based on levodopa and carbidopa (4: 1 ratio)

*In patients with advanced PD (stage 4-5), who are not effectively controlled with standard oral therapy*
Direct agonists of dopaminergic receptors
Dopamine receptors

- **D1**
  - Activation of adenylate cyclase
  - Cortex ++
  - Limbic system +++
  - Basal ganglia ++
  - Hypothalamus ++

- **D5**
  - Basal ganglia +
  - Hypothalamus +

- **D2**
  - Cortex ++
  - Limbic system +++
  - Basal ganglia +++
  - Pituitary gland +++

- **D3**
  - Limbic system +
  - Basal ganglia +

- **D4**
  - Dopamine +
  - Apomorphine +
  - Bromocriptine +

- **Antagonists**
  - Chlorpromazine +
  - Haloperidol +
  - Clozapine +

- **Low Potency Agonists (PA)**
  - Chlorpromazine +
  - Haloperidol +
  - Clozapine +

- **Distribution**
  - Chlorpromazine +
  - Haloperidol +
  - Clozapine +

- **2nd Messenger Effect**
  - Chlorpromazine +++
  - Haloperidol +++
  - Sipirone +++
  - Sipirone +++
  - Risperidone +++
  - Clozapine +
  - Olanzapine +

©CNSforum.com
D4 RECEPTOR DISTRIBUTION

A

B

C

D
<table>
<thead>
<tr>
<th></th>
<th>Bromocriptine</th>
<th>Pergolide</th>
<th>Pramipexole</th>
<th>Ropinirole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of compound</td>
<td>Ergot derivate</td>
<td>Ergot derivate</td>
<td>Non-ergoline</td>
<td>Non-ergoline</td>
</tr>
<tr>
<td>Receptor specificity</td>
<td>$D_2$, $D_1$ $\alpha_1$, $\alpha_2$, 5-HT $\alpha_1$, $\alpha_2$, 5-HT $\beta$</td>
<td>$D_2$, $D_1$ $\alpha_1$, $\alpha_2$, 5-HT $\beta$</td>
<td>$D_2$, $D_3$, $D_4$ $\alpha_2$</td>
<td>$D_2$, $D_3$, $D_4$ $\alpha_2$</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>8%</td>
<td>20%</td>
<td>&gt; 90%</td>
<td>55%</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>70 – 100</td>
<td>60 – 120</td>
<td>60 – 180</td>
<td>90</td>
</tr>
<tr>
<td>Protein binding</td>
<td>90 – 96%</td>
<td>90%</td>
<td>15%</td>
<td>40%</td>
</tr>
<tr>
<td>Elimination route</td>
<td>Metabolic (hepatic)</td>
<td>Metabolic (hepatic)</td>
<td>Renal</td>
<td>Metabolic (hepatic)</td>
</tr>
<tr>
<td>Half-life (hr)</td>
<td>3 – 8</td>
<td>27</td>
<td>8 – 12</td>
<td>6</td>
</tr>
</tbody>
</table>

* Antagonist

Adapted from *Applied Therapeutics: The Clinical Use of Drugs, 8th ed.*, 2005
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 ($D_2$, $D_1$)

**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 \((D_2/D_3, \text{alfa})\)

*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, alfa)

**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 ($D_2/D_3, D_1/D_4, alfa$)

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.)
Side effects of bromocriptine and ergolinic derivatives

- lower limb edema
- pleuropulmonary, pericardial, valvular and retroperitoneal fibrosis
- drowsiness
- impulsive / compulsive behaviors (5%)
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 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.
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 (\(D_1/D_2, D_3/D_4, \text{alfa}\))

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.
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
Non motor complications associated to DA replacement therapy in PD
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
Anticholinergic
Anticholinergic
(tremor, muscular rigidity)

- Orfenadrine
- Triesifenidile
- Biperidene
- Metixene
- Bornaprine

**Side Effects:**
- blurred view
- dry mouth
- urinary retention
- constipation
- memory, mental confusion
# Anticholinergic

<table>
<thead>
<tr>
<th></th>
<th>$T_{max}$</th>
<th>$T_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orfenadrina</td>
<td>1.30-2.30</td>
<td>16</td>
</tr>
<tr>
<td>Triesifenidile</td>
<td>1.30-2.30</td>
<td>33</td>
</tr>
</tbody>
</table>
MAO and COMT inhibitors
MAO Inhibitors

▪ Selegiline
▪ Rasagiline
▪ Safinamidine
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 *
Entacapone

*Efficacy:* Efficacious on wearing-off phenomena

*Marketed preparations:*
   Comtan 200 mg tablets (Novartis Farma)

*Posology:* 200 mg with every L-dopa administration
Deep Brain Stimulation (DBS)
Deep brain stimulation (DBS)
Antagonists of glutamate receptors
Glutamate antagonists

- **Amantadine**
  (NMDA-R, DA release-reuptake)

- **Memantine**
  (NMDA)

- **Budipine**
  (NMDA-R, DA release, MAO-B, M-R)
Amantadine

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.