Agonisti diretti dei recettori dopaminergici
D5 RECEPTOR DISTRIBUTION

A

B

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D
# Pharmacologic & Pharmacokinetic Properties of Dopamine-Agonists

<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>$D_2, D_1$  $\alpha_1, \alpha_2, 5$-HT</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>$D_2, D_3, D_4$</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>8%</td>
<td>20%</td>
<td>&gt; 90% (1st-pass metabolism)</td>
<td>55%</td>
</tr>
<tr>
<td><strong>T_{max} (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>Renal</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>

*Antagonist

Adapted from *Applied Therapeutics: The Clinical Use of Drugs, 8th ed., 2005*
Dosi efficaci equivalenti dei dei principali agonisti della dopamina

<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>
Bromocriptina (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)
Diidroergocriptina (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).
Cabergolina (D₂/D₃, 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<sub>2</sub>/D<sub>3</sub>, D<sub>1</sub>/D<sub>4</sub>, 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.)
Effetti collaterali della *bromocriptina* e dei derivati ergolinici

edema agli arti inferiori

fibrosi pleuropolmonari, pericardiali, valvolari e retroperitoneali

sonnolenza

comportamenti impulsivi/compulsivi (5%)
Pramipexol (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 pramipexol) (Pharmacia & Upjohn)
- Mirapexin 0.7 mg tablets (equal to 1 mg of pramipexol) (Pharmacia & Upjohn)

Posology: 1.05–3.3 mg/day (equal to 0.375–4.5 mg of pramipexol 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%.
Ropinirolo ($D_3 \geq D_2 \geq D_4$)

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

_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.
**Rotigotina preparazione transdermica (D₃/D₂)**

Problemi con la cristallizzazione locale della rotigotina e reazioni locali, ne limitano l’uso
Non motor complications associated to DA replacement therapy in PD

**DA dysregulation syndrome**

Hypersexuality

Euphoria and hypomania

Punding

Pathological shopping

Pathological Gambling

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Sandro Fenu, Jadwiga Wardas and Micaela Morelli
Behav Pharmacol. 2009 Sep;20(5-6):363-79

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**Table 4: Nonmotor symptoms in PD**

<table>
<thead>
<tr>
<th>Sensory symptoms</th>
<th>Hyposmia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td>Neurogenic bladder disturbance</td>
</tr>
<tr>
<td></td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td>Neuropsychiatric symptoms</td>
<td>Anhedonia</td>
</tr>
<tr>
<td></td>
<td>Apathy</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Bradyphrenia</td>
</tr>
<tr>
<td></td>
<td>Frontal executive dysfunction</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>Dementia</td>
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<tr>
<td></td>
<td>Psychosis</td>
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<tr>
<td></td>
<td>Sleep fragmentation</td>
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<td></td>
<td>Reduced sleep efficiency</td>
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<td></td>
<td>Reduced slow-wave sleep</td>
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<tr>
<td></td>
<td>Reduced REM sleep</td>
</tr>
<tr>
<td></td>
<td>RBD</td>
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<tr>
<td></td>
<td>Excessive daytime sleepiness</td>
</tr>
<tr>
<td></td>
<td>Nocturnal akinesia/tremor</td>
</tr>
<tr>
<td></td>
<td>RLS/PLMS</td>
</tr>
</tbody>
</table>

REM, rapid eye movement; RBD, REM sleep behavior disorder; RLS, restless leg syndrome; PLMS, periodic limb movement disorder.
Anticolinergici
(tremore, rigidità muscolare)

- Orfenadrina
- Triesifendile
- Biperidene
- Metixene
- Bornaprina

- Effetti collaterali:
  - offuscamento vista
  - secchezza fauci
  - ritenzione urinaria
  - costipazione
  - memoria, confusione mentale
<table>
<thead>
<tr>
<th>Medicamento</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>
Inibitori delle MAO e delle COMT
Inibitori delle MAO

- Selegilina
- Rasagilina
Selegilina

*Efficacy:* Probably efficacious

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

*Posology:* 10 mg/day
Inibitori delle COMT

- Entacapone
- Tolcapone *
Entacapone

Efficacy: Efficacious on wearing-off phenomena

Marketed preparations:
  Comtan 200 mg tablets (Novartis Farma)

Posology: 200 mg with every L-dopa administration
Antagonisti dei recettori del glutammato
Antagonisti del glutammato

- Amantadina
- Memantina
- Budipina
Amantadina

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.