

# Medications used to treat Parkinson's disease

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# Treatment of Parkinson's Disease

LEVODOPA	
<b>Peripheral Decarboxylase Inhibitors</b> Carbidopa Benserazide	<b>Dopamine Agonists</b> Bromocriptine      Apomorphine Pergolide            Ropinirole Lisuride*             Pramipexole Cabergoline*        Rotigotine
<b>MAO-B Inhibitor</b> Selegiline Amantadine Rasagiline	<b>Anticholinergics</b> Trihexyphenidyl Benztropine Biperiden Procyclidine
<b>COMT INHIBITORS</b> Tolcapone              Entacapone	

\*not marketed in the US for Parkinson's disease

# Anticholinergics

- Often the most effective choice to treat Parkinsonian tremor
- Best tolerated in younger patients
- Discontinue anticholinergic medications first if cognitive dysfunction occurs
- Amantidine has both anticholinergic and MAO-B inhibitory effects

# Anticholinergics: Side-Effects

- Memory impairment
- Confusion
- Hallucinations
- Dry eyes and dry mouth
- Exacerbation of constipation
- Urinary retention

# Selegiline

- Provides good symptomatic treatment in early Parkinson's disease
- Well tolerated in most patients, BID dosing is convenient
- Can be used effectively to delay initiation of dopaminergic therapy
- May have a mild neuroprotective effect
- Alleged increase in mortality is only in combination therapy with dopamine, if at all

# Rasagiline

- Provides moderate efficacy as monotherapy in patients with early Parkinson's disease, may provide efficacy as adjunctive therapy to levodopa
- Well tolerated in most patients, once per day dosing is convenient
- Can be used effectively to delay initiation of dopaminergic therapy
- Has more neuroprotective effect than selegiline in preclinical studies

# Dopamine Agonists

- Pramipexole = Mirapex
  - Tablet three times per day or daily long-acting
  - Cognitive side-effects > cardiovascular side-effects
- Ropinerole = Requip
  - Tablet three times per day or daily long-acting
  - Cardiovascular side-effects > cognitive side-effects
- Rotigotine = Neupro
  - Patch daily
- Apomorphine
  - Subcutaneous injection for short action

# Receptor Properties of Dopamine Agonists Used to Treat Parkinson's Disease

## Relative Potency at Dopamine Receptors

Drug	D <sub>1</sub>	D <sub>2</sub>	D <sub>3</sub>	Half-life (h)	Ergot Structure
Bromocriptine	0/-	++	+	3	Yes
Pergolide	0/+	++	++	4	Yes
Pramipexole	0	++	+++	12	No
Ropinirole	0	++	+	4	No
Cabergoline	0	++	+	65	Yes

# Apomorphine

- Dopamine agonist with strong emetic properties
- Used in patients with severe oscillations in motor control
- CONTINUOUS SUBCUTANEOUS INFUSIONS of apomorphine have been used (Stibe et al, 1988). The initial rate was 1 mg/hr for 10 hrs with a minipump that delivered the dose into the abdominal wall. The dose was increased and the interval extended to 14 hours. The mean infusion rate was 0.04 mg/kg/hr (range, 0.02 to 0.07), with a mean daily dose of 77 mg (range, 30 to 150). In similar studies, patients required doses of 1.5 to 3.5 mg/hr for control (Ruggieri et al, 1989; Frankel et al, 1990)
- Subcutaneous injections of apomorphine were given as 0.02 ml/dose (10 mg/ml) PRN. The dose was gradually increased to a total of 0.14 ml (1.4 mg) until a good clinical response was consistently noted (Stibe et al, 1988). Under a similar protocol, patients required 2.5 to 7 mg (mean 4.7) for a positive clinical response (Poewe et al, 1988). Repeated injections (range 1.2 to 4 mg) do not decrease the sensitivity of receptors over time to dyskinesia episodes (Hughes et al, 1991)

# Dopamine Agonist Side-effects

- Orthostatic hypotension and syncope
- Somnolence and sleep attack
- Hallucinations and delusions
- Compulsive behaviors

# Carbidopa/Levodopa

- Most patients require 50-100 mg of carbidopa per day to prevent side-effects due to peripheral conversion of levodopa to dopamine
- Tablets of carbidopa alone are available to combine with carbidopa/levodopa
- Clinical effects of excess carbidopa are very rare
- Some patients can benefit from domperidone to block dopamine effects in the GI tract

# Tolcapone

- Trade name: TASMAR
- Dosage
  - 100 mg TID (200 mg TID)
  - Liver enzymes every 2 weeks during the first year, every 4-8 weeks thereafter
- Tablets: 100, 200 mg
- Adverse effects
  - Diarrhea, nausea, dyspepsia, abdominal cramps, and dizziness
  - Risk of potentially fatal fulminant liver failure

# Entacapone

- Trade name: COMTAN
- Dosage
  - 200 mg with each dose of levodopa
  - Maximum 1600 mg/day
- Tablets: 200 mg
- Adverse effects
  - Nausea, urine discoloration, abdominal pain, orthostatic hypotension and diarrhea

# Stalevo

- Carbidopa/entacapone/levodopa tablets
  - 12.5 MG-200 MG-50 MG
  - 18.75 MG-200 MG-75 MG
  - 25 MG-200 MG-100 MG
  - 37.5 MG-200 MG-150 MG
- MAX 8 tablets per day
  - individual tablets should not be fractionated
  - only 1 tablet should be administered at each dosing interval
- **FDA labeled indications:** Idiopathic Parkinson's disease
  - Substitute (with equivalent strength of each of the 3 components) for immediate release carbidopa/levodopa and entacapone previously administered as individual products
  - Replace immediate release carbidopa/levodopa therapy (without entacapone) when patients have end-of-dose "wearing off"; only if total daily dose of levodopa is 600 mg or less and without dyskinesias

# New Forms for an Old Therapy

## RYTARY formulation

**A NEW extended-release carbidopa and levodopa treatment**

RYTARY is formulated in a 1:4 carbidopa to levodopa ratio.



Each capsule contains both:

- Immediate-release beads.
- Extended-release beads.<sup>2</sup>

# New Forms for an Old Therapy

Current Levodopa	Rytary Capsules
levodopa-naive	Carbidopa 23.75 mg/levodopa 95 mg 3 times daily
400 mg to 549 mg/day	Carbidopa 23.75 mg/levodopa 95 mg 3 capsules 3 times daily; total dose levodopa 855 mg/day
550 mg to 749 mg/day	Carbidopa 23.75 mg/levodopa 95 mg 4 capsules 3 times daily; total dose levodopa 1140 mg/day
750 mg to 949 mg/day	Carbidopa 36.25 mg/levodopa 145 mg 3 capsules 3 times daily; total dose levodopa 1305 mg/day;
950 mg to 1249 mg/day	Carbidopa 48.75 mg/levodopa 195 mg 3 capsules 3 times daily; total dose levodopa 1755 mg/day;
1250 mg or more/day	Carbidopa 48.75 mg/levodopa 195 mg 4 capsules 3 times daily; total dose levodopa 2340 mg/day OR carbidopa 61.25 mg/levodopa 245 mg 3 capsules 3 times daily; total dose levodopa 2205 mg/day

Micromedex/ Package insert: Impax Laboratories (per FDA),

# New Forms for an Old Therapy



Duopa is a gel for continuous intestinal administration. For long-term administration, the gel should be administered with a portable pump directly into the duodenum or upper jejunum by a permanent tube via percutaneous endoscopic gastrostomy with an outer transabdominal tube and an inner intestinal tube.