



# Introduction

Parkinson's disease: is a slow, progressive, neurodegenerative disease of the extrapyramidal motor system.

- Dopamine neurons in the substantia nigra are primarily affected, and degeneration of these neurons causes a disruption in smooth motor control.

Parkinson's disease is also known as *primary Parkinsonism* or as the idiopathic Parkinson's disease (IPD).

There is no cure, and treatment is aimed at controlling symptoms and slowing disease progression and maintaining quality of life (QOL)

# *Etiology and pathophysiology*

- Two hall mark features in the substantia nigra are :
  1. Loss of neuron(dopamine neurons): The etiology of neuron degeneration in PD remains unknown, but aging is a primary risk factor. Cell death may be caused by oxidative stress, mitochondrial dysfunction, immune system disorders, signal-mediated apoptosis, and environmental toxins.
- Presence of lewy bodies (primarily alpha-synuclein): associated with nonmotor symptoms of PD (e.g., psychiatric, autonomic symptoms).
  - ❖ As dopamine neurons die, dopamine relayed messages cannot communicate to other motor centers of the brain, and patients develop motor symptoms
  - The degree of dopamine loss correlate positively with motor symptoms.
  - Clinical improvement correlate with D<sub>2</sub> receptor more than D<sub>1</sub> receptor.

# Clinical presentation

- PD progress slowly. It's relatively asymptomatic Until 70%-80% of substantia nigra neurons has depleted.
- Interestingly, patients with a history of smoking or who drink coffee or tea have demonstrated decreased risk of PD through unknown mechanisms.

# Clinical Presentation of PD

Patients with PD display both motor and nonmotor symptoms. The nonmotor symptoms may precede the motor symptoms.

## Motor Symptoms (Mnemonic TRAP)

T = Tremor at rest ("pill rolling")

R = Rigidity (stiffness and cogwheel rigidity)

A = Akinesia or bradykinesia

P = Postural instability and gait abnormalities



## Nonmotor Symptoms (Mnemonic SOAP)

S = Sleep disturbances (insomnia, REM sleep behavioral disorder, restless legs syndrome [RLS])

O = Other miscellaneous symptoms (problems with nausea, fatigue, speech, pain, dysesthesias, vision, seborrhea)

A = Autonomic symptoms (drooling, constipation, sexual dysfunction, urinary problems, sweating, orthostatic hypotension, dysphagia)

P = Psychological symptoms (anxiety, psychosis, cognitive impairment, depression)

## Response Fluctuations (Mnemonic MAD)

M = Motor fluctuations (delayed peak, wearing off, random off, freezing)

A = Akathisia      inability to remain in a sitting posture( restlessness ),

D = Dyskinesias (eg, chorea, dystonia, diphasic dyskinesia)

involuntary movement that is abnormal and uncontrolled



# DIAGNOSIS

A diagnosis of PD can be made with a high level of confidence when there is **bradykinesia** (along with resting tremor and/or rigidity), prominent **asymmetry**, and a **positive response to dopaminergic medication**.

several other conditions must be excluded, such as medication-induced Parkinsonism (eg, induced by **antipsychotics**, **phenothiazine** antiemetic, or **metoclopramide**).

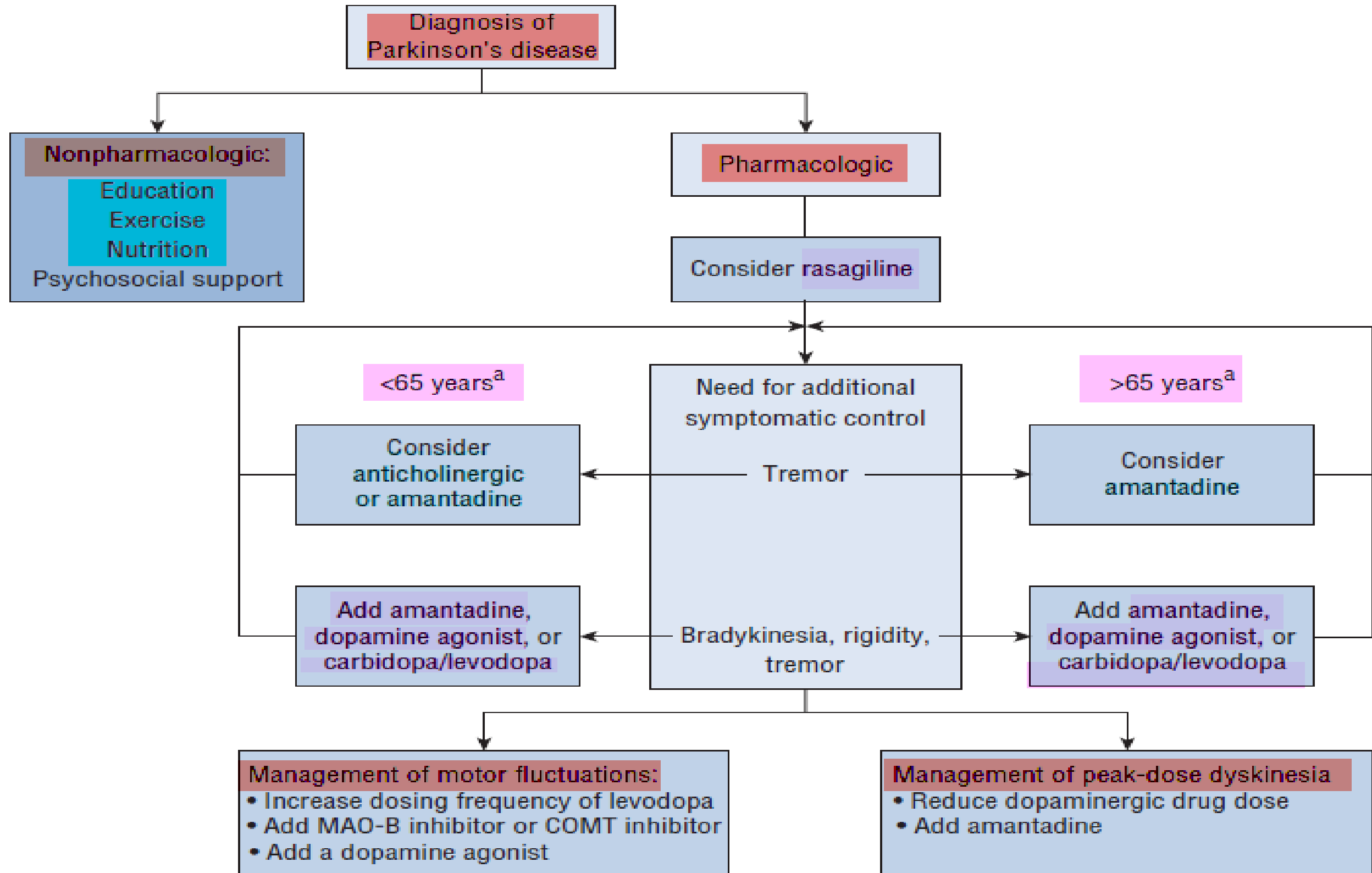
# Goal of treatment

- The goals of treatment include:
  - maintaining patient independence,
  - minimizing the development of response fluctuations
  - limiting medication-related adverse effects
  - improvement of nonmotor features such as :
    - cognitive impairment, depression, fatigue, and sleep disorder.
- Education of patient and caregivers.

**Anticholinergic** medications, **amantadine**, or **MAO-B** inhibitors is recommended only for patients who have **mild symptoms** because **they are not as effective as dopamine agonists or levodopa**.



*General approach to the management of early to advanced Parkinson's disease.*



# PD

No significant symptoms/no effect on daily living or quality of life

Significant symptoms requiring drug therapy

<sup>a</sup>Consider delaying Rx treatment or starting a dopamine agonist, MAO-B inhibitor, or levodopa/carbidopa

<sup>a</sup>Typically begin therapy with levodopa/carbidopa

Periodically assess motor symptoms for drug efficacy and assess for motor fluctuations

## Dyskinesias

Consider adjusting the dose or timing of PD drug or add amantadine

## Poor control of motor symptoms/wearing off

Consider increased dose of PD drug or adding another agent such as a COMT inhibitor if on levodopa

# Pharmacological Therapy

- TREATMENT OPTIONS:
  - Anticholinergic drugs (benztropine, trihexyphenidyl)
  - COMT inhibitors(entacapone, Tolcapone)
  - MAO-B inhibitors(rasagiline, Selegiline)
  - (amantadine)
  - Dopamine agonist( **bromocriptine**, apomrphine, pramipexole, ropinirole, rotigotine)
  - Carbidopa/levodopa products

# Anticholinergic medications

- Anticholinergic drug can improve:
  - Tremor and drooling,
  - Some times dystonic features (EPS)
    - but they are not as effective as other agents for rigidity, bradykinesia, and gait problems.
- They inhibit gastric motility, leading to erratic and decreased levodopa absorption



# Anticholinergic S/E

- *Anticholinergics side effect*
  - Dry mouth
  - Blurred vision
  - Constipation
  - Urinary retention

More serious side effect (central reaction)

- Forgetfulness , confusion sedation, depression and anxiety
- Elderly are at high risk of central side effects.

- **Amantadine** (NMDA antagonist)
- Provide **modest** benefit for:
  - Tremor
  - Rigidity
  - and bradykinesia
  - It's the only drug approve for **Dyskinesia** .

### **Adverse effect**

- ☐ Dry mouth
- ☐ Hallucination
- ☐ Dizziness
- ☐ Confusion
- ☐ Livedo reticularis (diffuse mottling of the skin ) is common but reversible .



- *Amantadine dose:*
  - initial dose : 100mg/day
  - Maintenance dose : 200-300 mg/day

*Patient with renal impairment*

CrCl:30-50ml/min....100 mg/day of amantadine.

CrCl:15-30ml/min....100 mg every other day of amantadine.

- Do not use in end-stage renal disease.



# Monoamine oxidase B inhibitors(MAO-B)

- MAO-B inhibitor : at therapeutic dose, **Selegiline** and **rasagiline** , **Safinamide** are selective, irreversible inhibitors of MAO-B .
- Selegiline: **block dopamine breakdown** then
  - it can **extend the duration of action** of L-dopa up to **1 hours**
  - It often **permit reduction in L-dopa** dose by **one half** .
- Selegiline **increase the peak effect** of L-dopa and can **worsen preexisting dyskinesia** or psychiatric symptom (e.g., delusion).
- Rasagiline consider **first-line agent** (like COMT Inhibitor)for managing **dose fluctuation of L-dopa** .

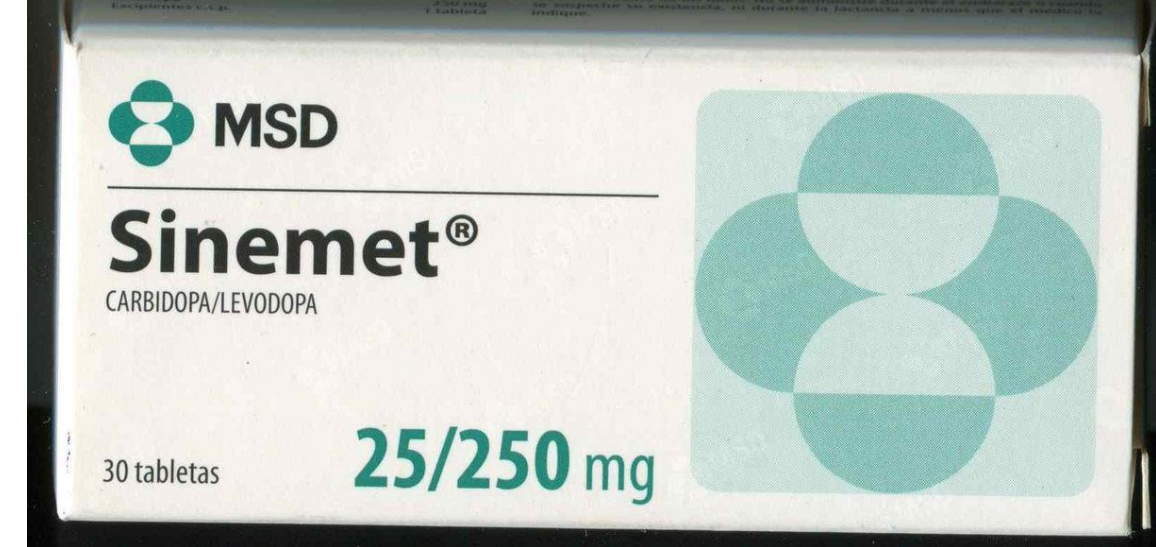
***Doses :***

- Selegiline : administered 5 mg twice daily
- Adverse effects are minimal but can include
  - insomnia (especially if administered at bedtime),
  - hallucinations,
- Selegiline and rasagiline induce (hypertension crisis )when large amount of tyramine are ingested or taken with sympathomimetics agents
- Combining MAO-B inhibitor with opioid analgesic is contraindicated .....risk of serotonin syndrome (muscle rigidity, fever and seizures) .

## *COMT Inhibitors* (Tolcapone, Entacapone and Opicapone)

- Tolcapone and Entacapone have been developed to extend the effects of L-dopa and are indicated for
  - managing wearing off (motor fluctuation).
- Tolcapone use is limited by reports of fatal hepatotoxicity
- Entacapone has a shorter half-life than tolcapone, and 200 mg needs to be given with each dose of carbidopa/L-dopa (three-four time a day).
- Brownish orange urine discoloration may occur (as with tolcapone), but hepatotoxicity is not reported with entacapone.

# Levodopa/carbidopa



L-dopa : is the most effective drug available Ultimately, all PD patient will need it

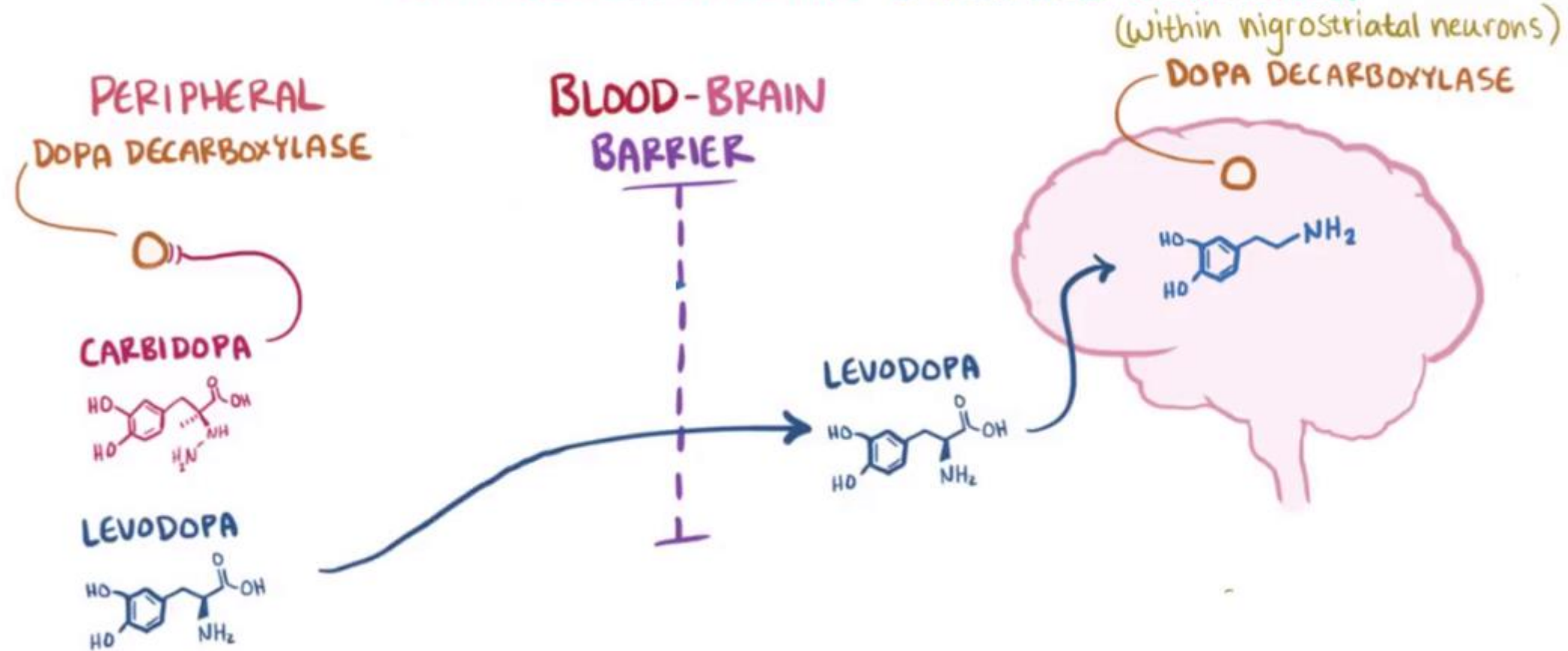
- It cross BBB
- dopa-decarboxylase (L-AAD) convert L-dopa to dopamine IN CNS and peripheries.
- In the periphery, Carbidopa inhibit dopa-decarboxylase, thus
  - Increase CNS penetration
  - Decrease dopamine adverse effect (nausea, arrhythmia and postural hypotension)

helps with  
SYMPTOMS

# TREATMENT

~ none stop neurodegeneration

## STRATEGY: INCREASE DOPAMINE SIGNALING

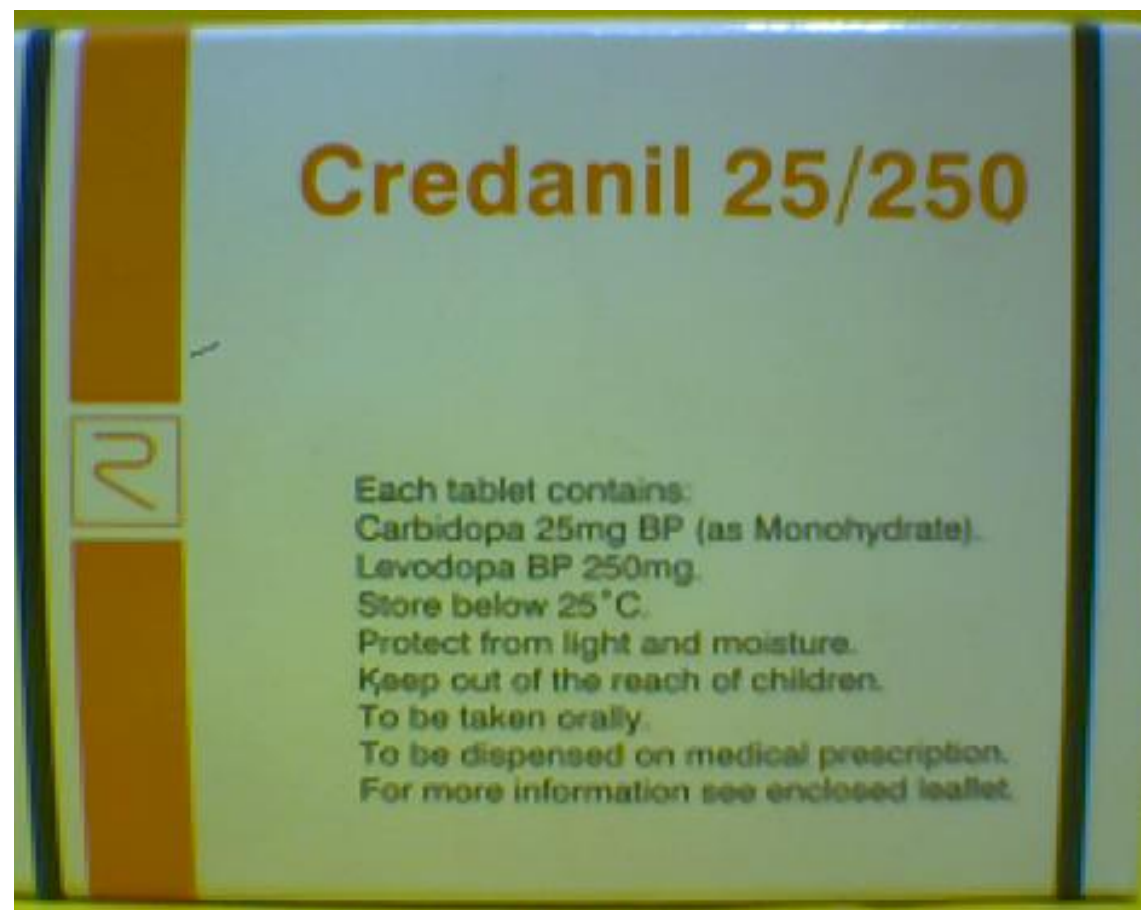


***L-dopa dose :***

- Initial dose 300 mg/day (in divided dose )
- Maximum dose is 800-1000 mg/day
- Usually dosed with Carbidopa (WHY)
- Most widely used Carbidopa/L-dopa dose is 25/100.
- L-dopa absorbed in proximal duodenum via saturated amino acid transport system
- L-dopa elimination half life approximately one hour

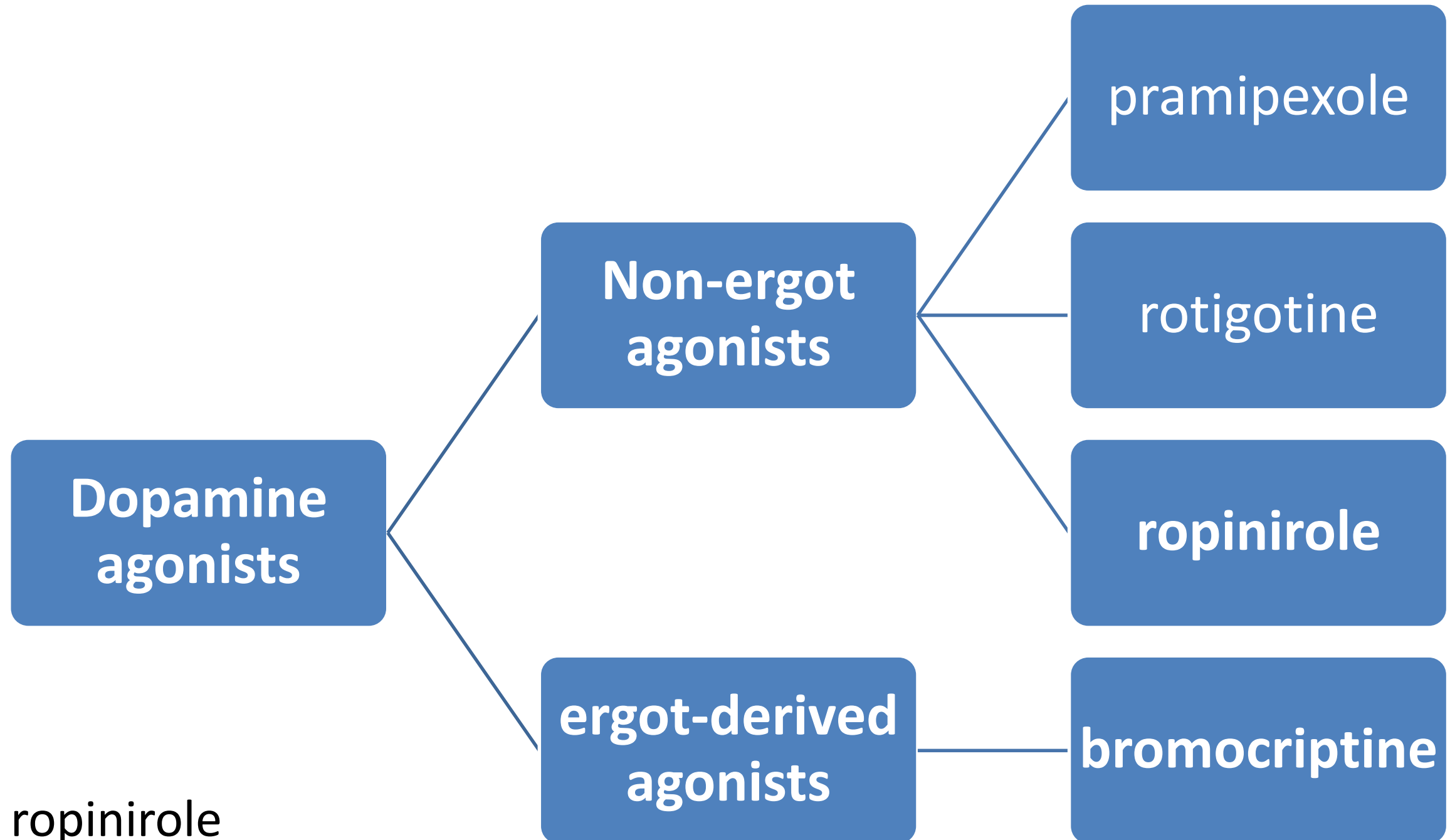


- Adding **Carbidopa** can extend the half-life to **1.5 hours**, and adding **COMT** inhibitor can extend it to **2-2.5 hours**.





# ***Dopamine Agonists***



bromocriptine 30 mg, ropinirole  
15 mg, and pramipexole 4.5 mg are equivalent,

- The non-ergot dopamine agonists are
  - safer than the ergot-derived agonists and stronger evidence of efficacy.
- The dopamine agonists
  - reduce the frequency of “off” periods
  - allow reductions in L-dopa dosage.
- Patients experience a 40% to 50% improvement in motor function with levodopa versus 30% with dopamine agonists.
- Usually, Dopamine agonist is dosed in the night and levodopa in the day.

- Older patients are more likely to experience intolerable side effects (e.g., hallucinations, orthostatic hypotension) from the dopamine agonists; therefore, carbidopa/L-dopa is preferred, particularly if cognitive problems or dementia is present.

*Common adverse effects of dopamine agonists* include

- nausea, vomiting (premedicated with the antiemetic trimethobenzamide, or domperidone)
  - Sedation (50% of PD patients).... Modafinil can be used
  - confusion, hallucinations, lower-extremity edema,
  - postural hypotension (orthostatic hypotension),
- *Bromocriptine* is not commonly used because of a risk of pulmonary fibrosis and less efficacy than the other agonists.

# Common Motor Complications and Possible Initial Treatments

- *1- End-of-dose “wearing off”* : due to
  1. Short half-life of L-dopa
- Can be overcome by
  - bedtime administration of dopamine agonist
  - Sustained Release(SR) formulation product (Carbidopa/L-dopa CR)
  - Add COMT inhibitor or
  - MAO-B inhibitor

- 2-“*Delay on*” or “*no on*” *Response* (delayed or absent onset of drug effect) Result from :

- ☐ Delay gastric emptying

- ☐ Decrease absorption from duodenum

*can be Overcome by :*

- Give Carbidopa/ L-dopa on empty stomach
- Use Carbidopa/ L-dopa oral disintegrating tablet (ODT)
- Use apomorphine SC (rescue therapy)

- 3-“*Freezing*”inhibition of lower extremities motor function.
- *Overcome*
  - Increase Carbidopa/ L-dopa dose
  - Add dopamine agonist or MAO-B inhibitor

#### *4-Dyskinesia (peak-dose dyskinesia)*

##### *Overcome*

- Provide smaller dose of Carbidopa/ L-dopa
- Add amantadine

- *5-"off-Period Dystonia"*
- (sustained muscle contractions): commonly affect a distal **lower extremity** (e.g., toes or foot). Occur often in **early morning** (**as a result of declining drug levels**).
- *Remedies for early morning dystonia include*
  - **bedtime** administration of a long acting **dopamine agonist**, or
  - **sustained-release Carbidopa/L-dopa**, or
  - **baclofen**, or focal injections of **botulinum toxin** (for persistent focal dystonia).



# Comorbidities of PD

## ***Depression (40% or more of patients):***

selective serotonin reuptake inhibitors may be considered because of their increased tolerability. Pramipexole has demonstrated to improve depression

## ***Dementia (80% of PD after 20 years of the disease):***

- Rivastigmine is considered useful with the highest quality of evidence and is FDA approved for dementia in PD.

## ***Psychosis :***

- Pimavanserin is the only antipsychotic specifically approved for PD psychosis.
- Two other antipsychotics (Clozapine or low-dose quetiapine ) are recommended for psychosis in PD. Neither is approved in PD but are preferred because of their weak dopamine antagonism



TABLE 56–1

Dosing of Drugs Used in Parkinson's Disease<sup>a</sup>

Generic Name	Trade Name	Starting Dose <sup>b</sup> (mg/day)	Maintenance Dose <sup>b</sup> (mg/day)	Dosage Forms (mg)
<b>Anticholinergic Drugs</b>				
Benzotropine	Cogentin	0.5–1	1–6	0.5, 1, 2
Trihexyphenidyl	Artane	1–2	6–15	2, 5, 2/5 mL
<b>Carbidopa/Levodopa Products</b>				
Carbidopa/L-dopa	Sinemet	100–300 <sup>c</sup>	300–1,000 <sup>c</sup>	10/100, 25/100, 25/250
Carbidopa/L-dopa ODT	Parcopa	100–300 <sup>c</sup>	300–1,000 <sup>c</sup>	10/100, 25/100, 25/250
Carbidopa/L-dopa CR	Sinemet CR	200–400 <sup>c</sup>	400–1,000 <sup>c</sup>	25/100, 50/200
Carbidopa/L-dopa/entacapone	Stalevo	200–600 <sup>d</sup>	600–1,600 <sup>d</sup>	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200
Carbidopa	Lodosyn	25	25–75	25
<b>Dopamine Agonists</b>				
Apomorphine	Apokyn	1–3	3–12	30/3 mL
Bromocriptine	Parlodel	2.5–5	15–40	2.5, 5
Pramipexole	Mirapex	0.125	1.5–4.5	0.125, 0.25, 0.5, 1, 1.5
Pramipexole ER	Mirapex ER	0.375	1.5–4.5	0.375, 0.75, 1.5, 3, 4.5
Ropinirole	Requip	0.75	9–24	0.25, 0.5; 1, 2, 3, 4, 5
Ropinirole XL	Requip XL	2	8–24	2, 4, 6, 8, 12
Rotigotine	Neupro	2	2–8	1, 2, 3, 4, 6, 8





## COMT Inhibitors

Entacapone

Tolcapone

Comtan	200–600	200–1,600	200
Tasmar	300	300–600	100, 200

## MAO-B Inhibitors

Rasagiline

Selegiline

Selegiline ODT

Azilect	0.5–1	0.5–1	0.5, 1
Eldepryl	5–10	5–10	5
Zelapar	1.25	1.25–2.5	1.25, 2.5

## Miscellaneous

Amantadine

Symmetrel	100	200–300	100, 50/5 mL
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