Anti-Parkinsonism Drugs

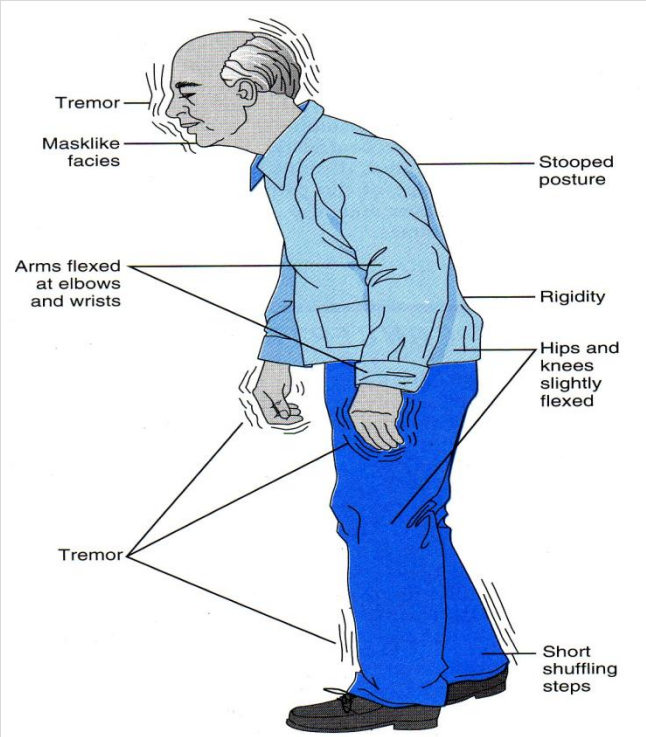

FIGURE 45–5. Clinical manifestations of Parkinson disease. (From Monahan FD, Neighbors M: *Medical-Surgical Nursing: Foundations for Clinical Practice*. Philadelphia, WB Saunders, 1998, p 787.)

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429

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Parkinsonism

- Could be:

primary [idiopathic] or secondary [viral infection or drug induced by drugs lowering dopamine levels]

- Pathophysiology:

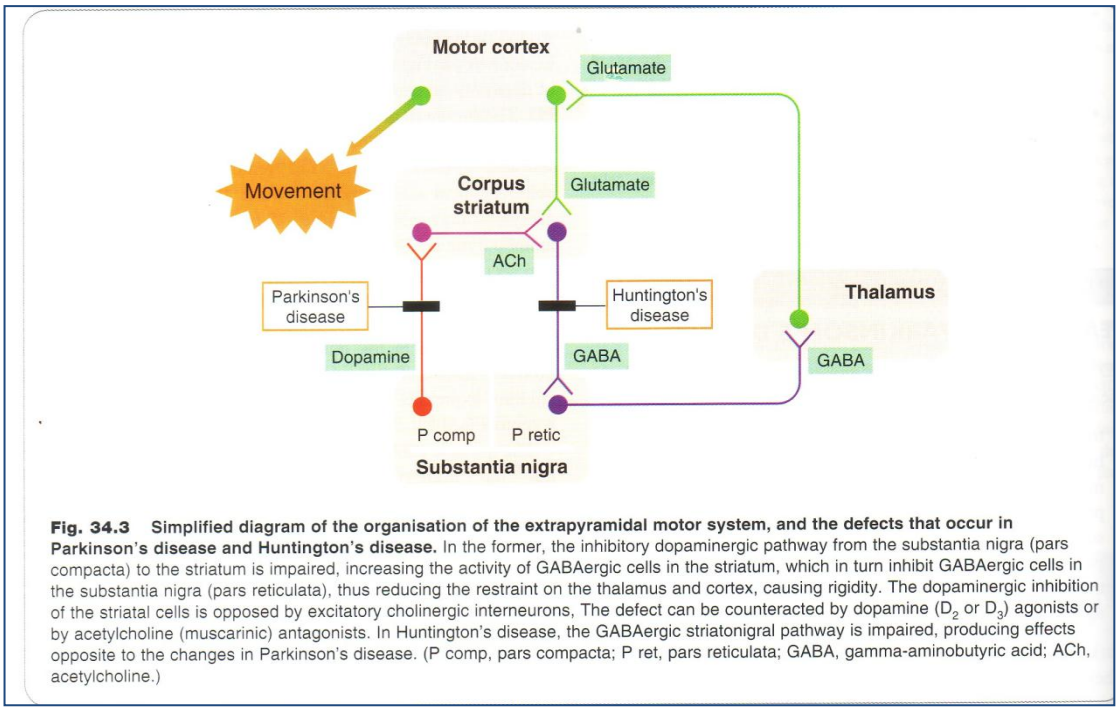


Fig. 34.3 Simplified diagram of the organisation of the extrapyramidal motor system, and the defects that occur in Parkinson's disease and Huntington's disease. In the former, the inhibitory dopaminergic pathway from the substantia nigra (pars compacta) to the striatum is impaired, increasing the activity of GABAergic cells in the striatum, which in turn inhibit GABAergic cells in the substantia nigra (pars reticulata), thus reducing the restraint on the thalamus and cortex, causing rigidity. The dopaminergic inhibition of the striatal cells is opposed by excitatory cholinergic interneurons, The defect can be counteracted by dopamine (D_2 or D_3) agonists or by acetylcholine (muscarinic) antagonists. In Huntington's disease, the GABAergic striatonigral pathway is impaired, producing effects opposite to the changes in Parkinson's disease. (P comp, pars compacta; P ret, pars reticulata; GABA, gamma-aminobutyric acid; ACh, acetylcholine.)

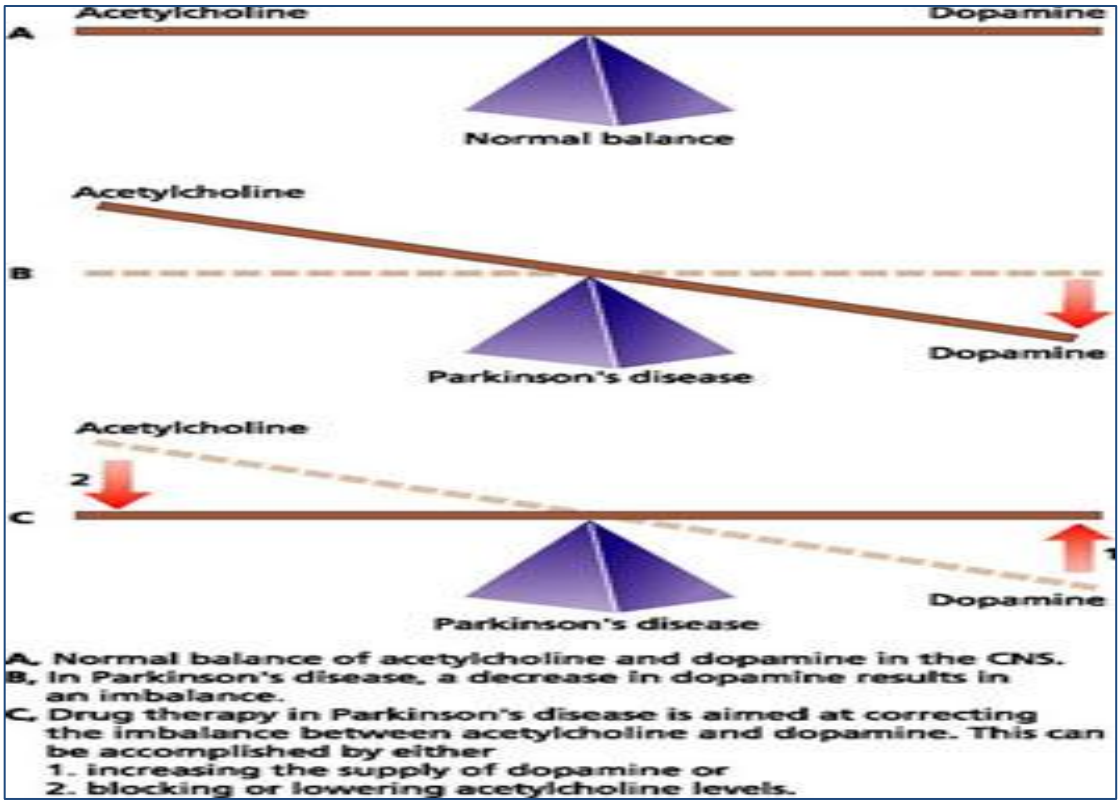
Degenerative damage to dopamenergic neurons in pars compacta of substantia negra

Loss of inhibitory effect on ACh excitatory neurons

Increase excitation of inhibitory GABAergic inhibitory neurons in corpus striatum

Increase Inhibitory effect on the inhibitory GABAergic neurons in pars reticulata of substantia negra.

This will lead to loss of restraint on the thalamus and cortex which will result in rigidity and limited mobility [hypokinesia]



- So, there's imbalance between dopamine and ACh [↓dopamine & ↑ACh]

Therefore, treatment is by reversing this.

- Treatment methods:

1) ↑ dopamine levels: Administering dopamine has no effect cause it can't cross **b**lood **b**rain **b**arrier.

So, levodopa [**L.Dopa**] which is a precursor of dopamine and can cross **b**lood **b**rain **b**arrier is given.

2) Use of substances that mimic dopamine [dopamine agonists]

3) Inhibition metabolism of dopamine <u>in the brain</u> which will ↑ dopamine levels. [MAO_B inhibitors].

Note: Mono**A**mine **O**xidase

<u>MAO</u>: are a family of enzymes that catalyze the oxidation of monoamines.

<u>MAO_A</u>: metabolize dopamine outside CNS

<u>MAO_B</u>: metabolize dopamine inside CNS

4) ↑ release of dopamine [Amantadine]

5) ↓ ACh [Muscarinic acetylcholine antagonists]

<u>1st: *Levodopa* [L.Dopa]:</u>

First-line treatment means best effect in reducing symptoms. Doesn't mean it has to be used first.

-First –line treatment [highest efficacy], combined with peripheral dopa decarboxylase inhibitor.

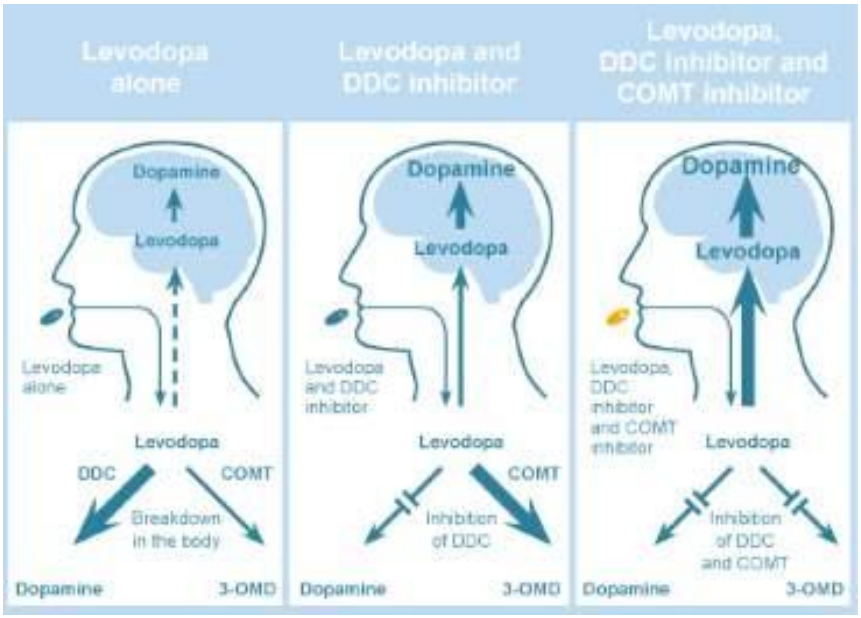
- Used in all types of parkinsonism except drug-induced.

MOA: It's an immediate precursor of dopamine that is metabolized to dopamine after crossing **BBB**.

PK:

- Absorbed by active transporter same that absorb aromatic amino acids. → high protein meal decrease absorption.

- Only **1%** reaches the brain due to peripheral metabolism by DOPA Decarboxylase. →Thus, it's given with DOPA Decarboxylase inhibitor, which is **Carbidopa**, to ↑ concentration in brain. It's also given with COMT inhibitor, which is **Entacapone** [but Carbidopa is more important].



Clinical problems with L.Dopa:

1) **Wearing- off effect**: gradual decrease in improvement after using the drug for years. That's why doctors spare the use of L.Dopa for advanced cases of Parkinsonism.

2) **On-off effect**: fluctuation of response. [sudden worsening when ↓ plasma levels of drug]

3) **Overdose causes dyskinesia** [excessive choreiform movements] → overcome by ↓ dose [but this will cause hypokinesia to reappear again]

Due to these reasons, we need to use combinations of anti-parkinsonism drugs.

ADR's:

Due to stimulation of CTZ in

1) Effects of dopamine outside CNS: vomiting, arrhythmias & orthostatic hypotension.

2) CNS effects of dopamine: psychosis, vivid dreaming depression.

Contraindications:

1) Proteins ingested with meals

2) Use with non-selective MAO inhibitors: in this case dopamine will be transformed into epinephrine [peripherally] causing hypertensive crisis.

3) Use with pyridoxine [vit. B6]:

cause it ↑ metabolism.

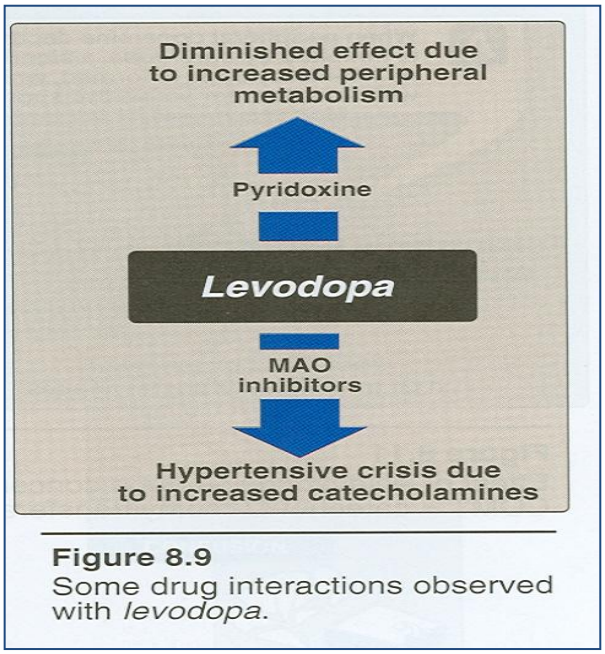


Figure 8.9
Some drug interactions observed with *levodopa*.

4) Melanoma patients: dopamine is a precursor for melanine.

5) Psychotic patient.

6) Angle closure glaucoma.

2nd: Dopamine Agonists: Example: **Bromocriptine**

Compared to L.Dopa, it has:

1) less efficacy.

2) longer duration of action → less clinical problems

3) more psychiatric adverse effects.

- It can be used with L.Dopa to decrease L.Dopa's dose.

MOA: dopamine agonist at the D2-receptors and a partial D1-antagonist.

ADR's:

Similar to L.Dopa with: more psychosis

Less dyskinesia

In order to minimize adverse effects, the dose is built up slowly over 2 or 3 months.

Contraindications:

- Causes peripheral vasoconstriction → contraindicated with peripheral circulation diseases.

- History of psychotic illness.

- Recent myocardial infarction.

- Active peptic ulceration.

3rd: Amantadine:

- Antiviral drug that has moderate antiparkinsonism and anticholenergic effect.

- Used in mild cases or combined with L.Dopa.

MOA: it has unknown mechanism but is affects dopamine release and .reuptake and act as antagonist at muscarinic and NMDA receptors.

ADR's:

- Ankle edema & levedo reticularis

purple discoloration of skin due to dilation of venules

- Should be used with caution in patients with a history of seizures or .heart failure

4th : MAO_B inhibitors:

Example:**Selegiline**

MOA: - Inhibit breakdown of dopamine in CNS by **MAO_B** → Blockade of dopamine metabolism makes more dopamine available for stimulation of its receptors.

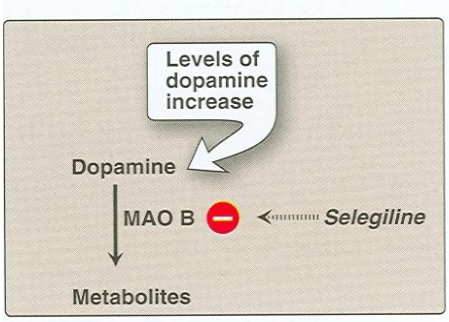


Figure 8.10
Action of *selegiline* (*deprenyl*) in dopamine metabolism. MAO = monoamine oxidase.

- It also has **anti-apoptic** effect against neurodegeneration and **free radical scavenging** [anti] effect. → best to start treatment with it to delay progression of disease.

ADR's:

High dose → inhibit MAO_A (in addition to MAO_B)

-The adverse effects of levodopa may be increased by selegiline. (So we only combine them in late stages of the disease)

Contraindications:

- ***Selegiline*** should not be coadministered with TriCyclic Antidepressants, meperidine or SSRIs. (may cause hyperpyrexia, agitation, delirium, coma).

5th: Anticholinergics:

Examples: **Benzotropine**

Trihexyphenidyl — **Drug of choice in drug-induced Parkinsonism**

- They're effective in relieving the tremor not the hypokinesia.

- Not all patients respond well to them.

- Anticholinergics can provide benefit in drug- induced parkinsonism.

ADR's:

-Anticholinergic adverse effects. (urinary retention, constipation ,, etc)

- Confusion, delirium, and hallucinations may occur at higher doses.

-Trihexyphenidyl may cause withdrawal symptoms in patients receiving large doses.

Contraindications:

Prostatic hypertrophy

MCQ's

1- All of the following are neurological characteristics of Parkinsonism except:

a) Tremors

b) Postural disturbances

c) Hyperkinesia

d) Rigidity

2- Crbidopa is useful in treatment of Parkinsonism because:

a) It is a precursor for Levodopa

b) It prevents peripheral biotransformation of L.dopa.

c) It prevents the breakdown of dopamine

d) It has an anti-apoptic effect.

3- Which statement about Bromocriptine is accurate?

a) It is contraindicated with psychotic patients.

b) Should not be administered with high protein meals.

c) It has an adverse effect of ankle edema

d) It is the drug of choice in drug-induced Parkinsonism

4- Which one of the following drugs is used in treatment of extrapyramidal side effects caused by neuroleptic drugs?

a)L.dopa

b) Trihexyphenidyl

c) Selegiline

d) Amantadine

5- Which one of the following drugs is contraindicated in prostatic hypertrophy and GIT block?

a) L.dopa

b) Carbidopa

c) Bromocriptine

d) Benzotropine

Answers	
1	**c**
2	b
3	a
4	b
5	d