

Drugs used in parkinsonism

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ILOs:

At the end of this lecture you will be able to:-

- ***Recognize the symptoms and pathophysiology of parkinsonism***
- ***Understand the pharmacology of drugs used for treatment of parkinsonism.***
- ***Define pharmacokinetics, pharmacodynamics and side effects of different drugs used for the treatment of parkinsonism.***

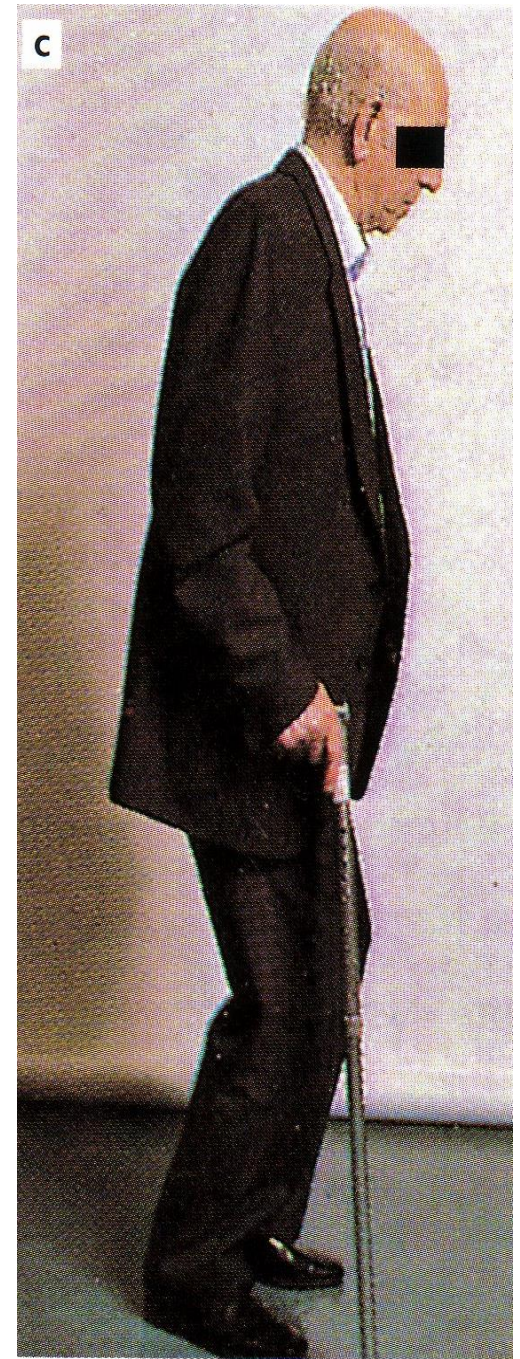
Parkinson's Disease

A progressive neurological disorder that occurs mainly in the elderly and can lead to disability unless effective treatment is provided.



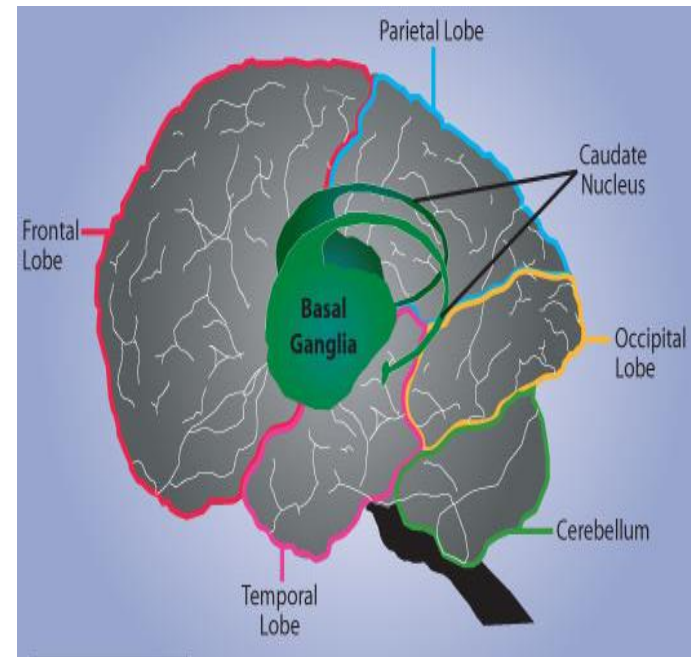
Characters of Parkinson's disease:

- simplified by the acronym “**TRAP**”
- **T**remors at rest
- **R**igidity of muscles
- **A**kinesia or **B**radykinesia
(slowness in initiating and carrying out voluntary movements)
- **P**ostural and gait abnormalities
- **A**nxiety or depression



Pathphysiology of Parkinson's disease

This movement disorder occurs mainly due to dopamine/acetylcholine imbalance in basal ganglia (caudate nucleus, substantia nigra & corpus striatum) that is involved in motor control.

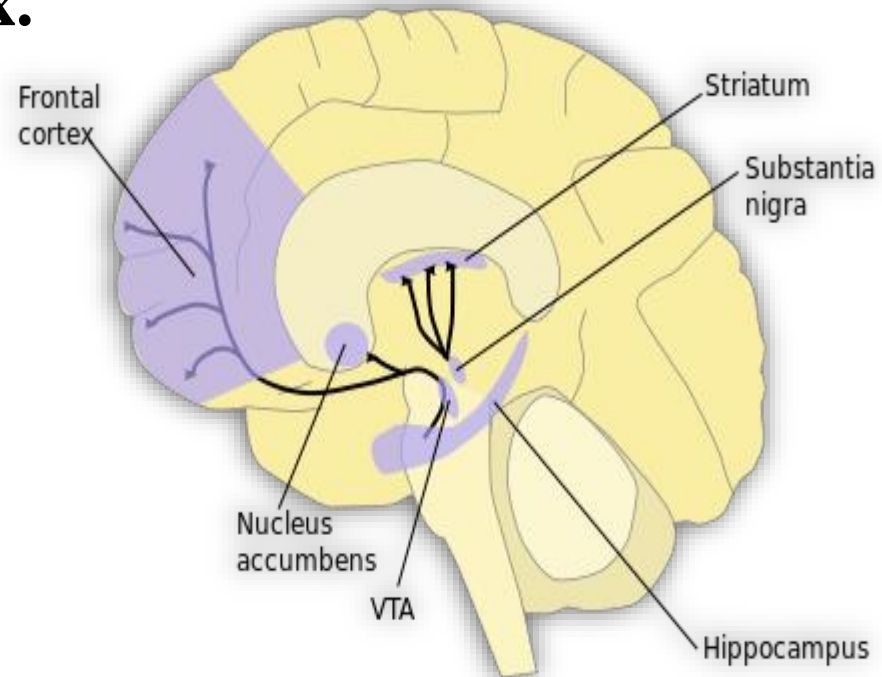


Dopamine Pathways

Reward pathway:

dopamine is manufactured in nerve cell bodies located within the **ventral tegmental area (VTA)** and is released in the nucleus accumbens and the prefrontal cortex.

Motor pathway: cell bodies in the **substantia nigra** that manufacture and release dopamine into the striatum.

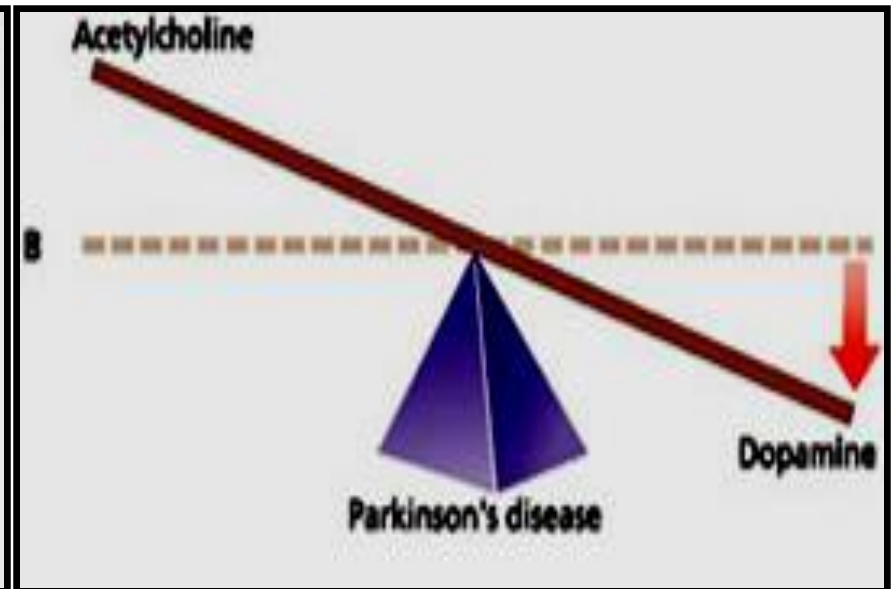
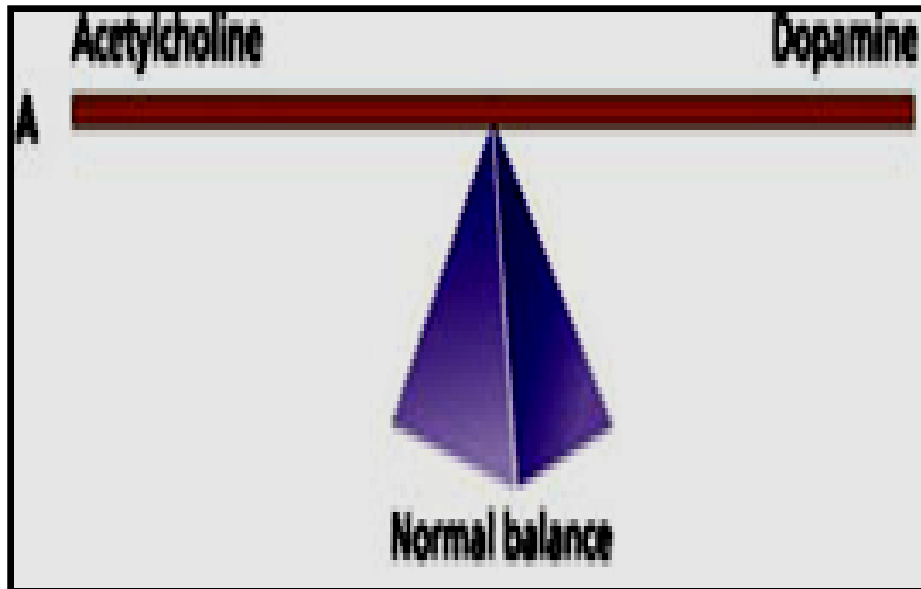


Causes

Parkinson's disease is an **idiopathic disease** but some causes may be:

- **Genetic.**
- **Toxins (MPTP= methyl phenyl tetrahydropyridine)**
- **Head trauma.**
- **Cerebral anoxia .**
- **Oxidative stress**
- **Drug-induced Parkinson's disease**
 - e.g. **antipsychotics** like haloperidol.
 - **Dopamine antagonists** as metoclopramide (antiemetic).

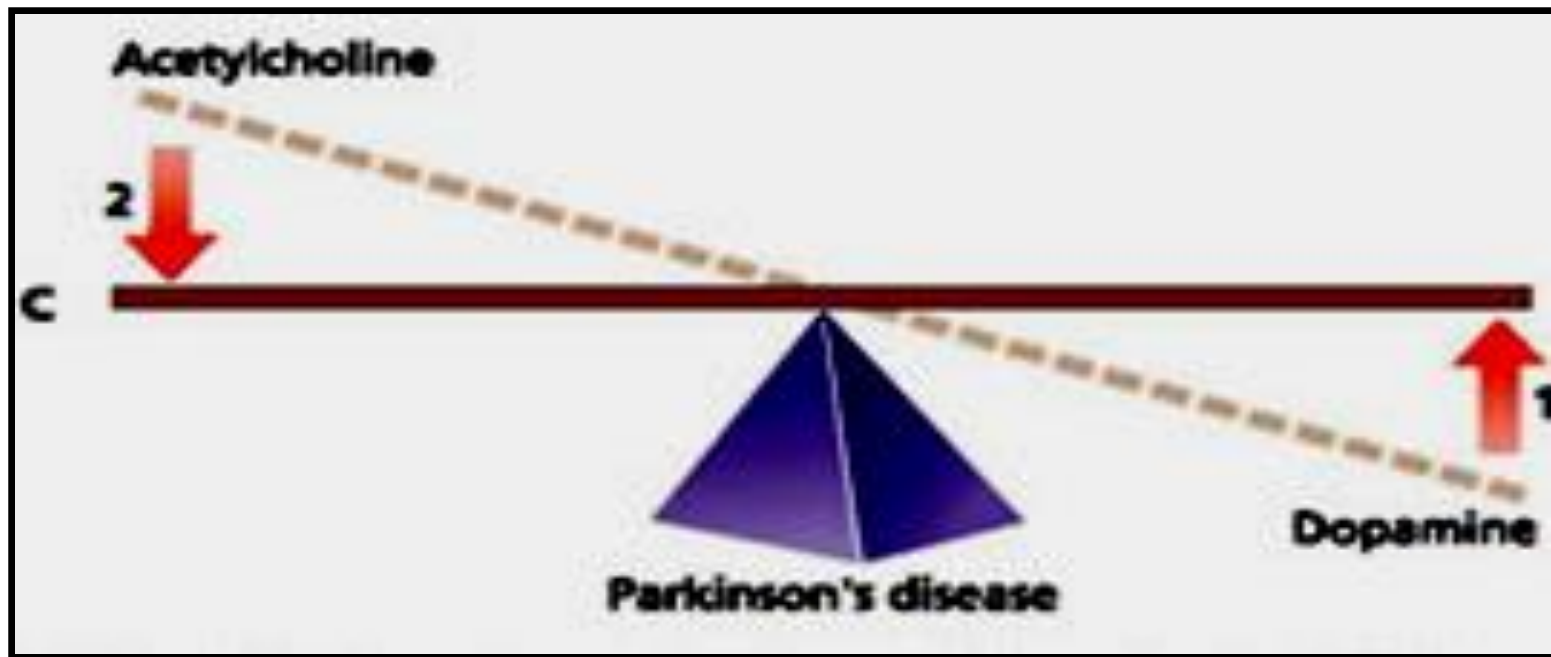
Parkinson's disease



Parkinson's disease

- **Deficiency of dopamine**
- **Predominance of Ach**

Drug Treatment



Main approach

Drugs to increase
dopaminergic
activity

Or

Drugs to block
cholinergic activity

1) Drugs that increase dopaminergic activities:

Dopamine precursor:

L-dopa + carbidopa

Dopamine agonists

- **Ergot derivatives: bromocriptine, pergolide**
- **Non ergot derivatives: pramipexole**

Dopamine releaser: amantadine

COMT inhibitors: entacapone

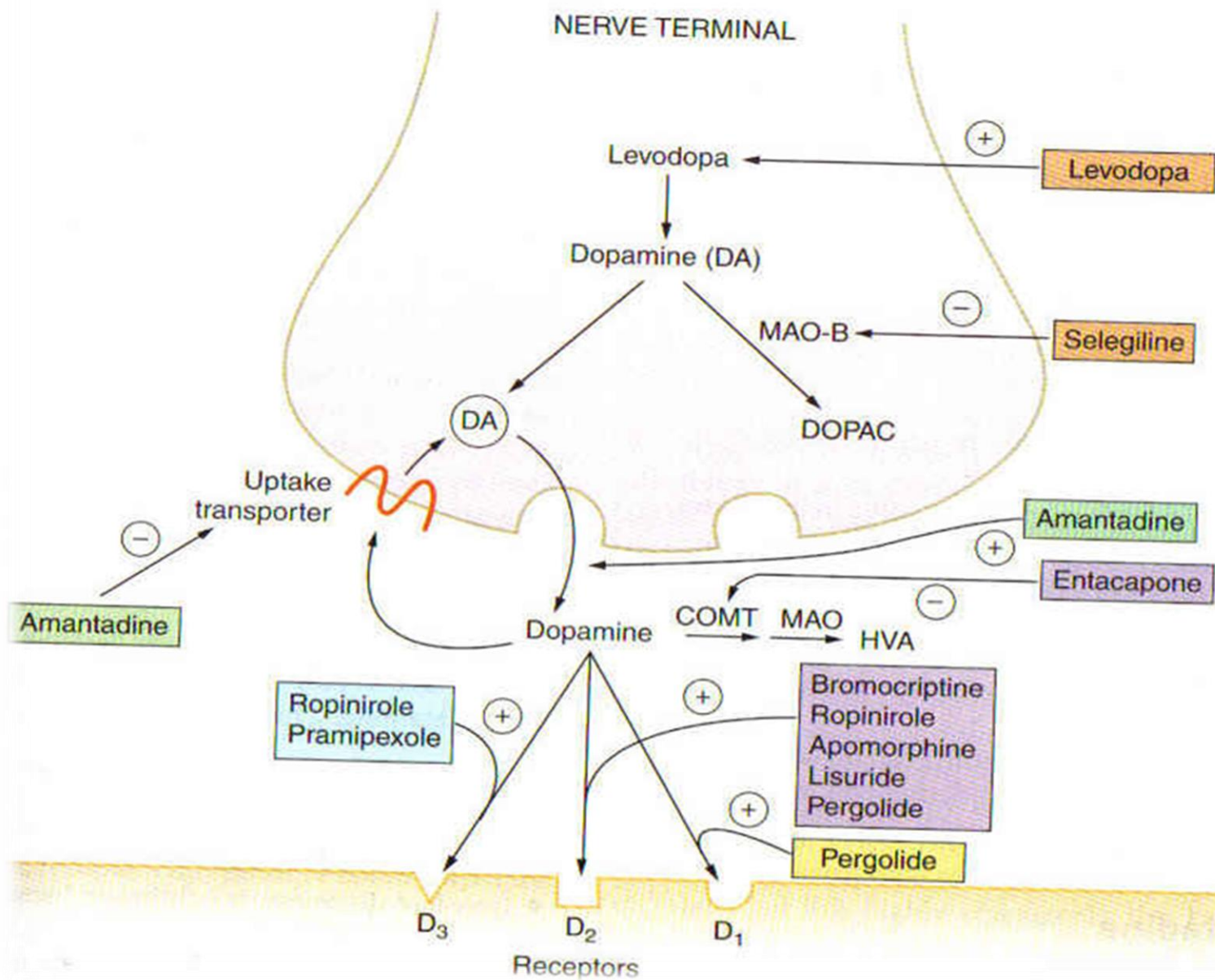
MAO-B inhibitors: selegiline

2) Drugs that decrease cholinergic activity (anticholinergic drugs):

Muscarinic antagonists

e.g. benztropine, trihexyphenidyl

Approach For treatment of Parkinson's disease

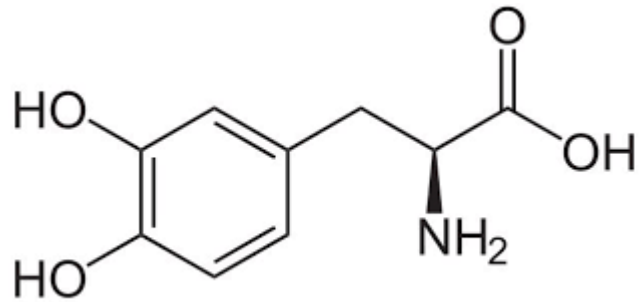


Levodopa (L-dopa)

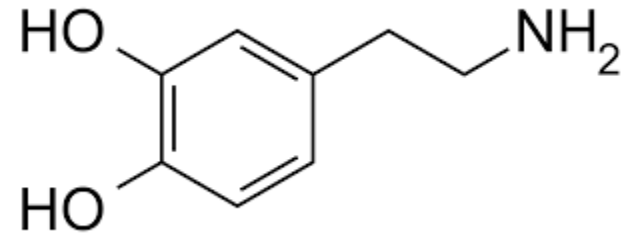
is a precursor of dopamine (converted into dopamine peripherally and centrally) by **dopa decarboxylase (*DC*)**.

99% L-dopa is decarboxylated to give dopamine in gut and liver.

L-dopa



dopamine



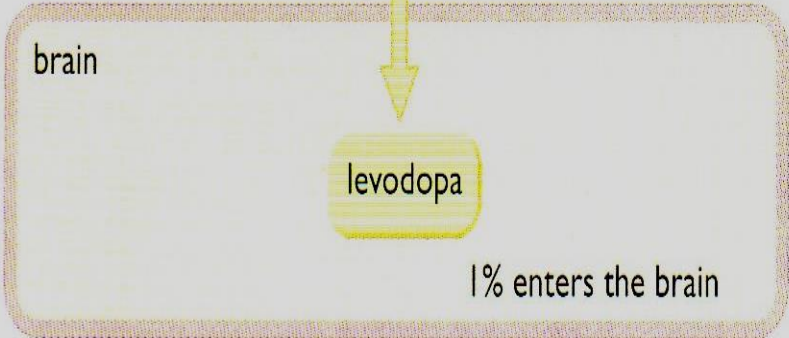
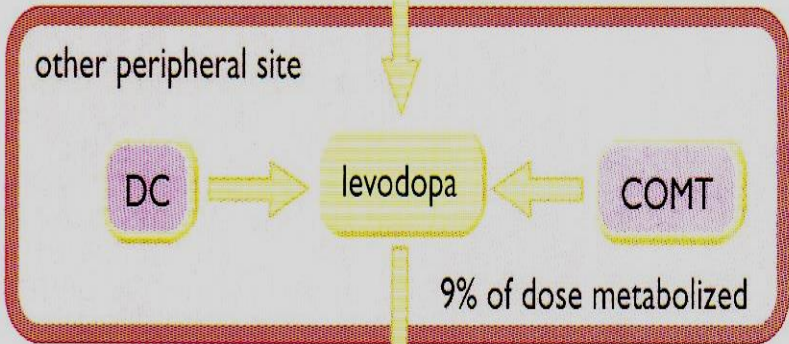
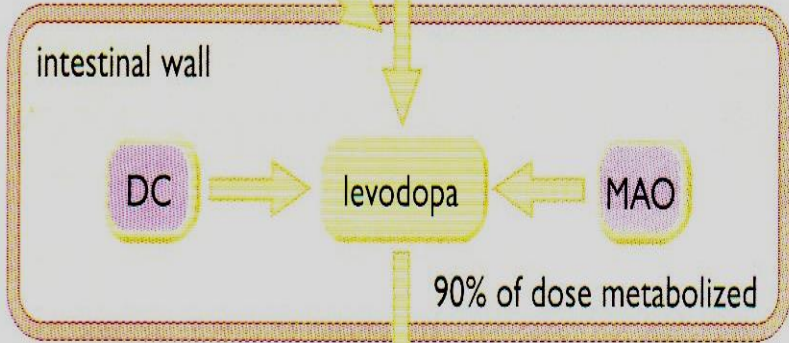
DC: Dopa decarboxylase enzyme

Levodopa (L-dopa)

- Dopamine formed peripherally is metabolized by **MAO & COMT enzymes**
- 1% L-DOPA crosses BBB to form dopamine centrally.
- L-dopa is usually given combined with **DC inhibitors (carbidopa or benserazide)** to prevent peripheral conversion of L-dopa to dopamine.

dietary aromatic amino acid competes for absorption

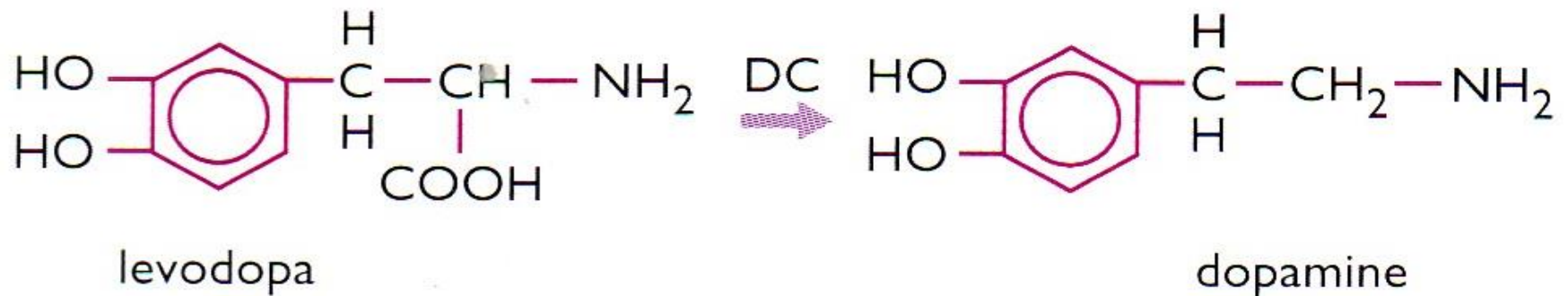
levodopa



DC: DOPA Decarboxylase

MAO: Monoamine Oxidase

COMT: Catechol-O-Methyl transferase



- DC = dopa decarboxylase
- AD = aldehyde dehydrogenase
- MAO = monoamine oxidase
- COMT = catechol-O-methyltransferase
- DOPAC = 3,4-dihydroxyphenylacetic acid
- HVA = homovanillic acid

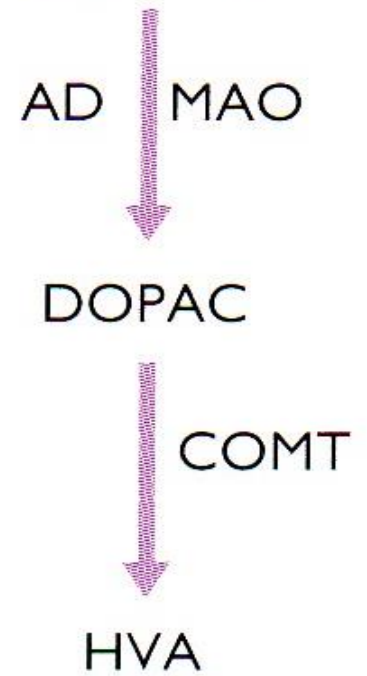


Fig. 14.51 Conversion of levadopa to dopamine and other metabolites.

DC inhibitors

Carbidopa, benserazide

- **are peripheral DOPA decarboxylase inhibitors**
- **Inhibit peripheral conversion of L-dopa to dopamine in GIT and other peripheral tissues (thus increasing $t_{1/2}$).**

Why do DC inhibitors act only peripherally?

Why are DC inhibitors combined with L-dopa?

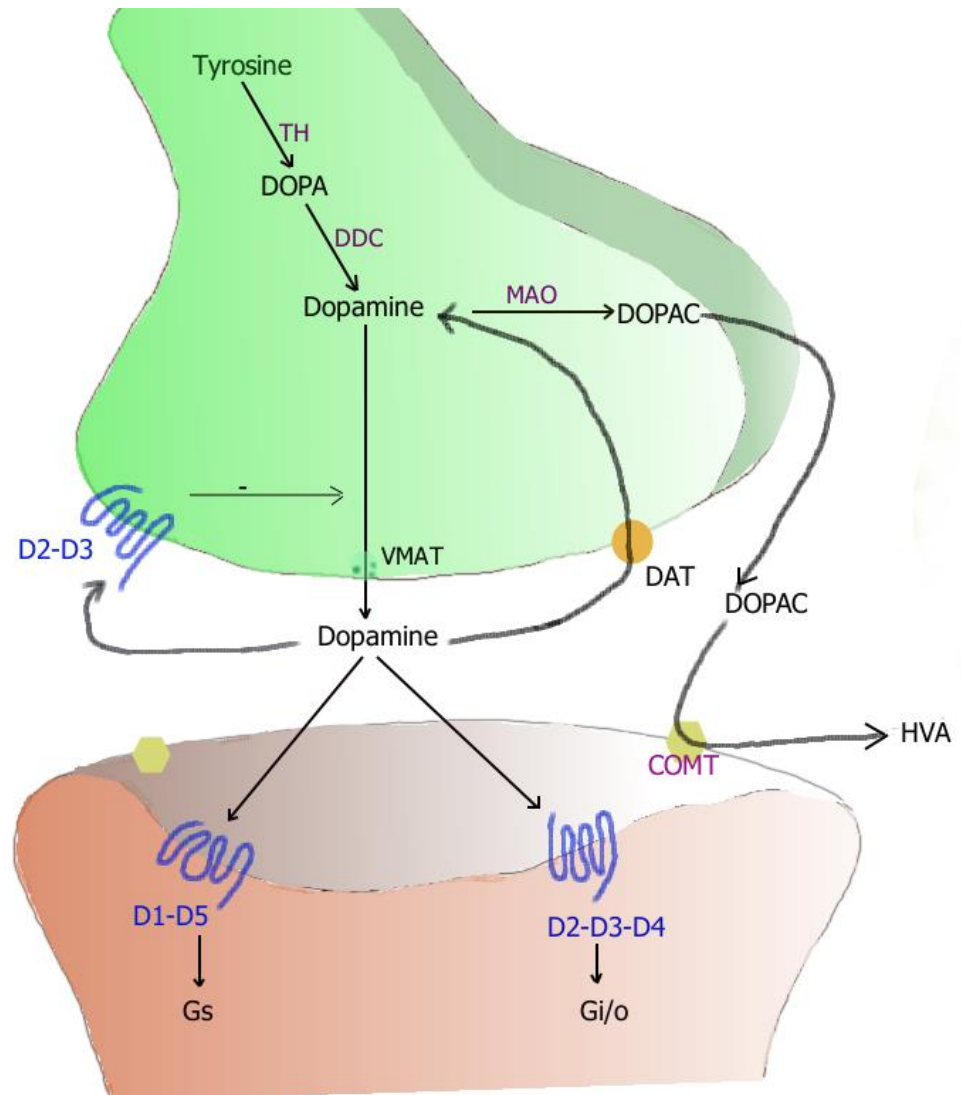
- **Lowers the effective levodopa dose**
- **Increase availability of levodopa to CNS.**
- **Reduce dose of levodopa and side effects.**

Levodopa (L-dopa)

- **Given orally (should be taken on empty stomach).**
- **absorbed from the small intestine and taken up to CNS by active transport system.**
- **High protein meal interferes with its absorption and transport into CNS**
- **Short duration of action ($t^{1/2} = 2$ h)
(fluctuation of plasma concentration).**

Levodopa (L-dopa)

- Dopamine acts upon dopaminergic
- (D1-D5) receptors
- G-protein linked receptors
- D1, D5: are excitatory
- D2, D3, D4 : are inhibitory.



Dopamine processing in a synapse. After release dopamine can either be taken up again by the presynaptic terminal, or broken down by enzymes. TH: **tyrosine hydroxylase** DOPA: **L-DOPA** DAT: **dopamine transporter** DDC: **DOPA decarboxylase** VMAT: **vesicular monoamine transporter 2** MAO: **Monoamine oxidase** COMT: **Catechol-O-methyl transferase** HVA: **Homovanillic acid**

Uses

- **The most efficacious therapy**
- **The best results of levodopa are obtained in the first few years of treatment.**
- **L-dopa ameliorates all signs of parkinsonism particularly bradykinesia & rigidity but does not cure the disease.**
- **Should not be used in parkinsonism associated with antipsychotic drug therapy.**

Adverse drug effects

Peripheral effects:

- **Anorexia, nausea, vomiting (due to stimulation of chemoreceptor trigger zone, CTZ).**
- **Cardiac arrhythmias.**
- **Mydriasis, orthostatic hypotension**

CNS effects (Psychological disorders):

mainly depression, delusions, hallucinations, confusion, sleep disturbances (insomnia).

Limitation of L-DOPA treatment

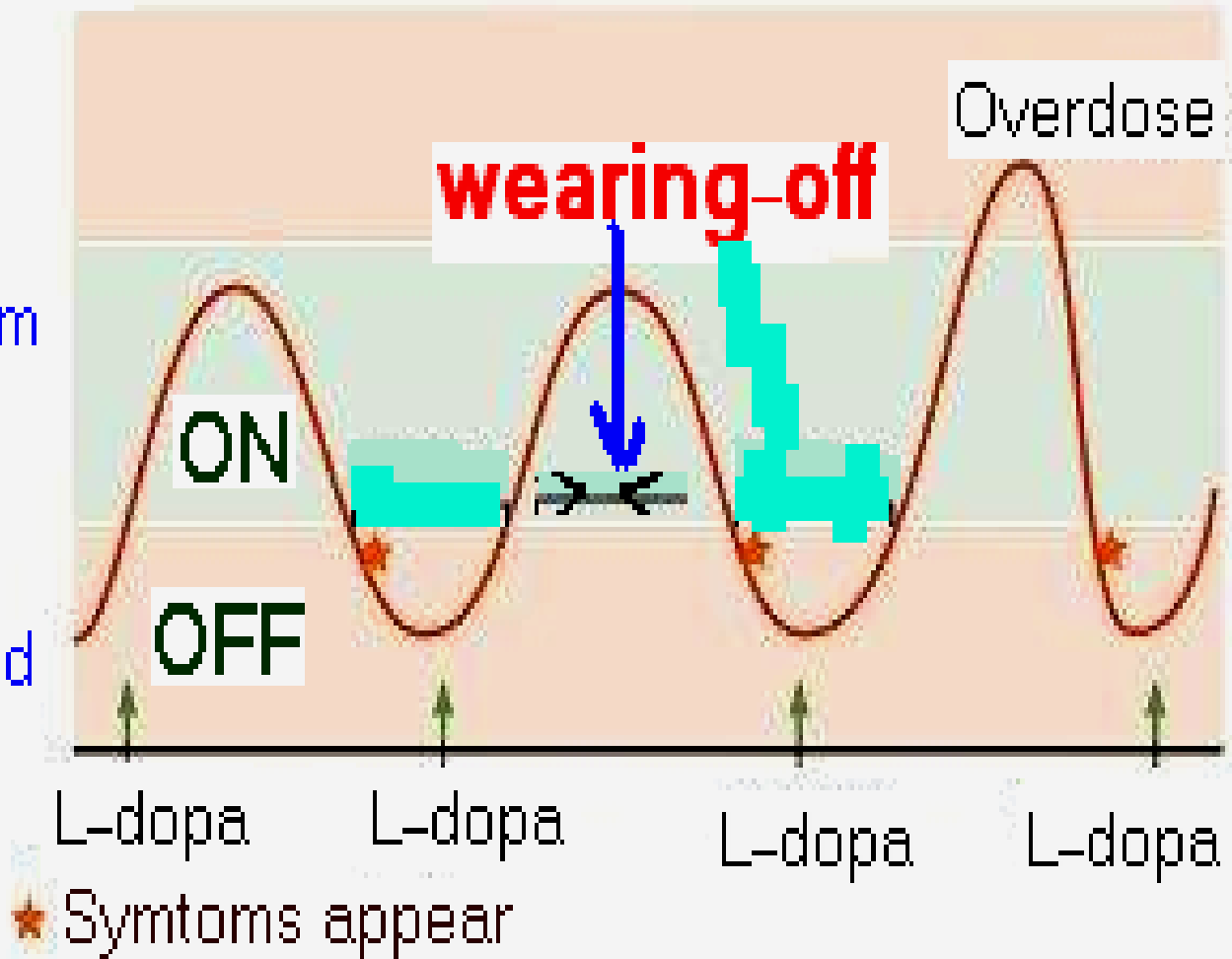
- **Dyskinesia** (involuntary movements occurs in 40 to 90% of patients) **due to fluctuating plasma levels of levodopa.**
- The dyskinesia can be reduced by lowering the dosage; however, the symptoms of parkinsonism may then reappear.
- **Wearing-off effect** (duration of “on” states becomes shorter).
- **On-off phenomenon** (On= improved mobility & Off=Akinesia or hypomobility).

Limitation of L-DOPA treatment

- Wearing off effect and on-off phenomena occur due to **progression of the disease and the loss of striatal dopamine nerve terminals.**

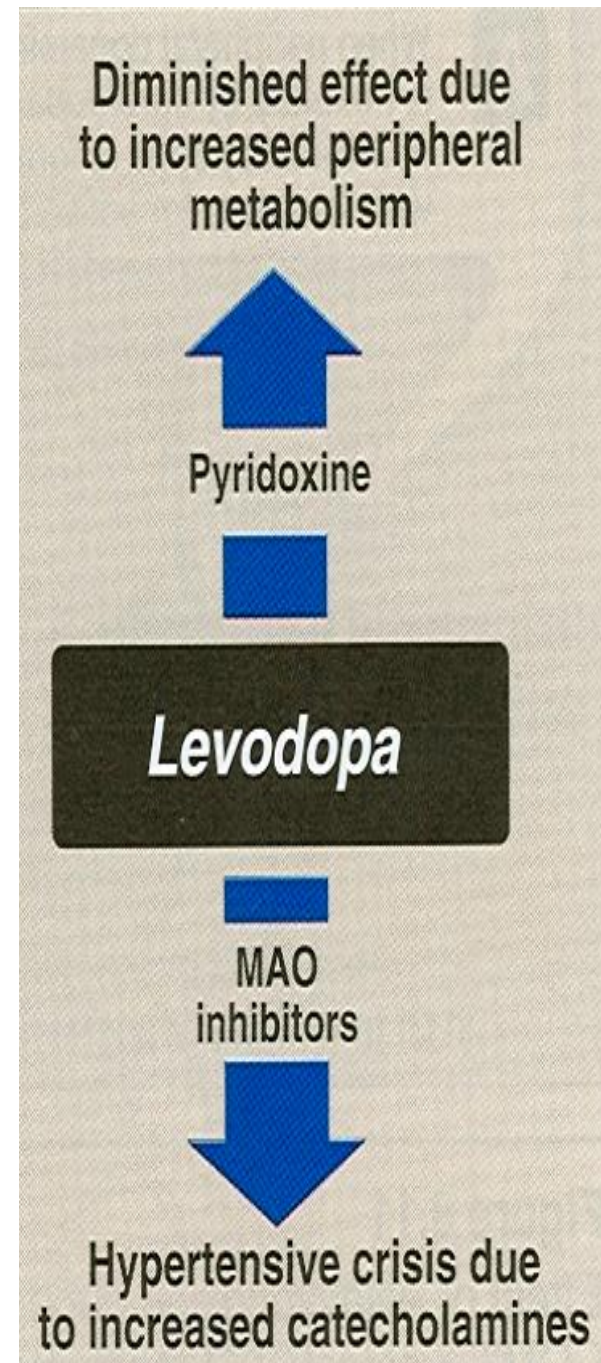
Dyskinesia and response fluctuations with L-DOPA

Overdose
Dyskinesia
Full symptom control
Symptoms uncontrolled



Drug Interactions:-

- High proteins meals.
- Pyridoxine (Vitamin B6).
- Nonselective MAO inhibitors (phenelzine)



Contraindications

- ✚ **Psychotic patient.**
- ✚ **Glaucoma (due to mydriatic effect).**
- ✚ **Patients with history of melanoma **Why?****

Note: L-dopa is a precursor of melanin

Dopamine receptor agonists

Bromocriptine, pergolide, Pramipexole

- **Ergot derivatives: Bromocriptine, pergolide**
- **Non ergot derivatives: Pramipexole**

Dopamine receptor agonists

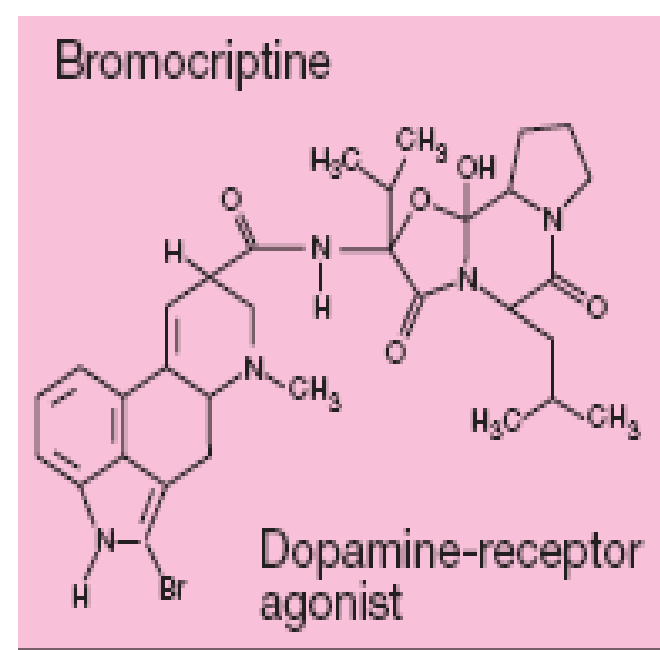
- **Have longer duration of action than L-dopa**
(less likely to cause dyskinesia than levodopa)
- **As monotherapy**, the dopamine agonists are less effective than levodopa.
- **In advanced stages, dopamine agonists are used as an adjunct to levodopa**, they may contribute to clinical improvement and reduce levodopa dosage needs.

Bromocriptine

- Is an ergot derivative
- D2 agonist
- Is given orally
- Half life= 6-8 h

Used for the treatment of

- Parkinson's disease
- Hyperprolactinemia (*galactorrhea*).
- Infertility in women.



Pramipexole

- ☀ **Non Ergot dopamine agonist**
- ☀ **D3 agonist**
 - **Is given orally**
 - **Has the advantage of being free radicals scavenger.**
- ☀ **Used alone as initial therapy or in combination with L-dopa.**
- ☀ **Side effects:** similar to L-dopa, but less dyskinesia.

Adverse effects of dopamine agonists

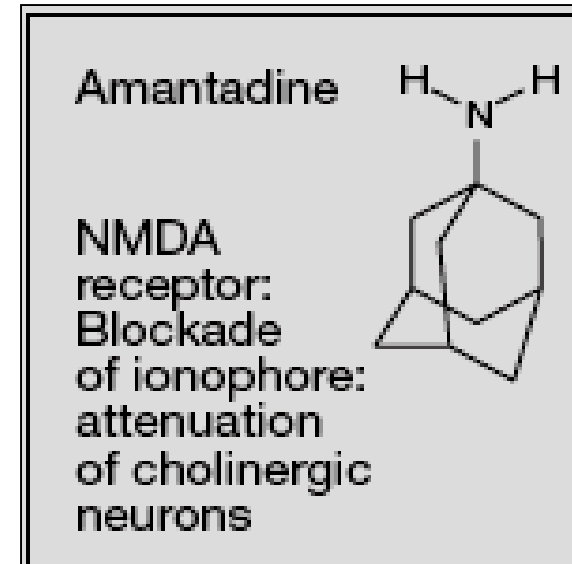
- **Nausea, vomiting, Cardiac arrhythmia**
- **Confusion, hallucinations, delusions**
- **Dyskinesia (*less prominent*).**

Contraindications

- **Psychosis**
- **Peripheral vascular disease (only ergot-derived agonists).**
- **Recent myocardial infarction**

Amantadine

- originally introduced as an **antiviral**.
- Amantadine increases dopamine release and reuptake.
- acts as an antagonist at **muscarinic** and **NMDA** receptors (*N-methyl-D-aspartate*).
- given orally with short half life
- most of the drug being excreted unchanged in the urine



Amantadine

- **Less efficacious than L-dopa**
- **Tolerance develops to its therapeutic effect after 6-8 months.**
- **Its benefits last only for short period and only used for L-dopa resistance.**
- **Useful in the early stages of parkinsonism or as an adjunct to levodopa therapy**
- **Amantadine and the anticholinergic drugs may exert additive effects on mental functioning.**

Adverse effects of amantadine

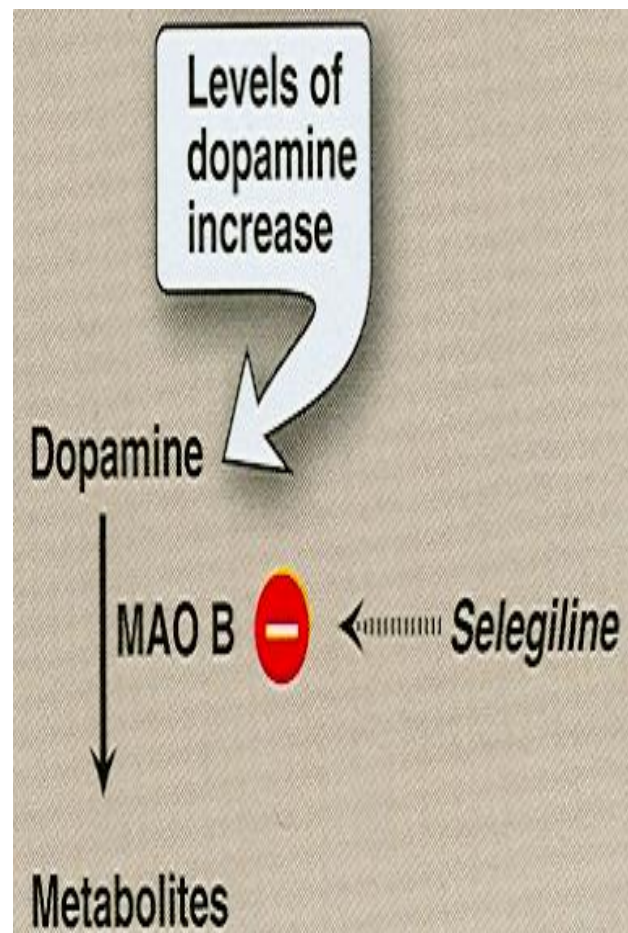
- Nausea, anxiety, insomnia, confusion, hallucinations (**dopamine like side effects**).
- Dry mouth, urinary retention (**anticholinergic effects**).
- Restlessness and hallucinations.
- Ankle edema, and livedo reticularis



Monoamine oxidase-B inhibitors

Selegiline

- is a selective irreversible inhibitor of MAO-B, an important enzyme for dopamine metabolism
- Blockade of dopamine metabolism makes more dopamine available for stimulation of its receptors.



Selegiline

- Selegiline may have neuroprotective effect due to:
- **Antioxidant activity** against **toxic free radicals** produced during dopamine metabolism.
- Selegiline is metabolized to desmethylselegiline, **Which is antiapoptotic.**

Uses of selegiline

- **Adjunctive to levodopa / carbidopa in later-stage parkinsonism to:**
 - **reduce the required dose of levodopa**
 - **delay the onset of dyskinesia and motor fluctuations that usually accompany long-term treatment with levodopa.**

Adverse effects of selegiline

- **At high doses, selegiline may inhibit MAO-A (hypertensive crises).**
- **May cause insomnia when taken later during the day.**

Contraindications

- co-administered with
 - Tricyclic antidepressants.
 - Selective serotonin reuptake inhibitors (may cause hyperpyrexia, agitation, delirium, coma).
 - Food restriction “low tyramine diet” is required.

COMT Inhibitors

(Catechol-O- methyl transferase) Inhibitors

Entacapone

- Acts peripherally to inhibit COMT enzyme required for L-dopa degradation
- Usually given in combination with L-DOPA and carbidopa to diminishes **peripheral** metabolism of L-dopa.

Side effects:

- L-Dopa side effects.
- Orange discoloration of urine

Tolcapone:

Peripheral and central COMT inhibitor

More lipid soluble than entacapone

More penetration into CNS

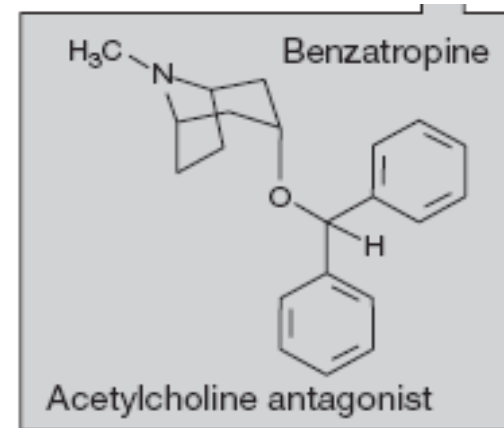
COMT inhibitors are used as adjuvant to L-dopa+ carbidopa to:

- **Decrease fluctuations**
- **Improve response**
- **Prolonged the ON-Time**

Anticholinergic Drugs

Benztropine, Trihexphenidyl

- **Central muscarinic antagonist.**
- **Has modest anti- parkinsonian actions.**
- **They improve tremor & rigidity but have little effect on bradykinesia.**
- **Provide benefit in drug-induced parkinsonism (due to antipsychotics).**
- **used during the early stages of the disease or as an adjunct to levodopa therapy.**



Adverse effects

- **Cycloplegia, mydriasis, dry mouth, urinary retention, constipation.**
- **Confusion, delirium, and hallucinations may occur at higher doses.**

Contraindications

- **Prostatic hypertrophy**
- **Glaucoma**
- **Intestinal obstruction**

Summary

- ❑ In mild cases, selegiline, amantadine or anticholinergics can be used.
- ❑ Levodopa and carbidopa is the main treatment
- ❑ All other medications are adjuncts to levodopa therapy
- ❑ Other useful drugs include bromocriptine (dopamine agonist), selegiline (monoamine oxidase-B inhibitor), amantadine (enhances dopamine release) and benztropine (muscarinic receptor antagonist, that is used for parkinsonism caused by antipsychotic drugs.

THANK YOU