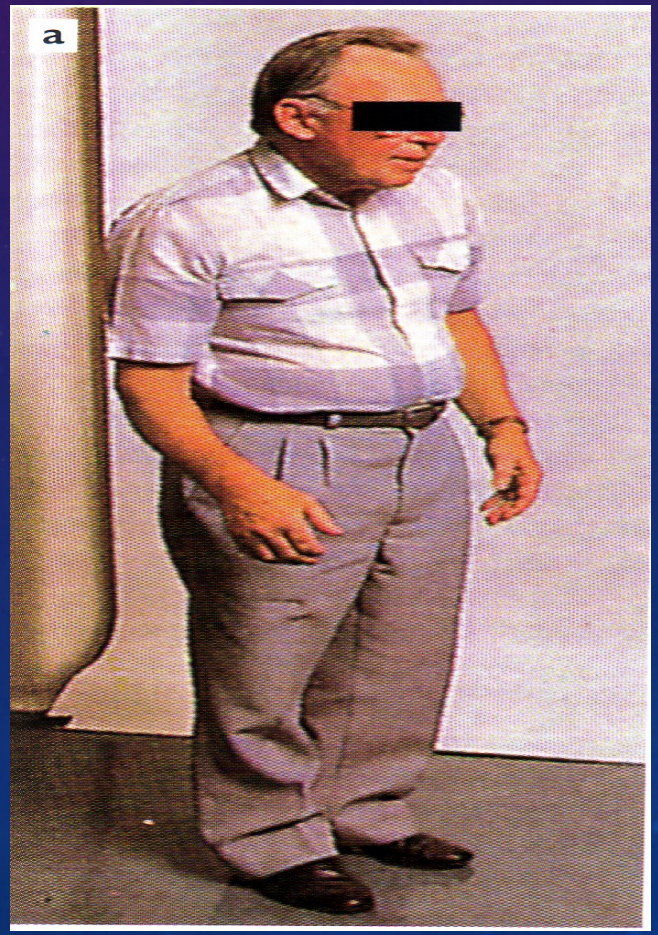
DRUGS IN PARKINSONISM

ILOS

Describe the pharmacological approach for treatment of Parkisonism

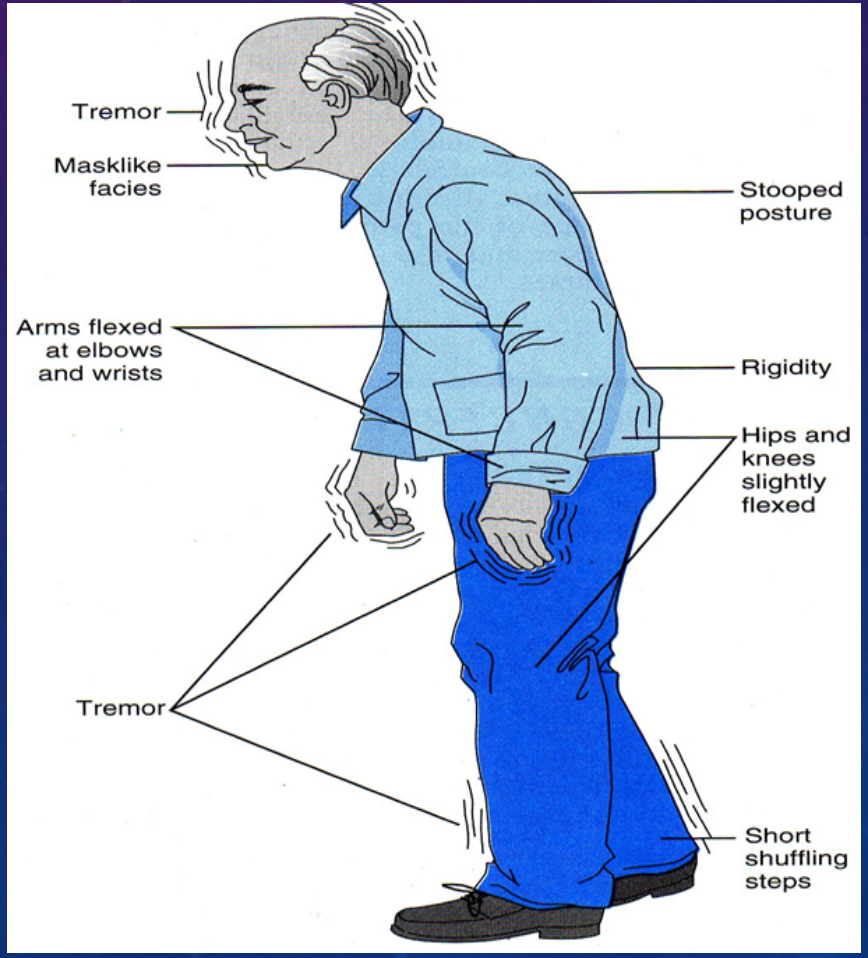
Detail on the pharmacokietic aspects and pharmacodynamic effects of drugs used to treat Parkisonism



DRUGS IN PARKINSONISM

A progressive disorder that occur mainly in the elderly

- Tremor at rest
- Muscle rigidity
- Hypokinesia
- Postural instability



APPROACH FOR TREATMENT

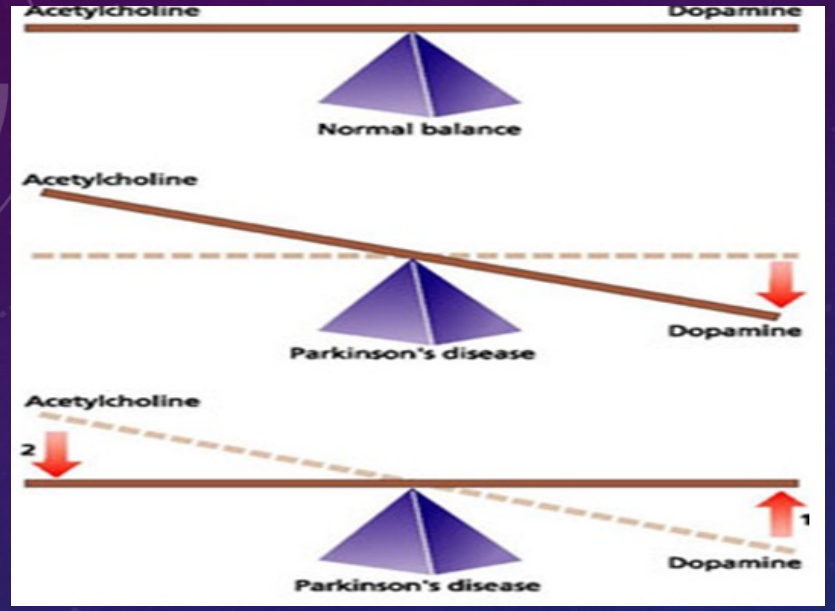
Replacement of dopamine by levodopa

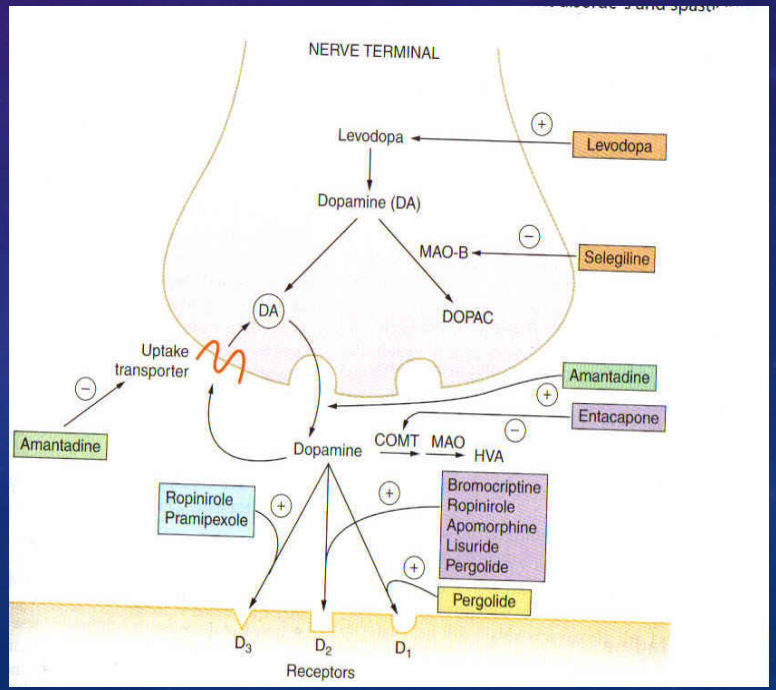
Drugs that mimic the effects of dopamine at D2& D3-receptors

MAO-B inhibitors e.g. selegiline

Drugs that release dopamine e.g. amantadine

Muscarinic acetylcholine antagonists e.g. benzatropine



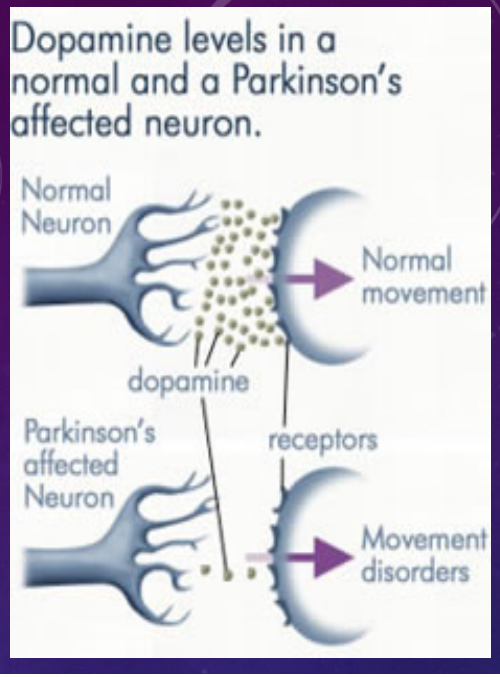


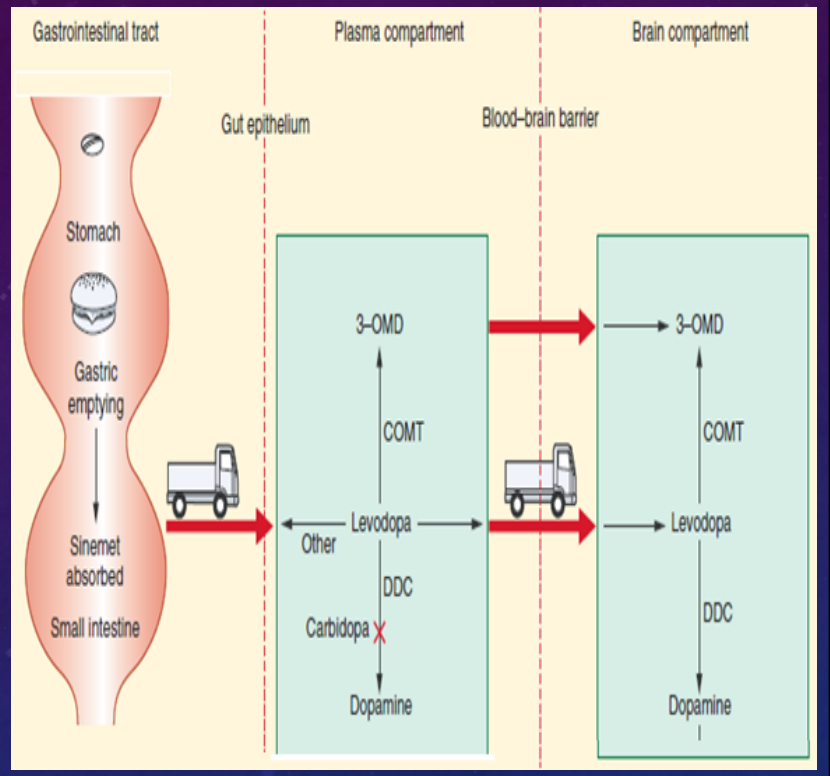
LEVODOPA

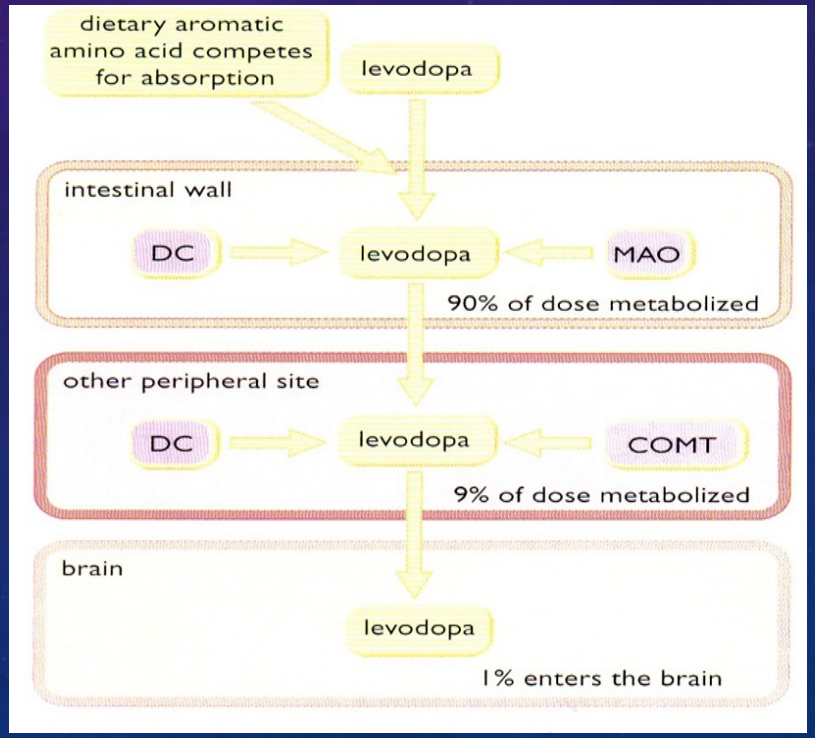
Combined with peripheral dopa decarboxylase inhibitors (carbidopa, benserazide)

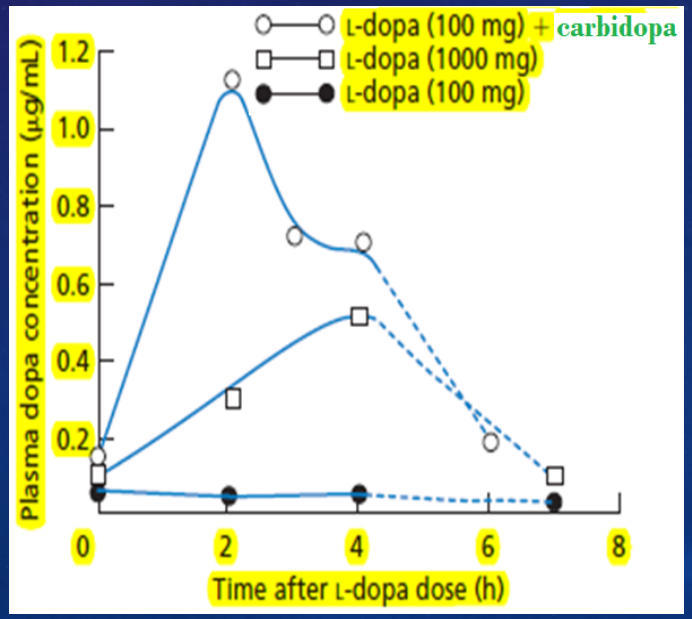
- Absorbed from the small intestine & crosses BBB by active transport, t½=2h

Effective against all types of parkinsonism except those associated with antipsychotic drug therapy.



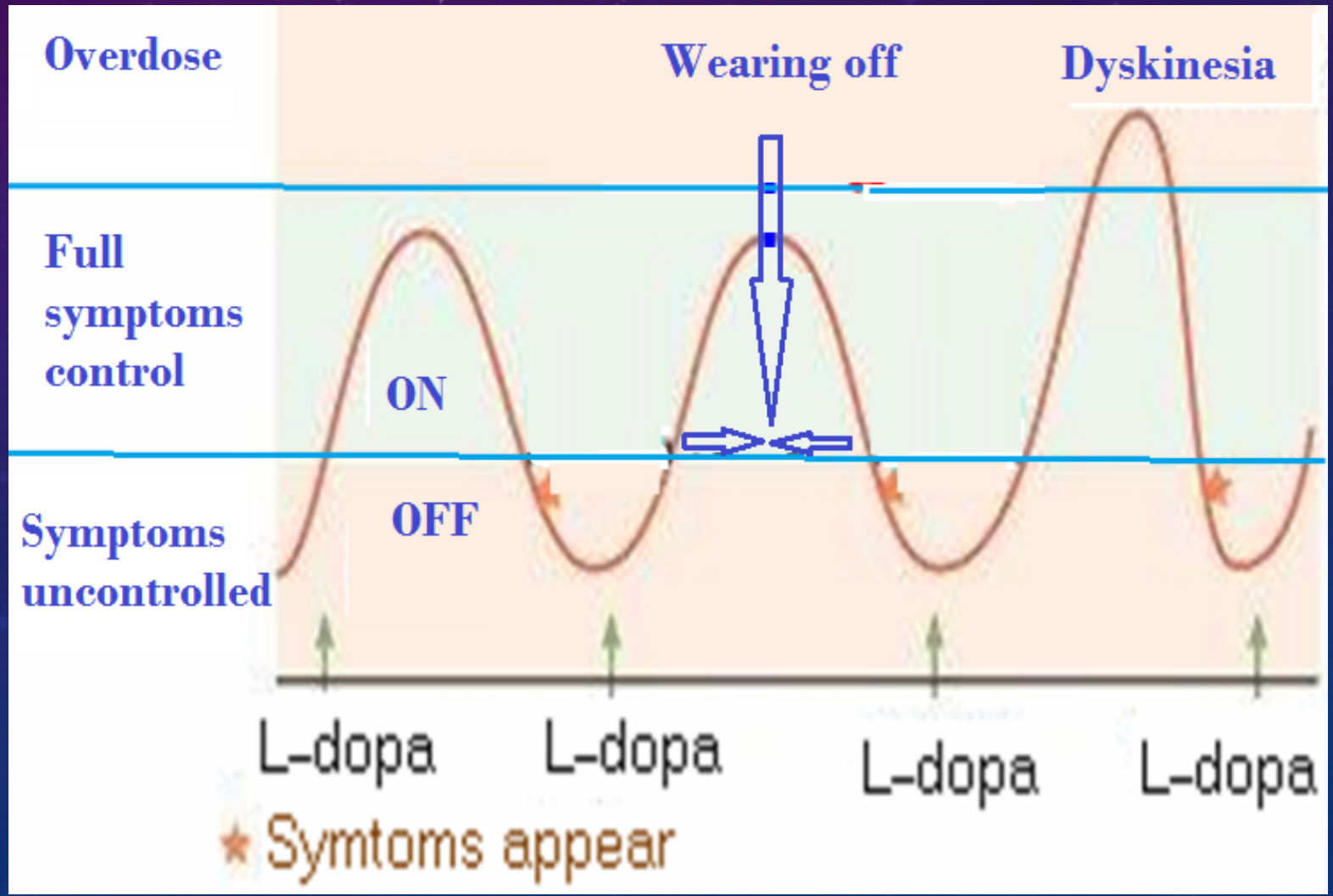






MOTOR FLUCTUATIONS

- *wearing-off* effect
- *on-off* effect
- *Dyskinesias*



ADRS

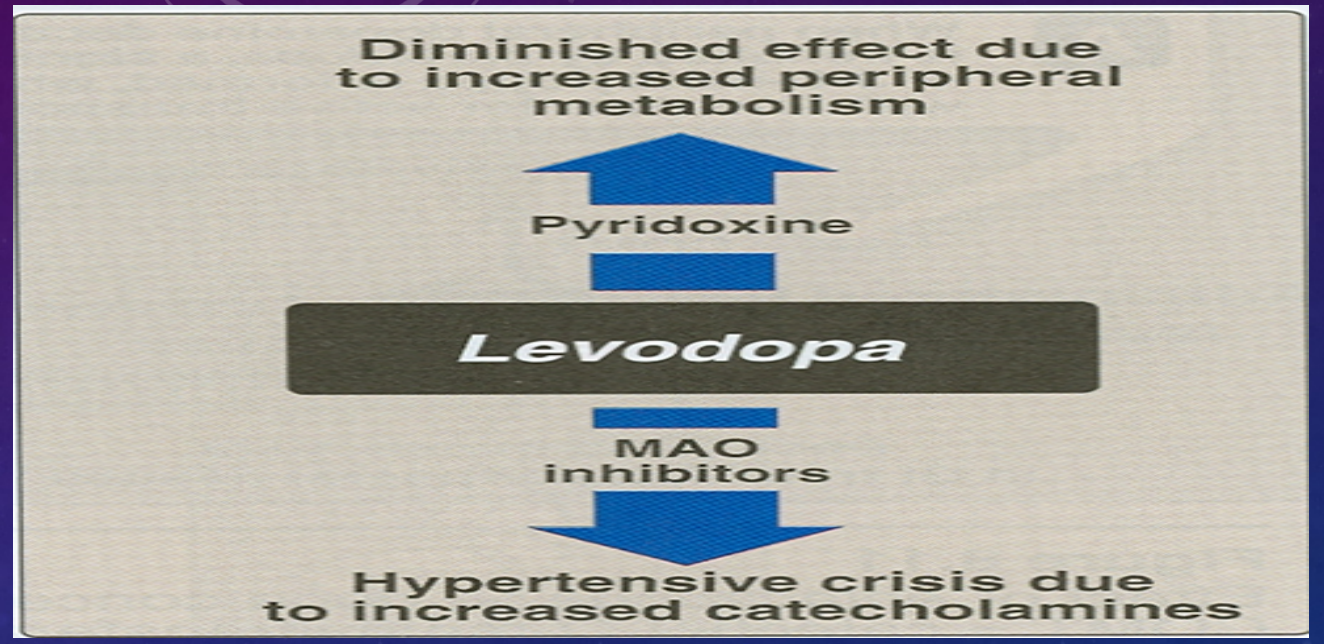
Orthostatic hypotension

Cardiac arrhythmias

CNS ADRs
vivid dreams, delusions, hallucinations, confusion and sleep disturbances

CONTRAINDICATIONS

- Nonselective MAO inhibitors (phenelzine, tranylcypromine)
- Pyridoxine
- Adrenomimetic amines
- Cardiac arrhythmias or recent cardiac infarction
- Proteins ingested with meals



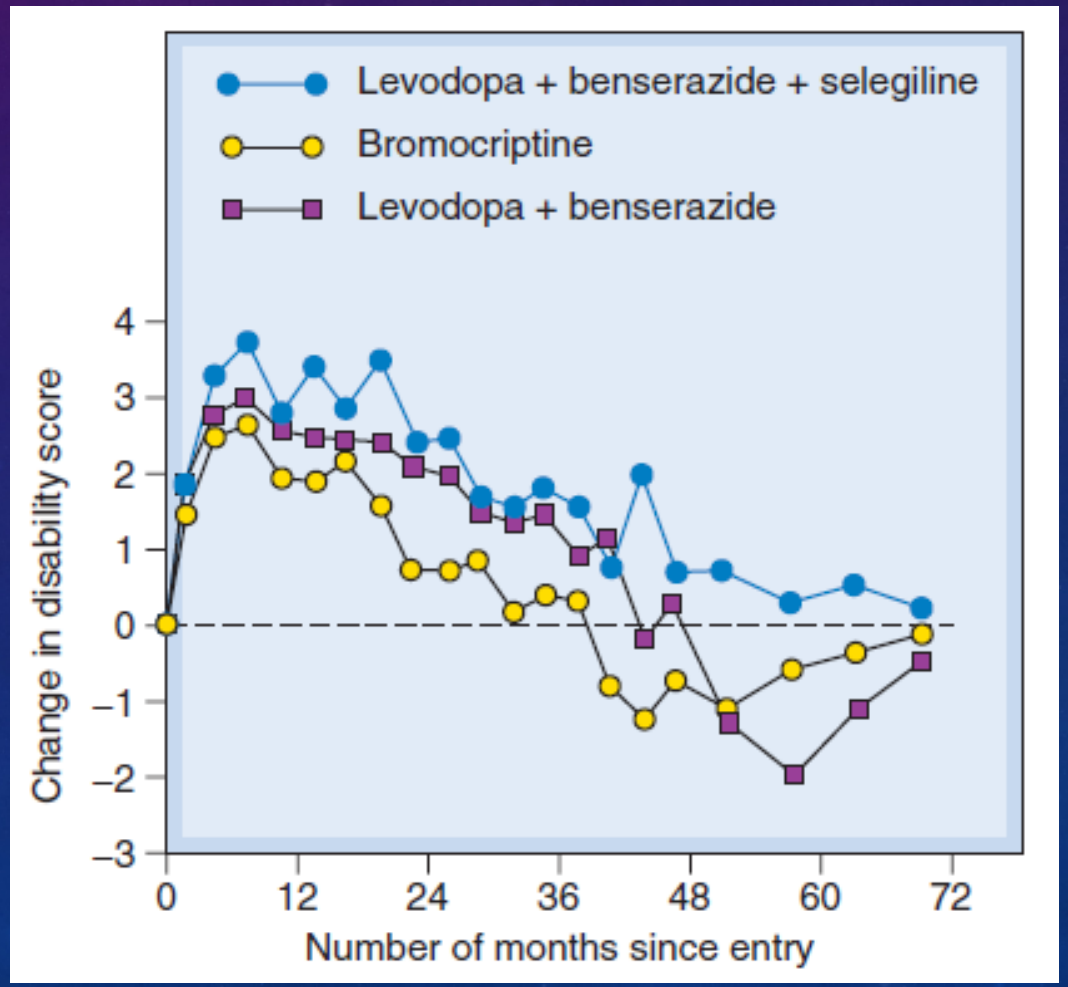
DOPAMINE RECEPTOR AGONISTS

Long duration of action ,less likely to cause dyskinesias than levodopa

As monotherapy, they are less effective than levodopa

Combined with levodopa in advanced stages →clinical improvement

+↓levodopa dosage needs



CLASSIFICATION

ERGOT DERIVATIVES

bromocriptine, pergolide

SYNTHETICS

pramipexole , ropinirole

BROMOCRIPTINE

An agonist at the D2-receptors and a partial D1-antagonist

Absorbed to a variable extent from the GIT ; peak plasma levels are reached within 1–2 hours after an oral dose.

Excreted in the bile and feces.

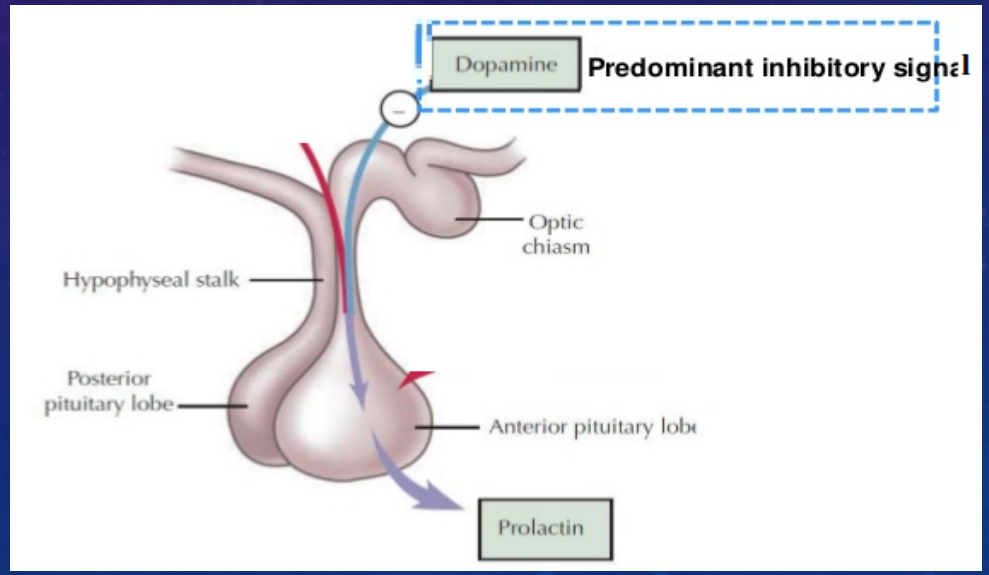
ADRS

Postural hypotension, nausea, somnolence

Confusion, hallucinations, delusions

Dyskinesias

Used for hyperprolactinemia



CONTRAINDICATIONS

- History of psychotic illness
- Recent myocardial infarction
- Active peptic ulceration
- Best avoided in patients with peripheral vascular disease

PRAMIPEXOLE

Has preferential affinity for the D3 family of receptors

Rapidly absorbed, reaching peak plasma concentrations in approximately 2 hours, excreted largely unchanged in the urine

Renal insufficiency may necessitate dosage adjustment

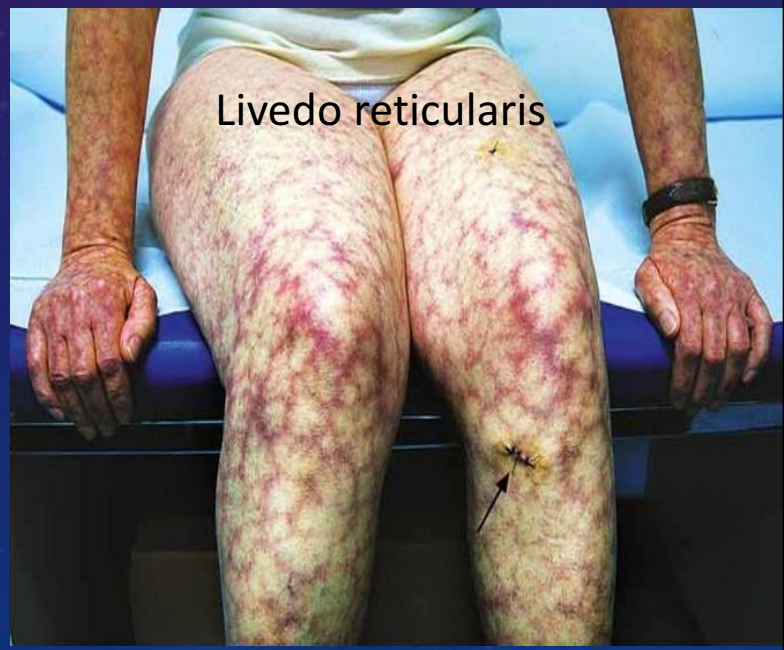
AMANTADINE

Modest effectiveness

Useful in the early stages of parkinsonism or as an adjunct to levodopa therapy

Affects dopamine release and reuptake, antagonist at muscarinic and NMDA receptors

t½=2-4h, most of the drug being excreted unchanged in the urine

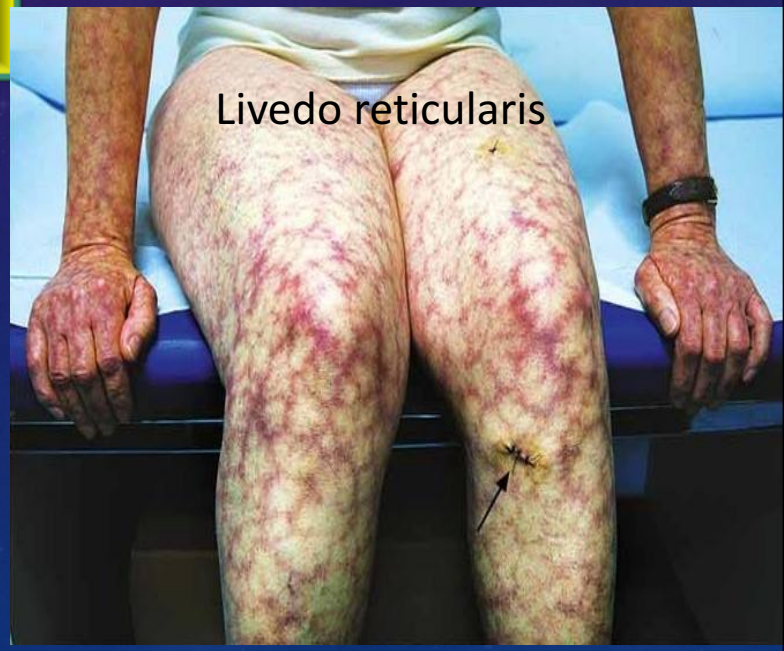


AMANTADINE

ADRS

Nausea, dizziness, insomnia, confusion, hallucinations

Ankle edema, and livedo reticularis



CONTRAINDICATIONS

Anticholinergics

In patients with a history of seizures or heart failure

SELEGILINE

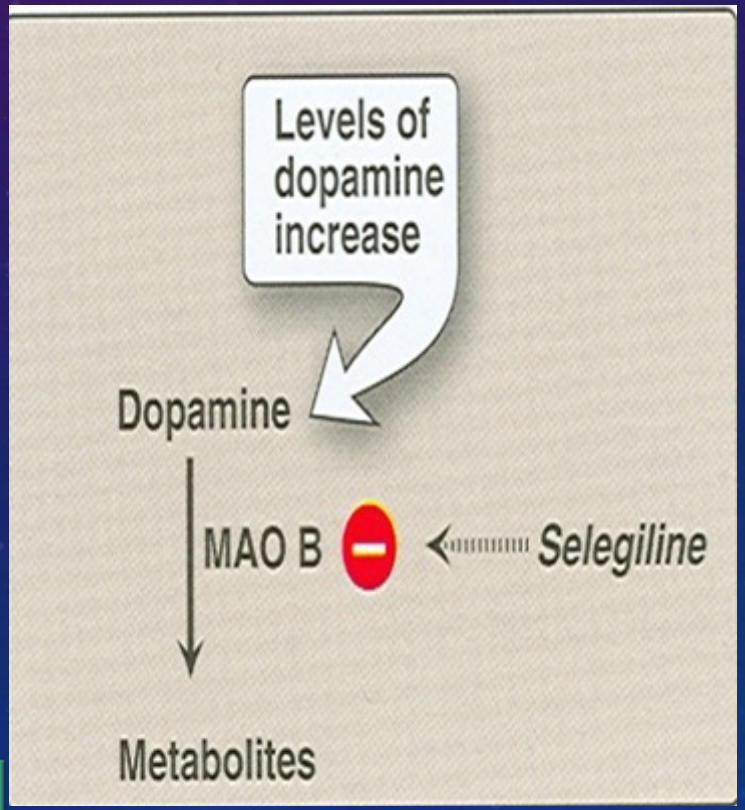
An irreversible inhibitor of MAO-B

Blockade of dopamine metabolism makes more dopamine available for stimulation of its receptors.

As monotherapy, may be effective in the newly diagnosed patient

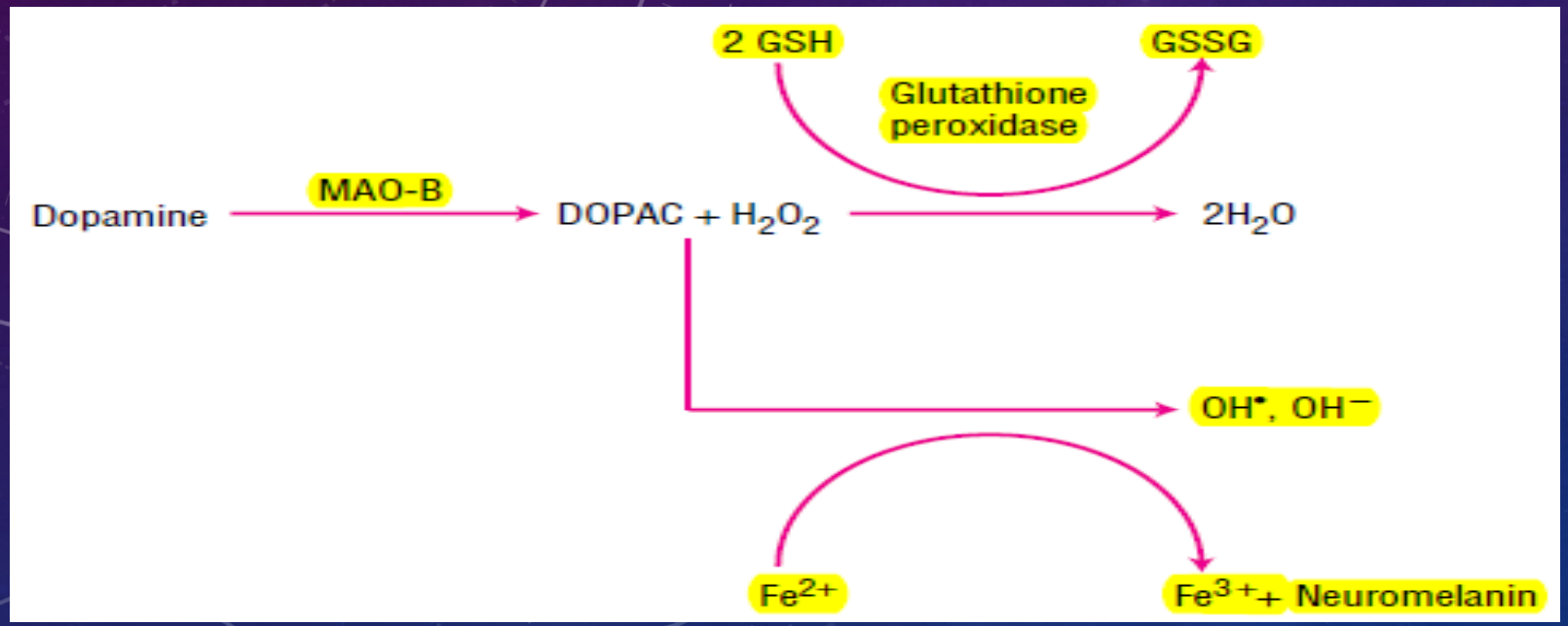
In later-stage, it is used in conjunction with levodopa-carbidopa →reduces levodopa dosage requirements

Minimize or delay the onset of dyskinesias and motor fluctuations that accompany treatment with levodopa



SELEGILINE, RASAGILINE

- It slows the progression of the disease by ↓the formation of toxic **free radicals** produced during the metabolism of dopamine.



Metabolized to desmethylselegiline, Which is **antiapoptotic**

SELEGILINE

ADRS

At higher doses may inhibit MAO-A

May cause insomnia when taken later during the day

May ↑the adverse effects of levodopa

CONTRAINDICATIONS

Should not be co administered with TCA, meperidine or SSRIs

ANTICHOLINERGIC DRUGS

Efficacy is due to blockade of muscarinic receptors in the striatum

Modest efficacy, used during the early stages of the disease or as an adjunct to levodopa

Anticholinergics can provide benefit in drug-induced parkinsonism

e.g. **Benztropine, Trihexyphenidyl.**

ADRS

Cycloplegia, dry mouth, urinary retention, and constipation

Confusion, delirium, and hallucinations may occur at higher doses

Trihexyphenidyl may cause withdrawal symptoms in patients receiving large doses.

CLINICAL CONTROVERSY

Some clinicians are concerned with possible long-term risks (motor fluctuations) of L-dopa and will delay or avoid its use even though it is more effective than other medications currently available. Others believe that motor fluctuations are a consequence of disease severity and progression rather than due to L-dopa itself. Individualized considerations of a patient's disability should guide all interventions for IPD.

case

M. S. is a 60-year old architect who designs buildings. His drawings are very detailed and they must be drawn to a specific scale. During the past month he has developed a slight tremor in his right hand that causes some embarrassment but does not interfere with function. He has, however, noticed that his writing and drawing have gotten much smaller, causing problems with his work. His primary care physician has referred him to a neurologist for evaluation. On examination, the neurologist notes some motor rigidity in the right arm. He also observes a slight slowing in the patient's walk and a reduction in the swing of his arms as he walks. What is the diagnosis, and how should the patient be treated?

Quiz 1?

- Great caution must be exercised in the use of this drug in parkinsonian patients who have prostatic hypertrophy :-
- (A) Benztropine
- (B) Carbidopa
- (C) Levodopa
- (D) Bromocriptine
- (E) Selegiline

Quiz 2?

- A drug that is used in the treatment of parkinsonism and will also attenuate reversible extrapyramidal side effects of neuroleptics is
- (A) Amantadine
- (B) Levodopa
- (C) Pergolide
- (D) Selegiline
- (E) Trihexyphenidyl