Parkinson’s disease (PD)

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:Objectives

Know drugs used in patients with Parkinson -1 .disease

.Know mechanism of action of each drug -2

Know side effects, interaction and -3 .contraindication of drugs

Parkinson's disease is a neurodegenerative muscle **movement** disorder that involves **dysfunction** in the basal ganglia (including **substantia nigra**) and the related .**brain** structures

Secondary Parkinsonism (pseudoparkinsonism) is the umbrella term given to a group of conditions that feature Parkinson's-type .symptoms (drugs effect)

Sign and symptoms : (the main !! RAFT)

Rigidity of skeletal muscles-1

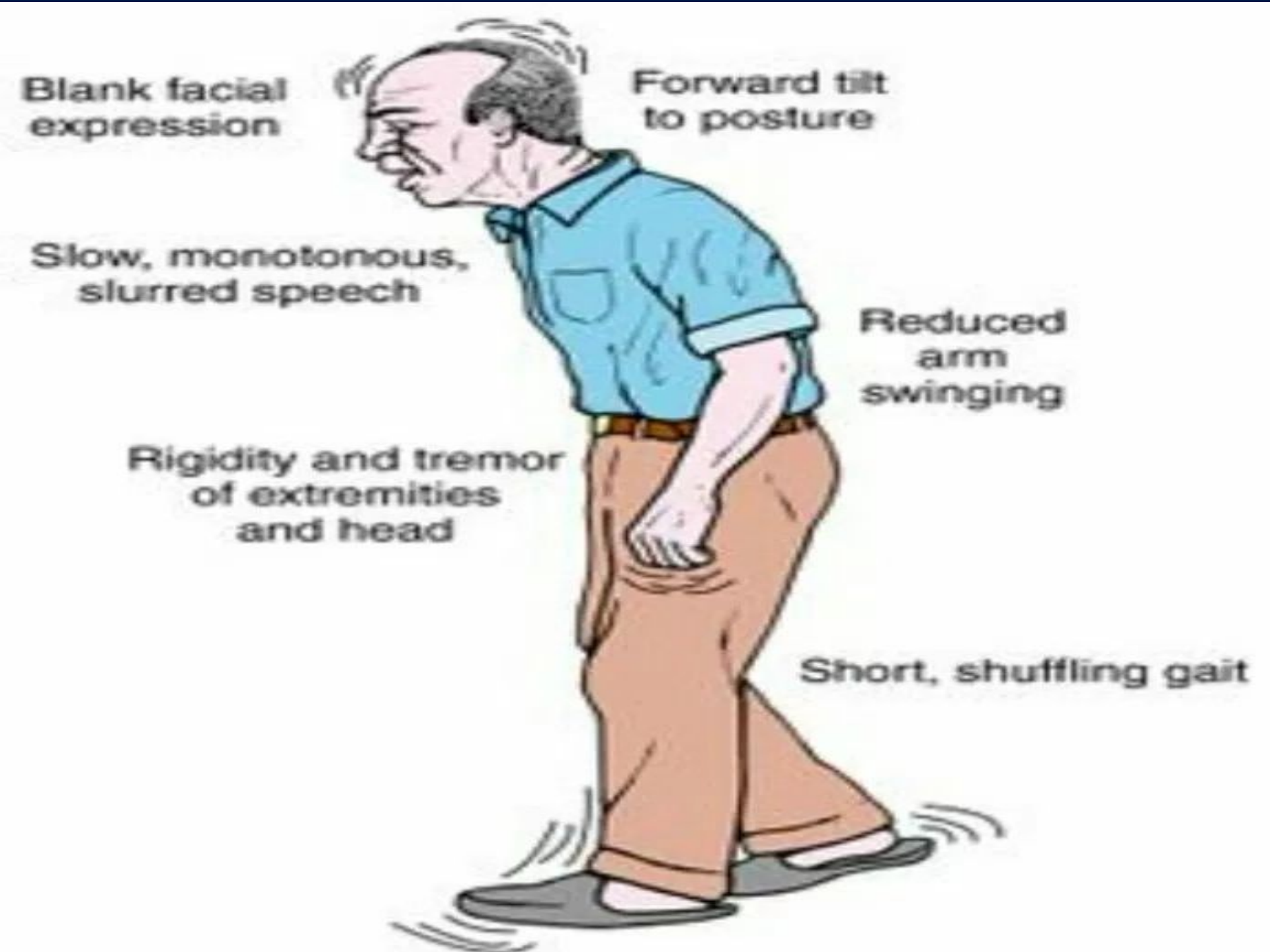
Akinesia (loss) or bradykinasea (slowing) of movement-2

Flat facies-3

Rest tremor -4

.. And Postural instability that can occur but is usually idiopathic

Other features: including


Blank facial expression
Forward tilt to posture
Slow, monotonous, slurred speech
Reduced arm swinging
Rigidity and tremor of extremities and head
Short, shuffling gait

Substantia nigra

The substantia nigra is part of the basal ganglia, it produces dopamine.

Dopamine plays a key role in the 'control' of movements via the signals it sends to the striatum

A healthy balance of dopamine enables precision of movement

Due to degeneration of the these neurons, less dopamine is produced

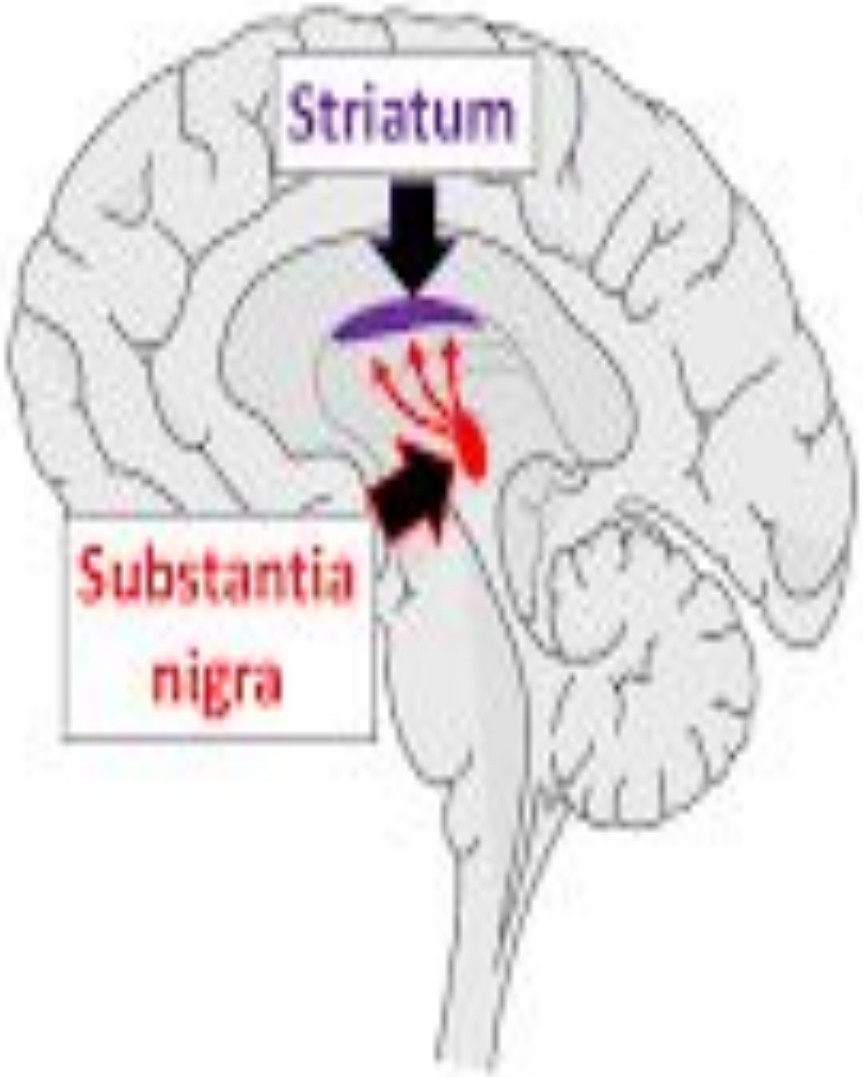
:What happen in PD

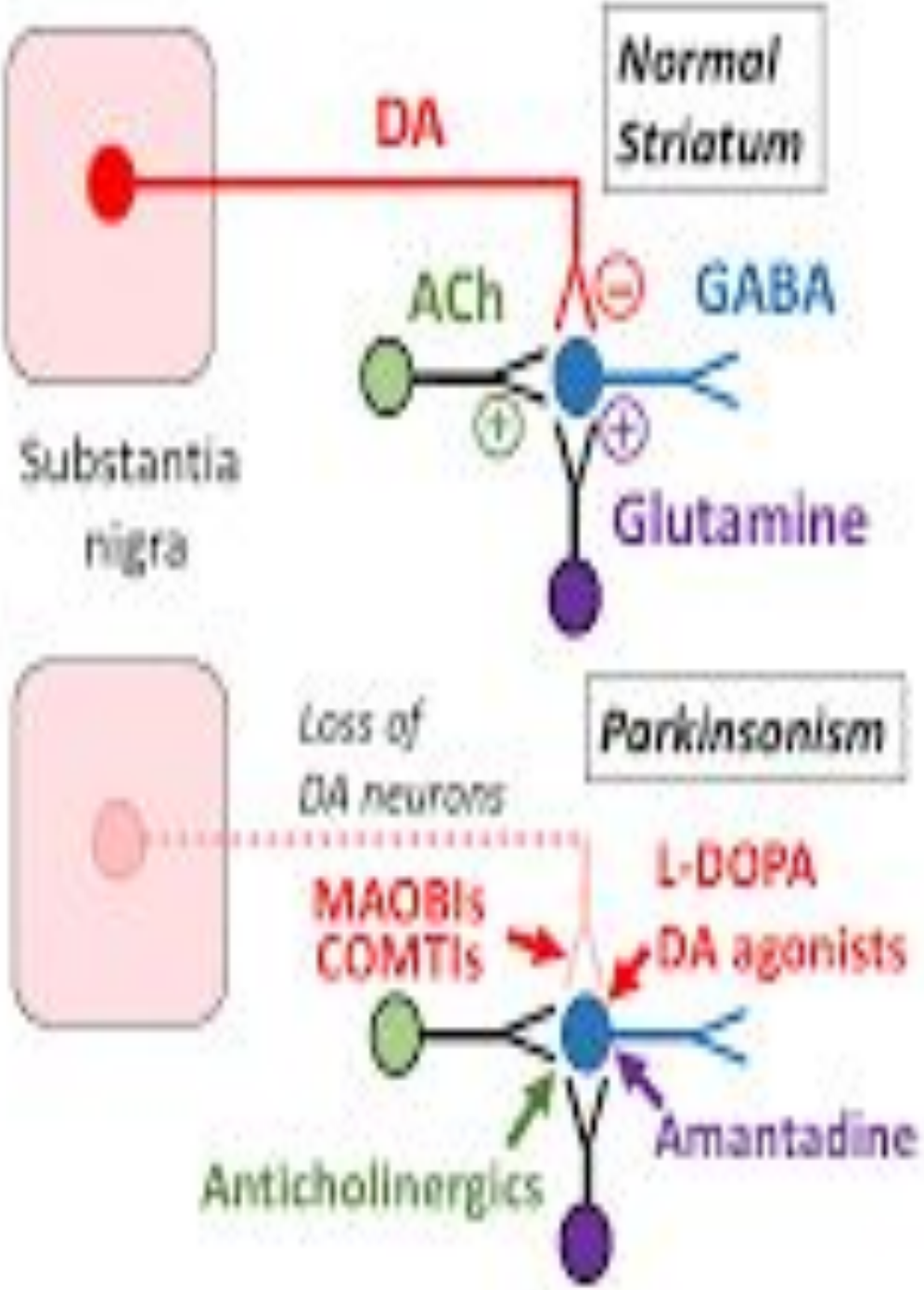
Normally Dopamine and Ach are present in balance in the .body

Degeneration of dopamine neurons (destruction of n.)in the substantia nigra leads to decrease in the levels of dopamine in straitum (straital dopamine normally responsible for .inhibitory activity of GABA) **occur in parkinsonism**

The reduction of dopamine leads to more dominant actions of Ach (cholinergic n.) On GABA. (Ach is an **excitatory** n. so .this lead to **more excitatory action**)

.So the **balance** between Ach and dopamine is **disturbed**


Striatum
Substantia nigra


Normal Striatum
DA
ACh
GABA
Substantia nigra
Glutamine
Parkinsonism
Loss of DA neurons
MAOBIs
COMTIs
L-DOPA
DA agonists
Amantadine
Anticholinergics

Note:
:Dopaminergic tracts in the brain

Mesolimibic-mesocrtical pathway: responsible for **-1** .regulation **mentation** and **mood**

.Nigrostraital tract: for **extrapyramidal** function **-2**

Tuberoinfundibular pathway: for **prolactin -3** .release

.Chemoreceptor trigger zone(CTZ): for **emesis -4**

The strategies of drug treatment in PD

To **restore** the balance between Ach and dopamine :WE MUST

A-**Increasing dopamine activity** in the brain by

Increase **synthesis** of dopamine or-1

Decrease **uptake** of dopamine or-2

Giving dopamine **agonist** -3

.Using drugs that **inhibit metabolism** of dopamine -4

or

B- Decreasing muscarinic cholinergic activity in the brain (anticholinergic drugs)

or

.C-Both

:DRUGS USED IN PD

LEVODOPA AND CARBIDOPA **-1**

DOPAMINE RECEPTOR AGONISTS **-2**

MONOAMINE OXIDASE **B** INHIBITORS (**MAOI B**) **-3**

CATECHOL-O-METHYLTRANSFERASE **-4**
INHIBITORS (**COMT inhibitors**)

AMANTADINE **-5**

ACETYLCHOLINE-BLOCKING DRUGS **-6**

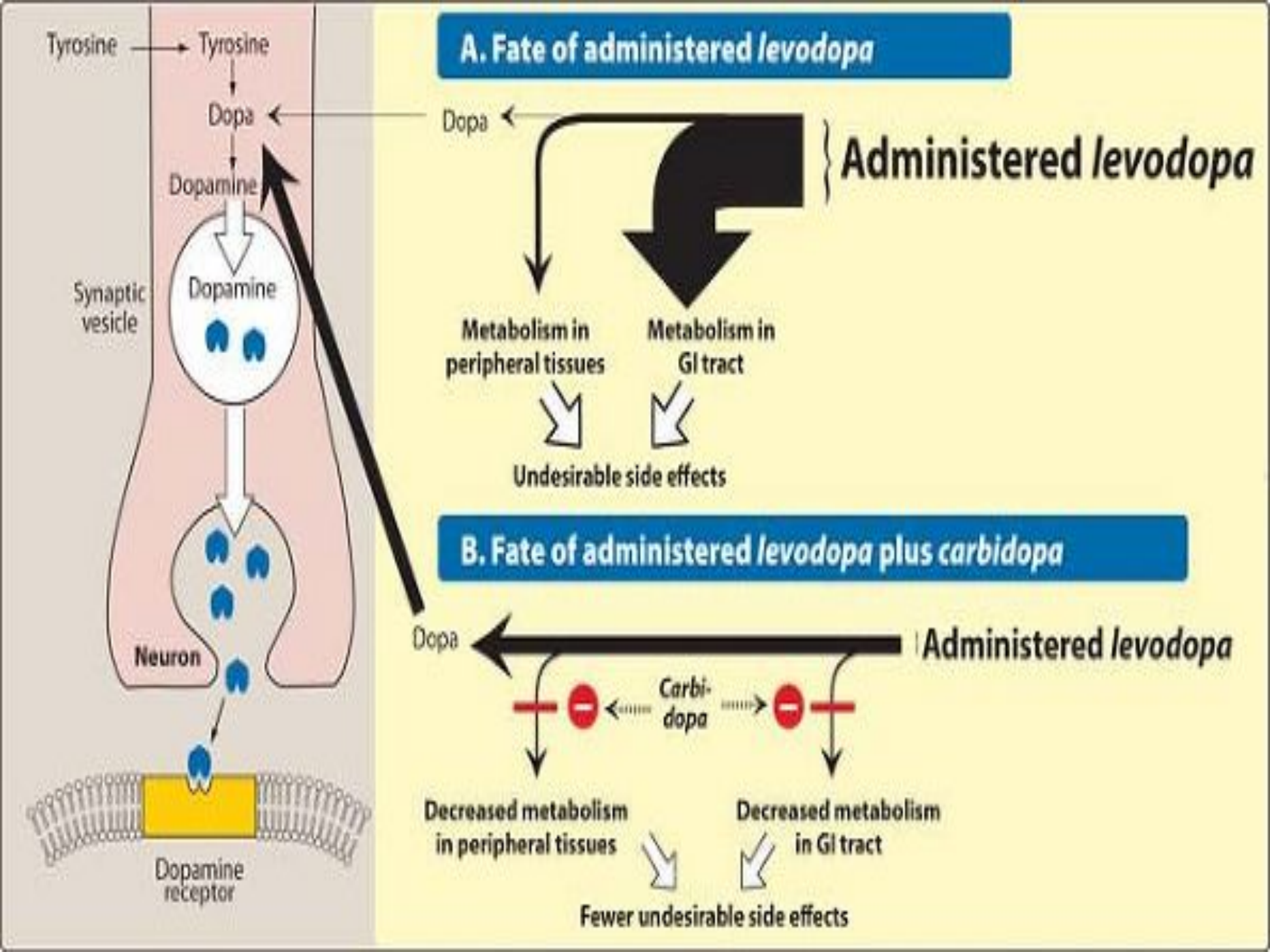
:DRUGS USED IN PD

:Levodopa(L-dopa) and carbidopa .1

L-dope is used because **Dopamine** has **low** bioavailability and does **not cross BBB**. (i.e dopamine is not benefit as .drug in PD)

Thus L-dopa is used bs it **crosses BBB** and converts **by dopa decarboxylase** to dopamine in **peripheral** tissues and .**brain**

The conversion of l-dopa to dopamine in periphery of no Benefit (**Bs** dopamine not cross BBB and the defect is central)so the amount of drug that enter CNS is small this means we **need large dose** of drug to produce) .(better effects but this will lead to **increase side effects**


Tyrosine
Tyrosine
Dopa
Dopamine
Synaptic vesicle
Dopamine
Neuron
Dopamine receptor
A. Fate of administered levodopa
Dopa
Administered levodopa
Metabolism in peripheral tissues
Metabolism in GI tract
Undesirable side effects
B. Fate of administered levodopa plus carbidopa
Dopa
Administered levodopa
Carbi-dopa
Decreased metabolism in peripheral tissues
Decreased metabolism in GI tract
Fewer undesirable side effects

For this reason Levodopa is usually given in **combination** with peripheral **decarboxylase inhibitors** (e.x: carbidopa or benserazide), this :combination of high benefit **because**

Carbidopa does **not cross** **BBB**-1

Inhibits dopa decarboxylase in the **peripheral** tissues, not -2 .centrally

More access of L-dopa to **CNS** -3

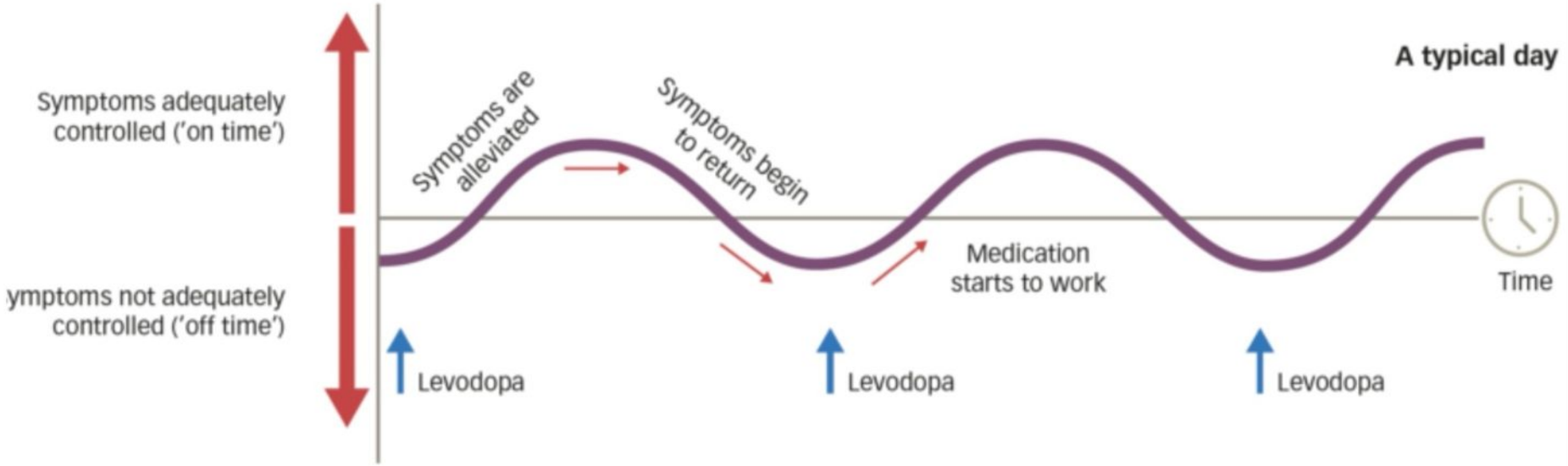
Lower doses of levodopa are benefit (administration of -4 carbidopa may **reduce** the **daily requirements** of levodopa .by approximately **75%**)

.Fewer side effects -5

This disease is **incurable** and leads to increasing disability with time, but pharmacologic treatment may **relieve motor symptoms** and **improve .the quality** of life for many years

The **response** to drug **decrease** by time, and change in response(from akinesia to dyskinesia) occurs due to **fluctuation in L-dopa level** in plasma and this called **on-off phenomenon** of l-dopa (i.e **levodopa** is intermittently taken over the course of a day, the level of dopamine will rise and fall. These dopamine level **fluctuations**, in combination with the **.loss of dopaminergic neurons**, are thought to **cause dyskinesia)**

.dyskinesia: uncontrolled, involuntary movement**



Pharmacokinetics: this drug

Absorbed **rapidly** from small intestine (especially when it's **empty).**-1 .Thus, Better to be prescribed **before meal**

.Taken by **mouth** -2

.**Peak plasma** conc. reached within **1-2 hrs** with t1/2 =1-3 hrs (**short**) -3

only about **1–3**% of administered levodopa actually enters the brain -4 unaltered, the remainder is metabolized extracerebrally by decarboxylation (**but** if carbidopa is added **10%** l-dopa enter brain)

Meals rich in **proteins** like lucin **interfere** with its **binding** and -5 .**absorption**

.**Iron** can **reduce** the amount of l-dopa **absorbed** by the body -6

About **two thirds** of the dose appears in the **urine** as metabolites -7 .within 8 hours of an oral dose

Should be **started** and **discontinued gradually** (to **decrease side** -8 .**effects**)

.**Adverse effects:** They are **dose related**

a- GIT : When levodopa is given **without** a peripheral decarboxylase inhibitor, **anorexia, nausea and vomiting** occur in about **80%** of patients, in addition anorexia, nausea, and vomiting due to stimulation of **CTZ**. this can be **decreased** by **dividing** the **dose** of the drug to 3-4 doses and by **increasing** the total daily dose very **slowly**. by time .**tolerance** will developed

: **b- CVS**

Tachycardia , arrhythmias and atrial fibrillation (bs of **increased-1** .**catecholamine** formation peripherally)

Postural hypotension (in early stages) Dopamine agonists tend to diminish **-2** blood pressure by **inhibiting** sympathetic neuronal discharge of **NE** and, to a lesser extent, by .**stimulating** dopamine **vascular** receptors

3- Hypertension may also occur, especially in the presence of **nonselective monoamine oxidase inhibitors** or when **large doses** of levodopa are being taken.

Anorexia

Nausea

Tachycardia

Hypotension

Psychiatric problems

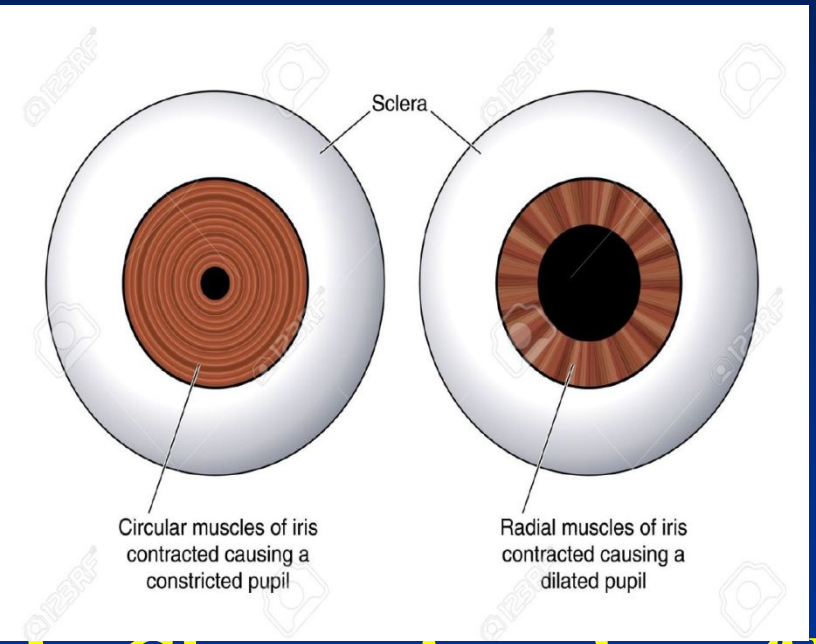
c- **Psychatric problem: (bs effects of dopamine in mesolimbic mesocortical pathway),** anxiety, agitation, hallucination, insomnia, confusion, delusions, nightmares .and depression

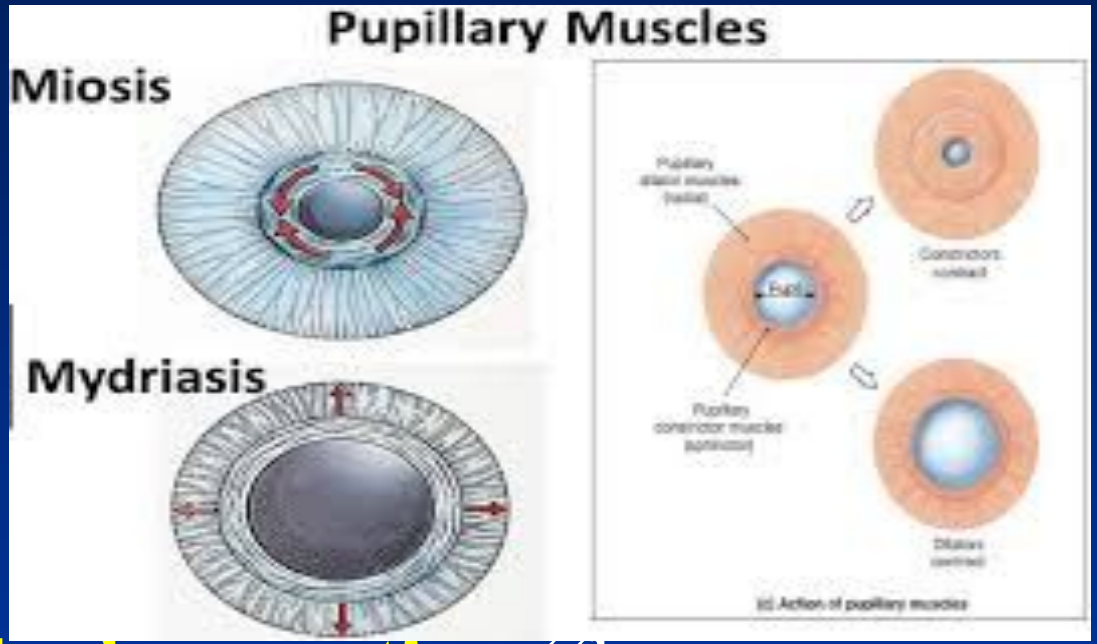
These are **more** common in patients taking levodopa in **combination** with a decarboxylase inhibitor rather than levodopa alone (because **higher** levels of l- dopa are .reached in the **brain)**

d- **Dyskinesea:** occur in up to **80%** of patients receiving levodopa therapy for more than **10 years, Choreoathetosis** of the face and distal extremities is the .most common presentation

.Some times myoclonics, tics, and tremors

e- Mydriasis (adrenergic action on alpha1 receptor) blurred vision





f- Change in color of body secretion ((brown discoloration of saliva and urine bs dopamine .<u>stimulates</u> **melanin** secretion))

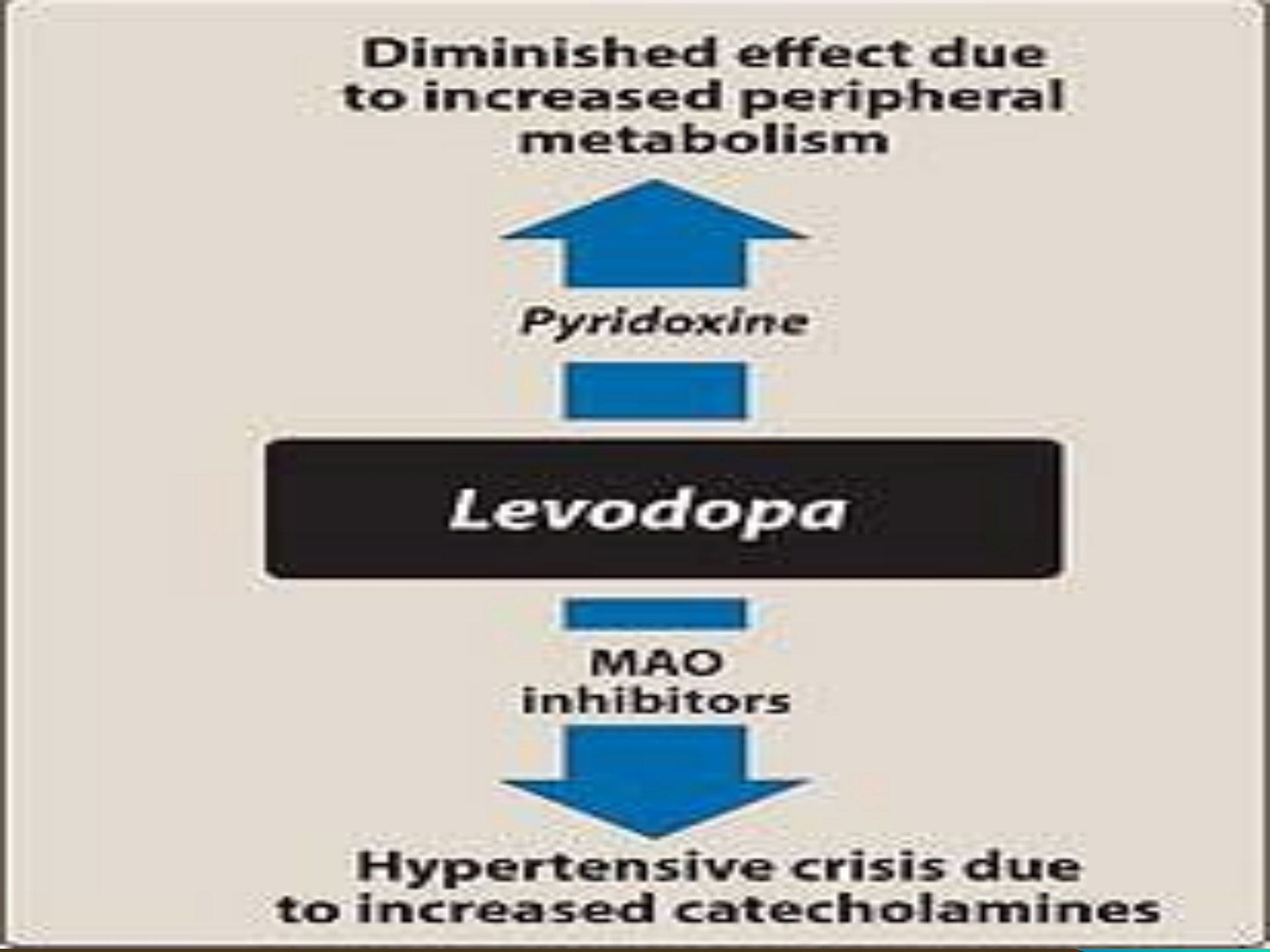
.

: Interactions

a- With vit. B6 (pyridoxine) because it **increases** the peripheral **metabolism** of L-dopa this lead to more .peripheral side effect and less central benefit of l-dopa

b- Monoamine oxidase A inhibitors or with General monoamino oxidase inhibitors (MAOIs) :bs it lead to hypertensive **crisis** because of **increased** catecholamines

Thus Levodopa should not be given to patients taking **these .drugs** or within 2 weeks of their discontinuance


Diminished effect due to increased peripheral metabolism
Pyridoxine
Levodopa
MAO inhibitors
Hypertensive crisis due to increased catecholamines

:Contraindication

.Antipsychotic drugs (antipsychotics **block D2 receptor**) -1

Glaucoma because **increases intraocular pressure (bs of** -2

.**mydriasis)**

……Cardiac problems -3

Melanoma (bs dopamine increase melanine secretion) -4

.History of active peptic ulcer -5

Thank you