Parkinson's disease (PD)

Professor Dr Sinaa A. Kadhim

M.B.Ch.B , GP.Rad., MSc., PhD.Pharm

:Objectives

know drugs used in patients with Parkinson -1 .disease

.know mechanism of action of each drug -2

know side effects, interaction, indication and -3 .contraindications

:**Dopamine agonists:** 2 types *.2*

Ergot alkaloids -1

Non - ergot alkaloids-2

:Ergot alkaloids -1

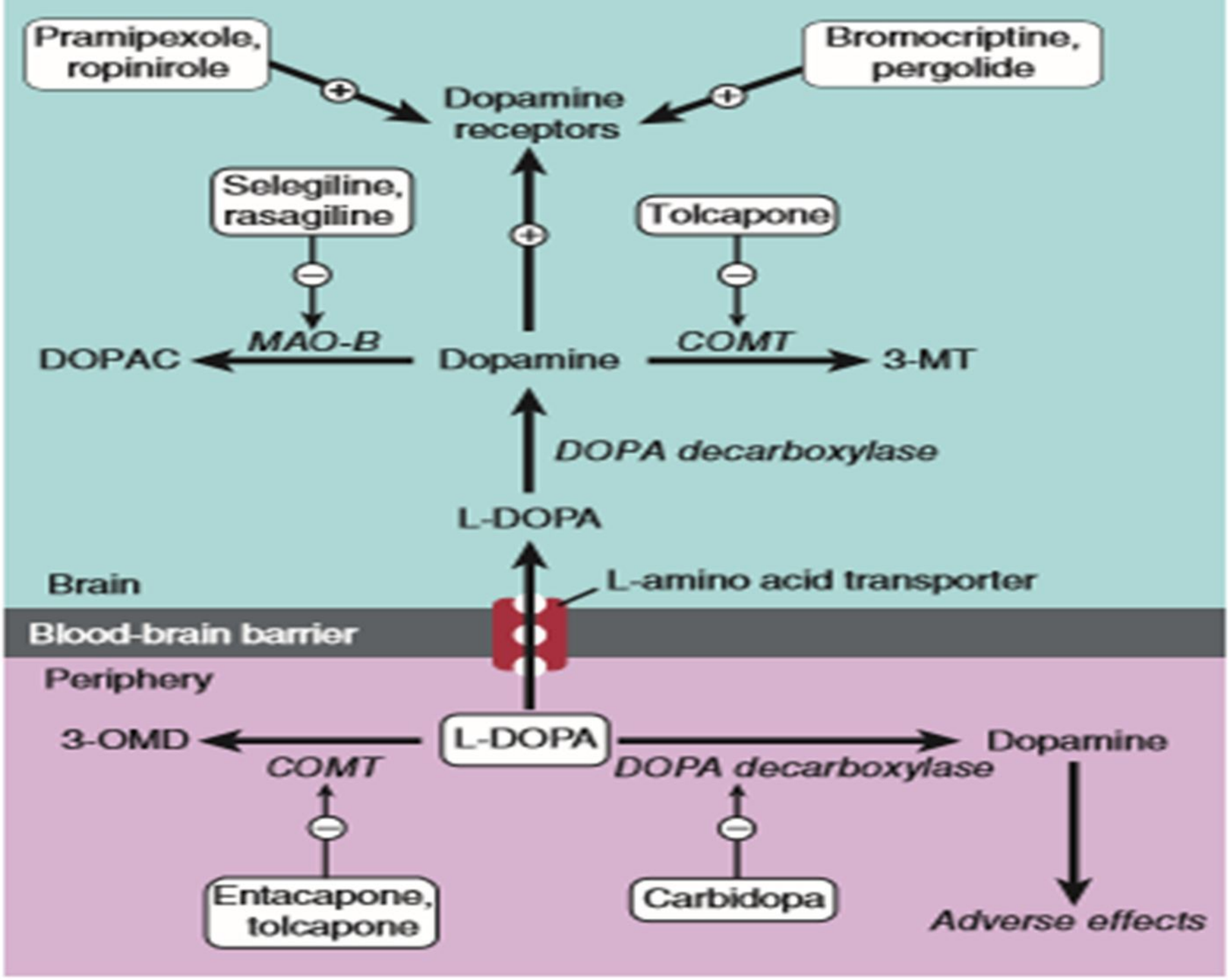
A- Bromocriptine: acts as

Partial agonist on **D2 receptor** in the brain -1

.Some **alpha 1 antagonist** effect -2

It increases the activity of dopamine neurotransmitter

B- Pergolide / cabregoline: act by activation of dopamine .receptors (**D1 and D2**)


Pramipexole, ropinirole
Bromocriptine, pergolide
Dopamine receptors
Selegiline, rasagiline
Tolcapone
MAO-B
COMT
DOPAC
Dopamine
3-MT
DOPA decarboxylase
L-DOPA
Brain
L-amino acid transporter
Blood-brain barrier
Periphery
3-OMD
L-DOPA
Dopamine
COMT
DOPA decarboxylase
Entacapone, tolcapone
Carbidopa
Adverse effects

: Clinical use

They are used in

:A- Parkinson disease as

.**Individual** drugs -1

.**Combined** with levodopa -2

.**End-of-dose** deterioration of l-dopa -3

.**Intoleration** to levodopa -4

B- Hyperprolactinemia

:Kinetics**

Bromocriptine is metabolized by cytochrome P450 3A4 , excreted .primarily in the feces via biliary secretion

Parent drug and metabolites are almost completely excreted via the .liver, and only 6% eliminated via the kidney

:Side effects

CVS: cardiac arrhythmias and postural hypotension(vasodilitation……)

……Dyskinesias

Behavioral : hallucination, confusion and delusion….(occur more than with L-dopa)

GIT : anorexia, nausea, and vomiting

:Contraindication

Psychosis (psychiatric problem)-

The ergot-derived agonists are **best avoided** in patients with-

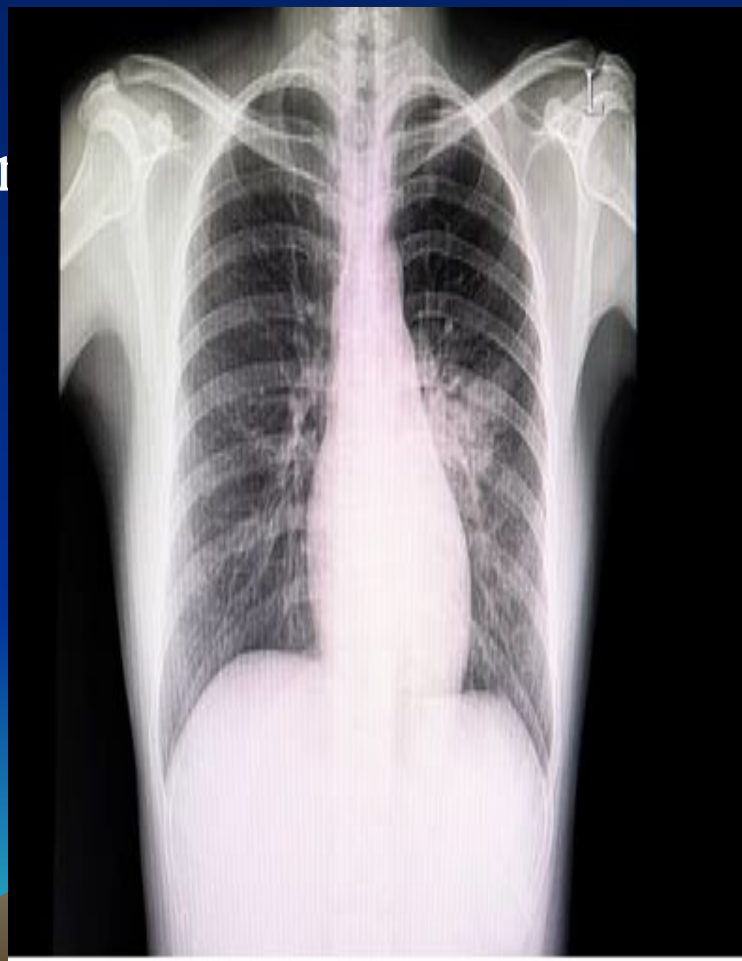
.**peripheral vascular disease (bs ergot cause Erthromelalgia)**

:Ergot relates side effects

Pulmonary infiltrates -1

:NOTE (for your informations)

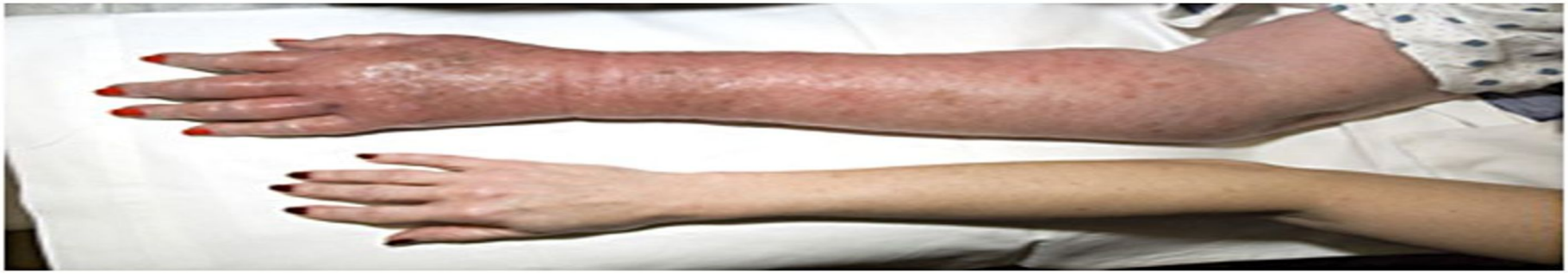
a pulmonary infiltrate is a substance denser than airthan air, such as pusthan ,as pus, blood or protein, which lingers within the parenchyma of the lungs. can be observed on a chest radiograph

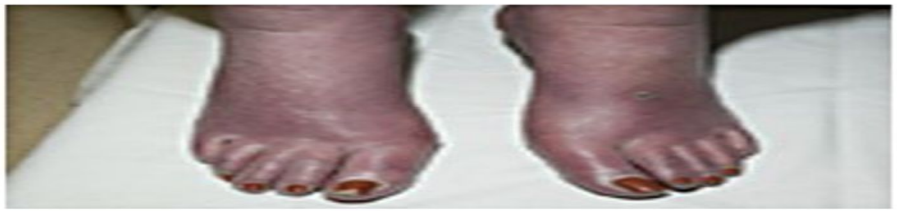


Erthromelalgia -2

:NOTE (for your informations)

Erythromelalgia is a disorder in which **blood vessels** are episodically blocked (frequently on and off daily) then become hyperemic and .inflamed with pain





:Non-ergot derivatives -2

pramipexole (preferential affinity for **D3 R), agonist**,less mental S/E , **excreted unchanged in the urine** (dosage **adjustments** are needed in .renal dysfunction)

ropinirole (pure D2 agonist), **more serious S/E.**(The **exact mechanism** of action of **ropinirole** as a treatment for Parkinson's .disease is **unknown)**

They are considered to be **first line** drugs in the **initial management** of Parkinsonism

Rotigotine : **non selective** dopamine R agonist with **more** selectivity to .**D3 R**, given as a **patch or injection**

Apomorphin : A **short**-acting **injectable** dopamine agonist temporary relief **off period** of akinesia, act on **D_2-like** and, to a much **lesser extent, D_1 -like** receptors. It also acts as an **antagonist** of **5-HT_2** and **α-adrenergic receptors** with .high affinity

Side effects: include

Postural hypotension

Dyskinesias

Fatigue

.Drowsiness and Sleepiness (should be taken at night)

Wt. gain (bs dopamine induce compulsive over eating)

Emesis(stimulation of CTZ induce vomiting)

:Clinical uses

a-Parkinsonism

b-Restlessness leg syndrome(RLS) {for your information: an unpleasant feeling when going to sleep and a **strong urge to move**. The movement makes it .hard **or impossible to get enough sleep}**

. **c-Apomorphine is used also in : 1-anxiety 2-emetic (to induce vomiting)**

.treating erectile dysfunction-3

: Drug interaction

Antipsychotics (like chlorpromazine, haloperidol which block D2 R)-

Metoclopramide (D2 antagonist)-

Sleep producing drug (diazepam)-

other CNS suppressant drugs like opiod and antihistamine-

Cimetidine and The fluoroquinolone antibiotics and other-- inhibitors of CYP450 1A2 isoenzyme (for example, fluvoxamine) may inhibit the metabolism of ropinirole, requiring an adjustment .in ropinirole dosage

:Contraindications

,History of **psychotic** illness 2- Recent **myocardial infarction** -1

.Active peptic **ulceration** -3

:Amantadine .3

:Is an antiviral drug. It enhances Dopamine activity by

Increasing **synthesis** and release of dopamine or-1

.Inhibition of **reuptake** of dopamine-2

.**Muscarinic blocking** actions -3

.inhibiting the N-methyl-D-aspartate (NMDA) type of glutamate recept-4

Side effects include

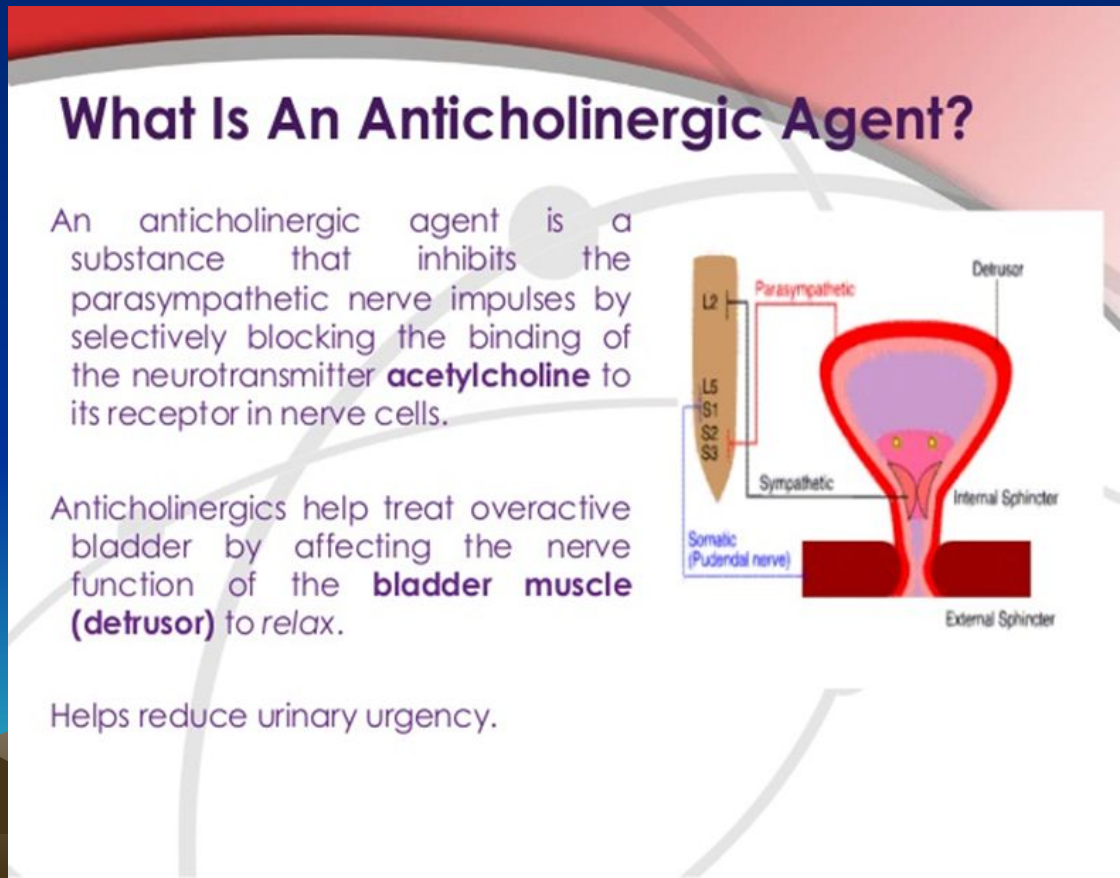
,Behavioral: restlessness-hallucination, agitation

,Urinary effects: retention-(anti cholinergic effects)

GIT : nausea and vomiting-

Postural hypotension-

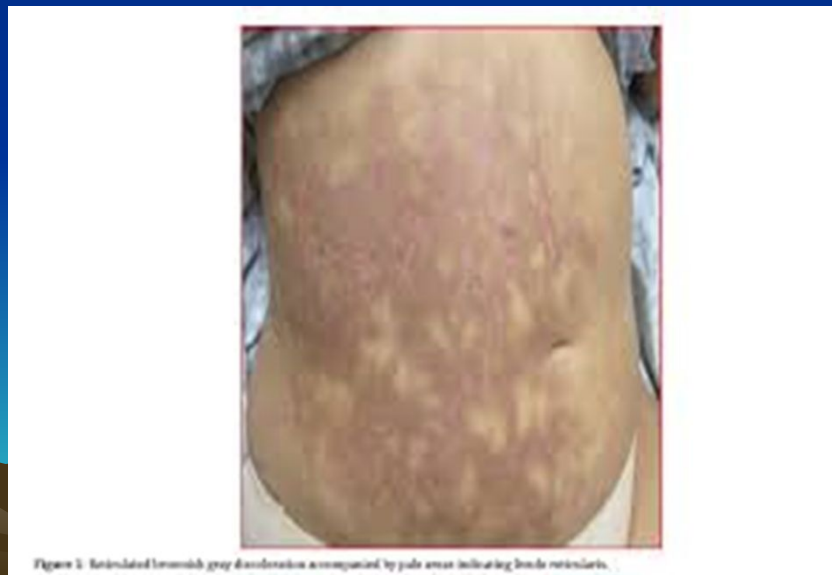
Dermatological reactions-include livedo reticularis



:NOTE (for your informations)

Livedo reticularis is a lace-like purplish discoloration of the skin caused by **swelling** of the **venules** owing to obstruction of capillaries .by small blood **clots**

As shown in the following picture



Selegiline, rasagiline and safinamide .4

Are selective inhibitors MAO-B (the enzyme that metabolizes dopamine to nor epinephrine and serotonin in brain)

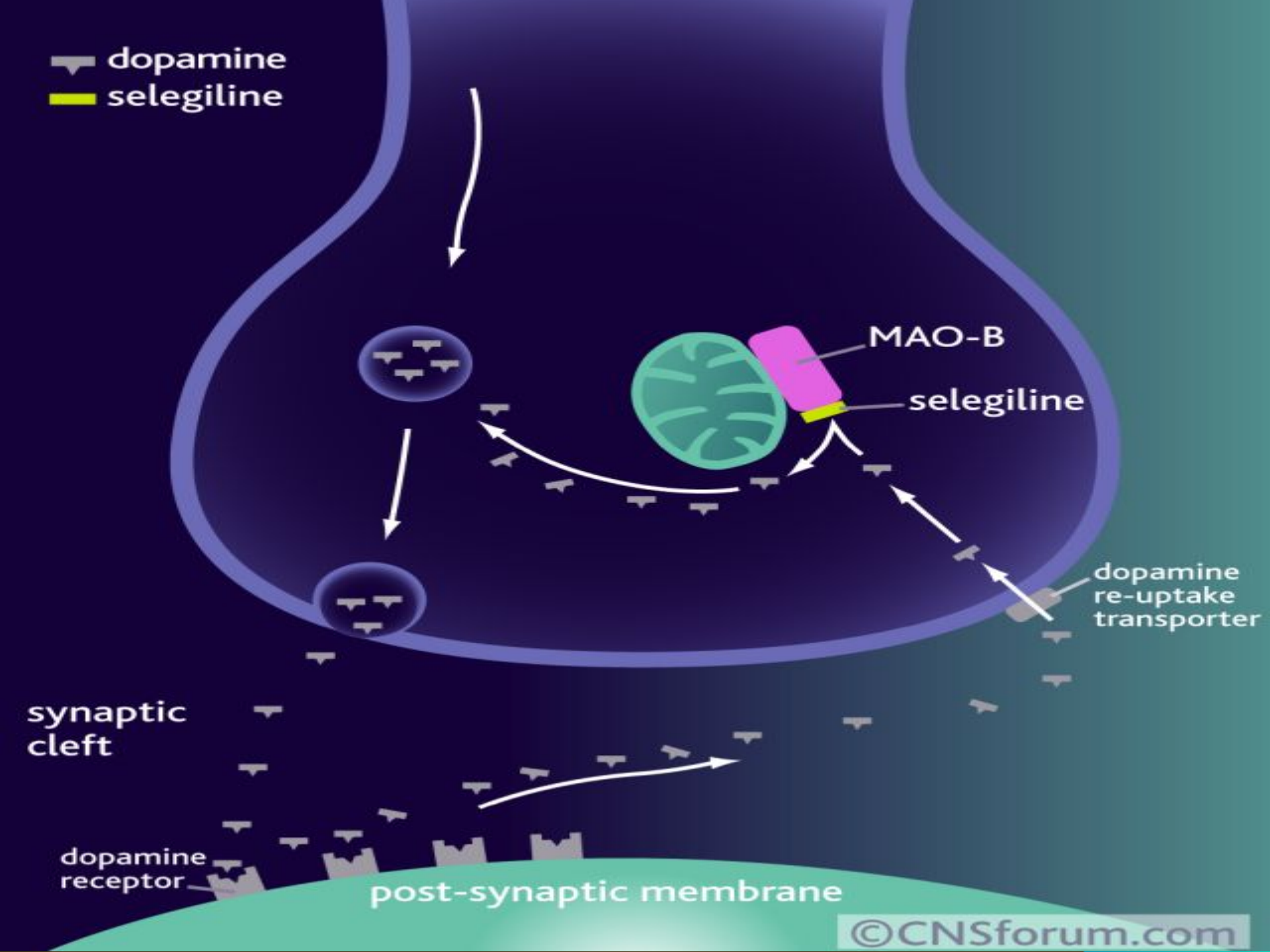
It enhance l-dopa effect(allowing the dose of levodopa to be reduced) .(and may reduce on-off or wearing-off phenomena

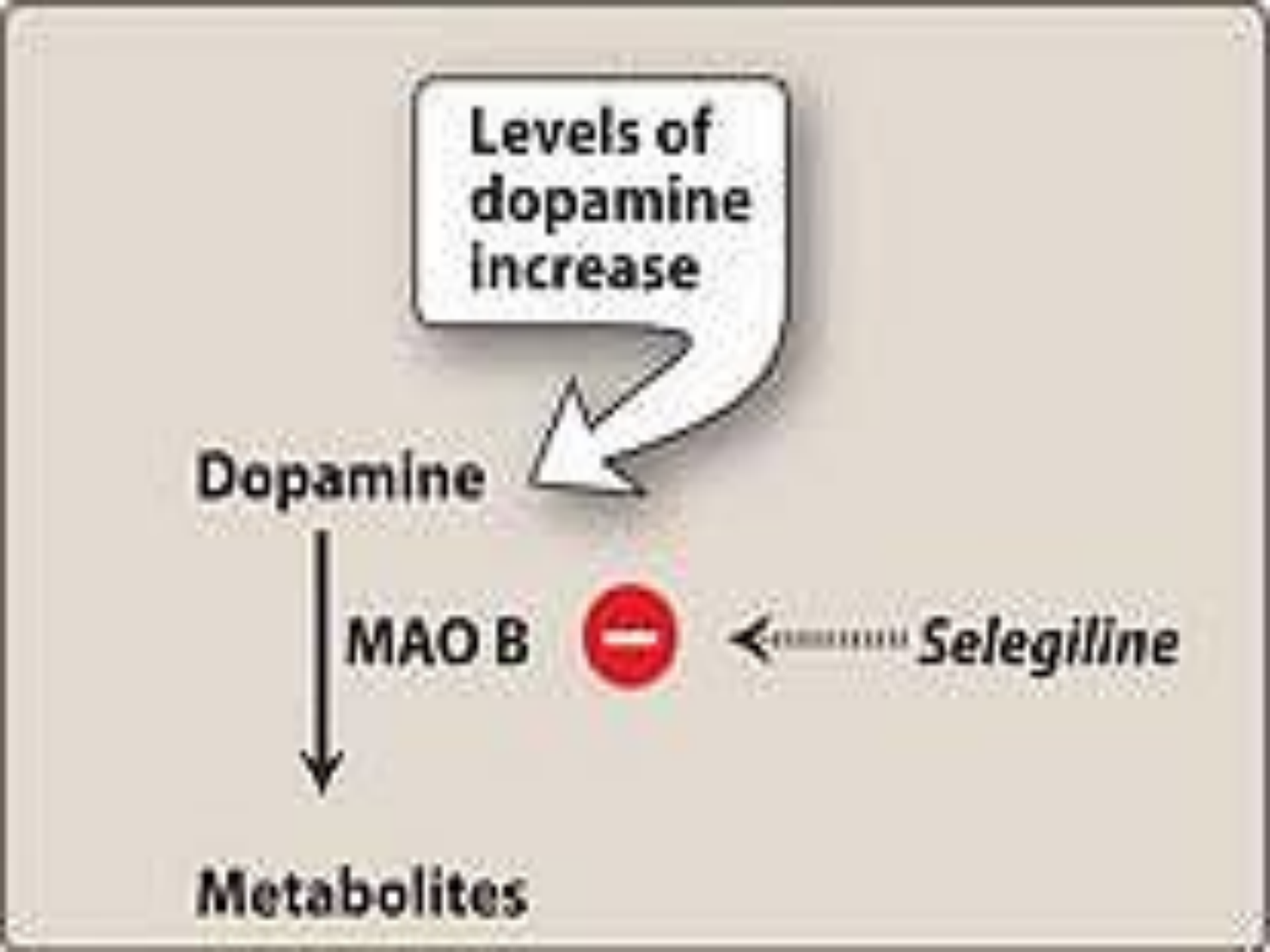
at **low** to **moderate** doses they **not** inhibit **MAO** Type A (which metabolizes dopamine, norepinephrine and serotonin). But in high doses they loses thier selectivity (inhibit .both MAO- A and B)

Selegiline is metabolized to methamphetamine and amphetamine, (whose stimulating properties may produce **insomnia** if the drug is .(administered later than mid-afternoon

Rasagiline(irreversible inhibitor of MAO B, is **more potent** than selegiline in preventing MPTP(drug induce parkinsonism), not ,metabolized to an amphetamine-like substance (**NO insomia**)

.and is being used for **early treatment** in patients with **mild** symptoms


dopamine
selegiline
MAO-B
selegiline
dopamine
re-uptake
transporter
synaptic
cleft
dopamine
receptor
post-synaptic membrane
©CNSforum.com


Levels of dopamine increase
Dopamine
MAO B
Selegiline
Metabolites

Contraindication: with

Mepridine-1

.Selective serotonin reuptake inhibitors-**2**

severe liver impairment -3

:Side effects

GIT: Nausea and vomiting

CNS: Confusion, visual hallucinations, dizziness, headache, and .insomnia, especially at higher doses

Psychatric: The combined use of these agents at high doses with .l-dopa results in an increased incidence of dyskinesia and psychosis

CVS: Postural hypotension

:Inhibitor of COMT-5

.Intacapone and Tolcapone

COMT is the enzyme that converts levo Dopa to 3-0-methyl dopa .(30MD)

.These drugs **selectively** and **irreversibly** inhibit C0MT

Increased 30MD are associated with less response to levodope;** .because it competes with **levo** dopa for active transport to the CNS

: Kinetics of tolcapone and entacapone

.Penetrates the blood-brain barrier -1

.**Tolcapone** has a relatively **long duration** of action -2

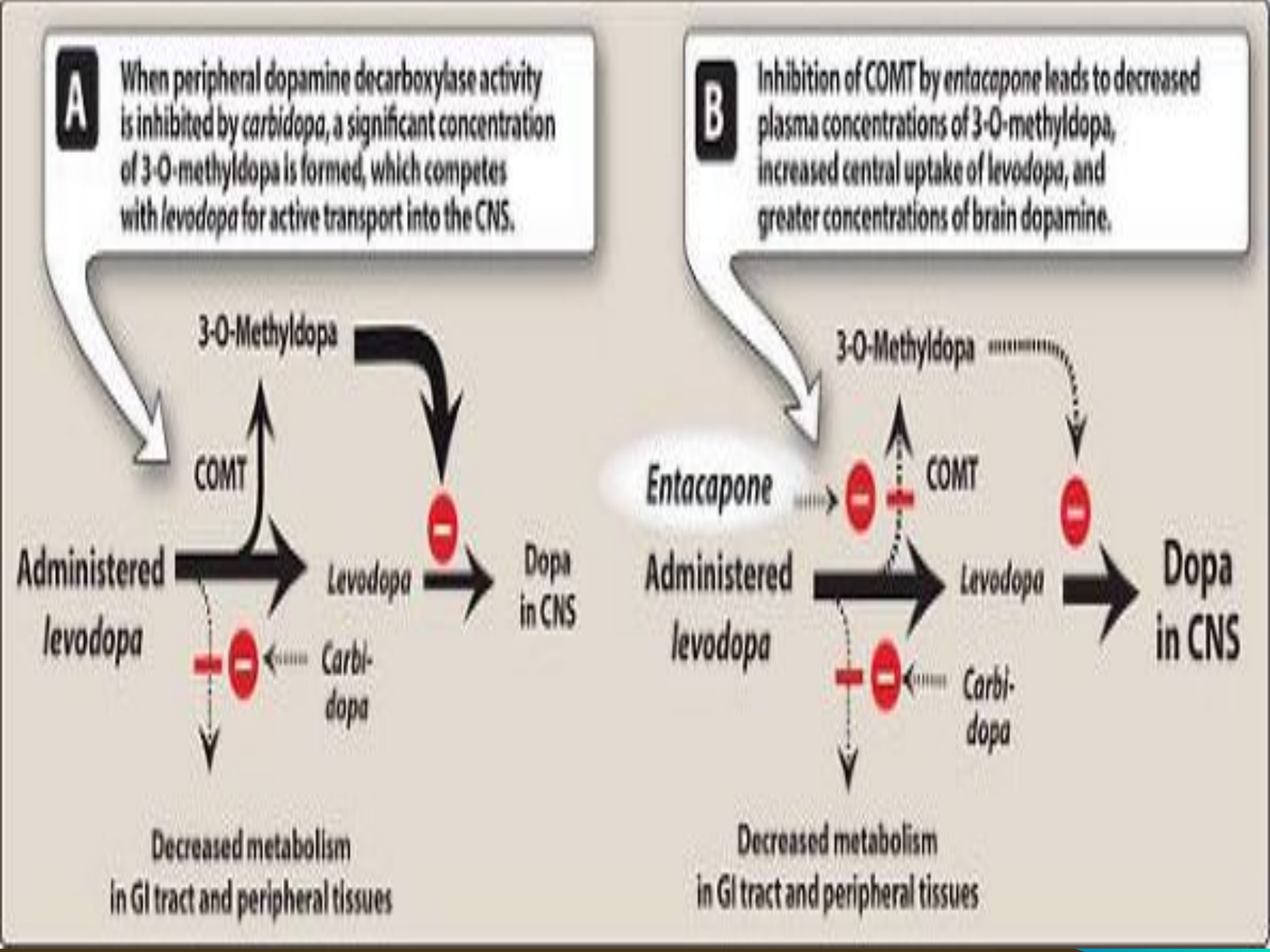
.Entacapone requires **more** frequent **dosing** -3

Both drugs are **extensively metabolized** -3

.Eliminated in the **feces** and **urine**-5

.**Oral absorption** of both are readily and is **not influenced by food** -6

They are extensively **bound to plasma** albumin, with a limited volume-7 of distribution


A
When peripheral dopamine decarboxylase activity is inhibited by carbidopa, a significant concentration of 3-O-methyldopa is formed, which competes with levodopa for active transport into the CNS.
3-O-Methyldopa
COMT
Administered levodopa
Levodopa
Dopa in CNS
Carbi-dopa
Decreased metabolism in GI tract and peripheral tissues
B
Inhibition of COMT by entacapone leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine.
3-O-Methyldopa
Entacapone
COMT
Administered levodopa
Levodopa
Dopa in CNS
Carbi-dopa
Decreased metabolism in GI tract and peripheral tissues

Adverse effects

Dyskinesias, hallucinations and sleep disorders.1

.Diarrhea (peripheral effect in GIT) .2

Tolcapone may cause severe liver damage**.3** (necrosis) there for should monitor hepatic function

Postural hypotension, nausea, anorexia -4

:USE

indicated as an **adjunct** to levodopa and carbidopa for the treatment of the signs and symptoms of **idiopathic** Parkinson's disease

:Antimuscarinic Drugs - 6

Centrally acting antimuscarinic drugs used to help control the tremor and regidity with little effect on bradykinesia. including

,Benzotropine

,Biperidin

,orphenadine

.Procyclidine

Trihexyphenidyl

:Mechanism of action

Decrease actions of cholinergic neurons in the .brain by blocking muscarinic receptors

.:Adverse effect

CNS effect: drowsiness, confusion, **-1** .delusion, and hallucination

Peripheral effects: urine retention , dry -2 mouth, constipation, blurred vision , …….etc (atropine like adverse effects)

Note:Drugs that induce parkinsonism

A-Reversible

Metoclopramide-

Neuroleptic (Antipsychotic) bs they block Dopamine-receptor) like butyrophenones & phenothiazines or haloperidol

B-Irreversible

MPTP (1-methyl 4-phenyl 1,2,3,6- tetrahydropyridine) .which is a byproduct of meperidine analog

In pregnancy: levodopa, rasagiline, pramipexole, and ropinirole **alone** or in **combination** with each other may be considered **relatively safe** during pregnancy with .**Expected risks** should be considered

THANK YOU 2022