DRUG TREATMENT OF PARKINSONISM

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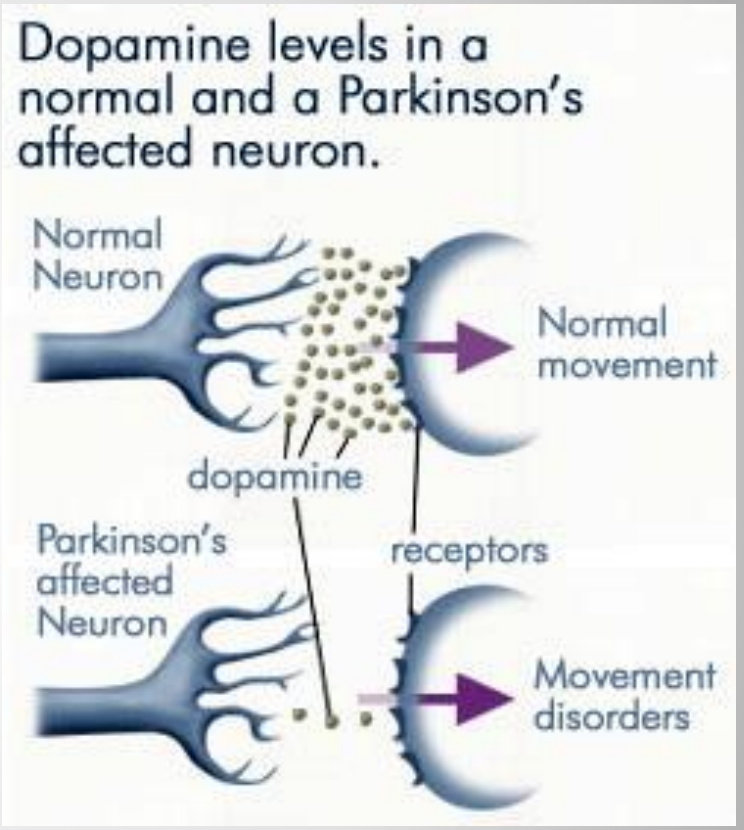
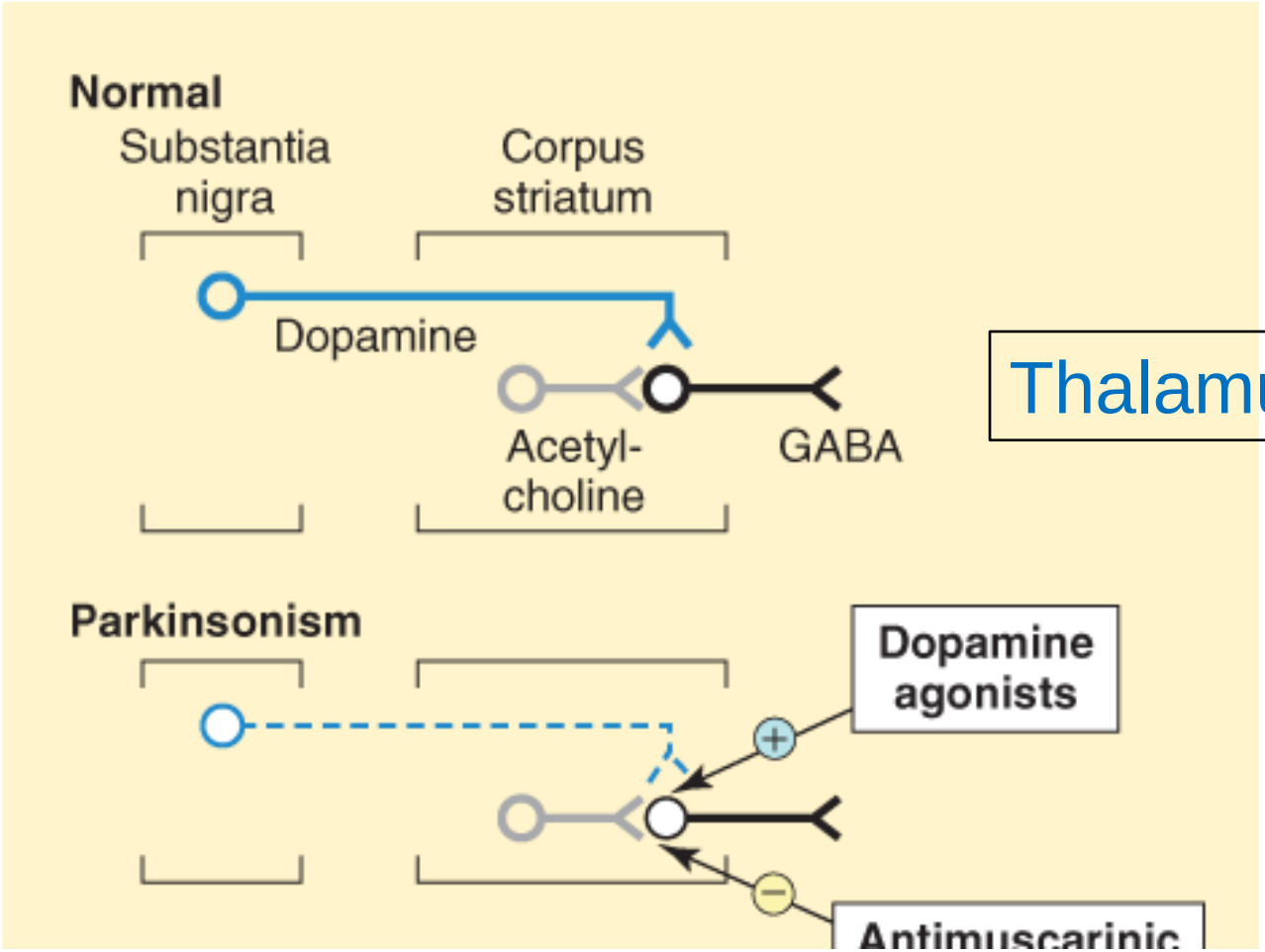
Parkinson's Disease:

- Dopamine Neurons of Substantia Nigra -
- Abnormal Control of Movement …..



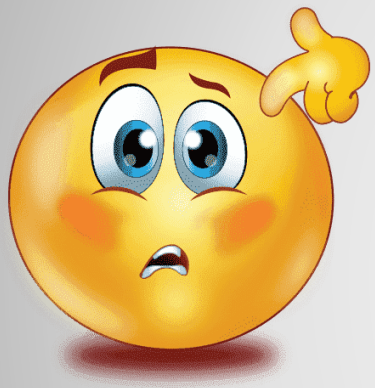

Normal
Substantia nigra
Corpus striatum
Dopamine
Acetyl-choline
GABA
Parkinsonism
Dopamine agonists
Antimuscarinic

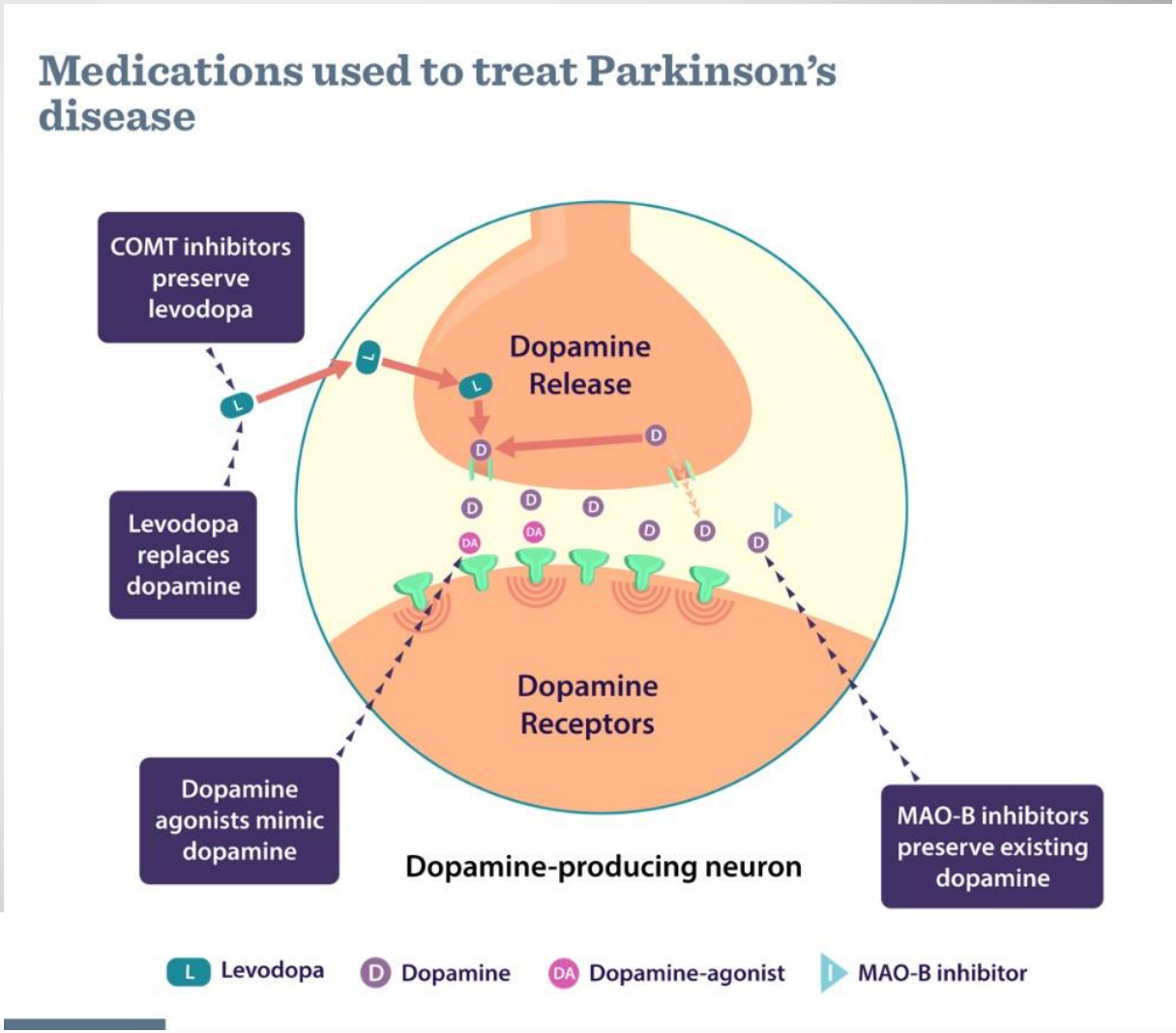
Thalamus

Line of Treatment

- To increase dopaminergic activity
- To decrease cholinergic activity

How to increase dopamine ?





CLASSIFICATION

I. Dopaminergic Drugs:

1. Dopamine Precursors: levodopa
2. Dopa Decarboxylase Inhibitors: Carbidopa, Benserazide
3. Dopamine Releasers: Amantadine, Rimantadine
4. Dopaminergic Agonists:

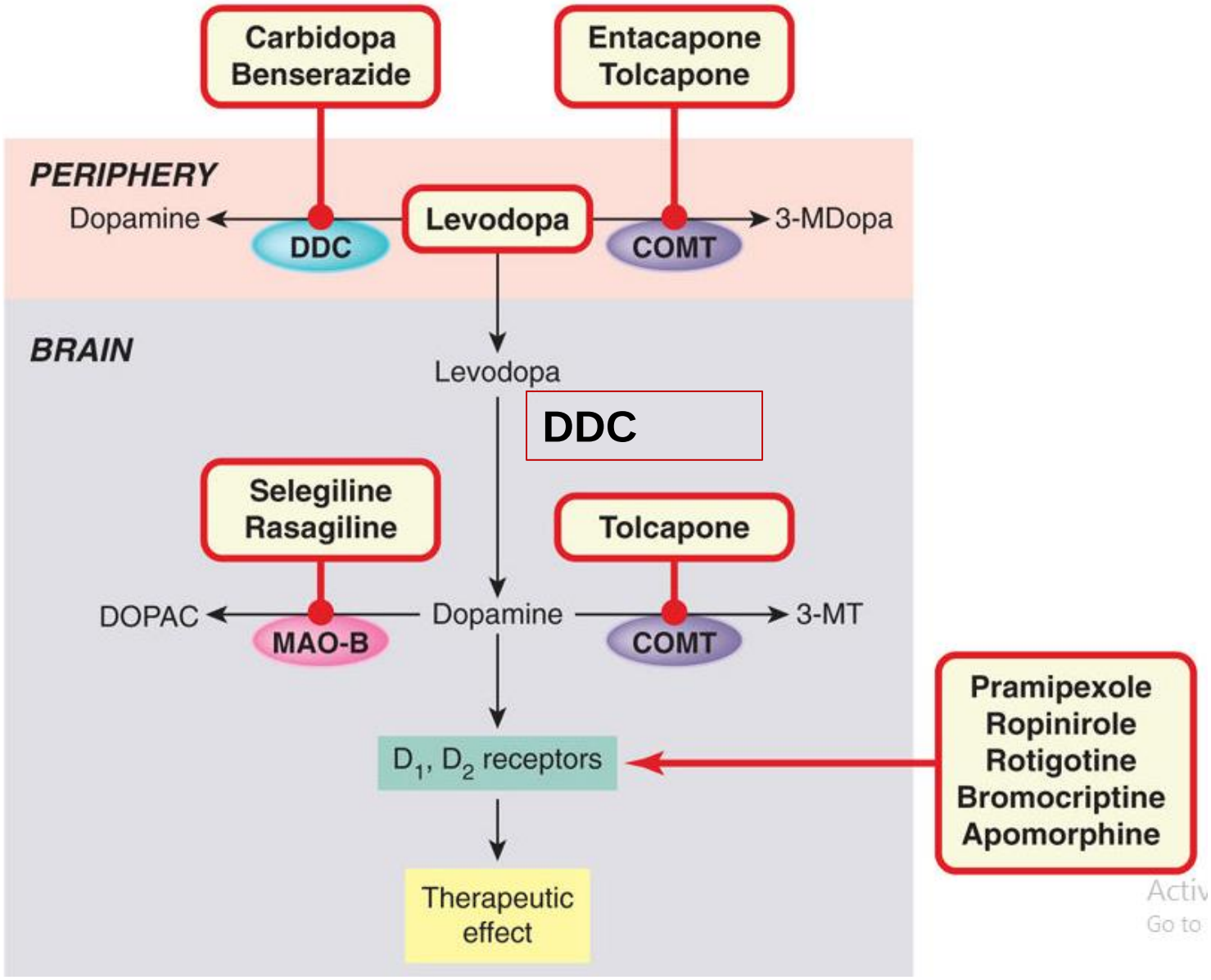
i. Ergot derivatives: Bromocriptine, Pergolide
ii. Non Ergot derivatives: Pramipexole,Ropinirole
iii. Apomorphines: Apomorphine

5. M.A.O-B Inhibitors: Selegeline, Rasagiline

6. COMT Inhibitors Selective: Tolcapone, Entacapone

II. Anticholinergic Drugs: Procyclidine, Benzhexol, Benztropine, Biperidine, Trihexyphenidyl

III. Anti-Histamines: Orphenadrine, Diphenhyderamine


Carbidopa
Benserazide
Entacapone
Tolcapone
PERIPHERY
Dopamine
DDC
Levodopa
COMT
3-MDopa
BRAIN
Levodopa
DDC
Selegiline
Rasagiline
Tolcapone
DOPAC
MAO-B
Dopamine
COMT
3-MT
D1, D2 receptors
Pramipexole
Ropinirole
Rotigotine
Bromocriptine
Apomorphine
Therapeutic effect

LEVODOPA

•Dopamine cannot cross the BBB.

- DOPA is a precursor of dopamine
- Levodopa: levorotatory form of DOPA
- Orally absorbed from small intestine
- Amino acids compete for absorption & transport to brain
- Absorbed from small intestine.. Depends on gastric emptying
- (Large Ist pass effect)
- Metabolites in urine: HVA & DOPAC

CVS:

Postural Hypotension in patients on anti-hypertensives

Any type of arrhythmia

GIT:

Nausea , vomiting & anorexia

Endocrine:

Decreased prolactin levels

Psychic Effects:

Increased dopaminergic activity → to a schizophrenia like syndrome with delusions & hallucinations

In 20% cases, confusion, disorientation, insomnia, or nightmares

Adverse Effects:

- ✓ Gastro-intestinal Tract
- ✓ Cardiovascular system
- ✓ Abnormal involuntary movements(dyskinesias)
- ✓ Behavioral disturbances
- ✓ Response fluctuations.
  - i. On & off Phenomenon
  - ii. End of dose akinesia

- ✓ Mydriasis
- ✓ Blood dyscrasias
- ✓ Aggravation of gout
- ✓ Brown discoloration of body secretions

Drug interactions: with

i. pyridoxine
ii. Mao–A inhibitors
iii. Anticholinergics
iv. Antipsychotics

Contra-indications:

i. Psychotics
ii. Glaucoma
iii. Melanoma
iv. Peptic ulcer
v. Cardiac disease

Carbidopa

DOPA Decarboxylase Inhibitors(Highly ionised)

Carbidopa:

- a peripheral DOPA *decarboxylase inhibitor* *increases the levels of* *levodopa in the blood* so ↑ed amounts reach the CNS.
- Levodopa penetrates BBB & there it is decarboxylated to dopamine.
- A Peripheral Dopa decarboxylase inhibitor ↓es levodopa requirement by 75%

Advantages of Combinations:

- Reduction in dose of levodopa(plasma half life is increased)
- ↓ed incidence of nausea & vomiting
- Better & early control
- Blockade of pyridoxine antagonism
- ↑ed degree & percentage of improvement

Amantadine

Mode of Action

- Release of Dopamine
- Delay Reuptake of Dopamine
- May Have Anticholinergic Effects
- Antagonize the effects of adenosine at adenosine A2A receptors(inhibit D2 receptor function)

Uses

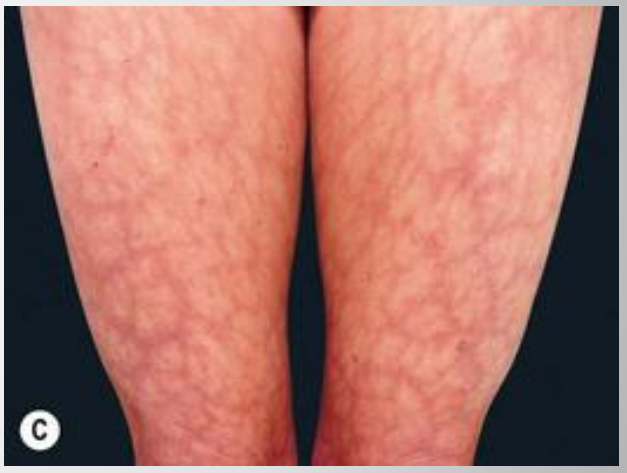
- Less Potent Than Levodopa
- Benefits Short Lived

Adverse effects

CNS:GIT, CVS same as L Dopa

Livedo reticularis.

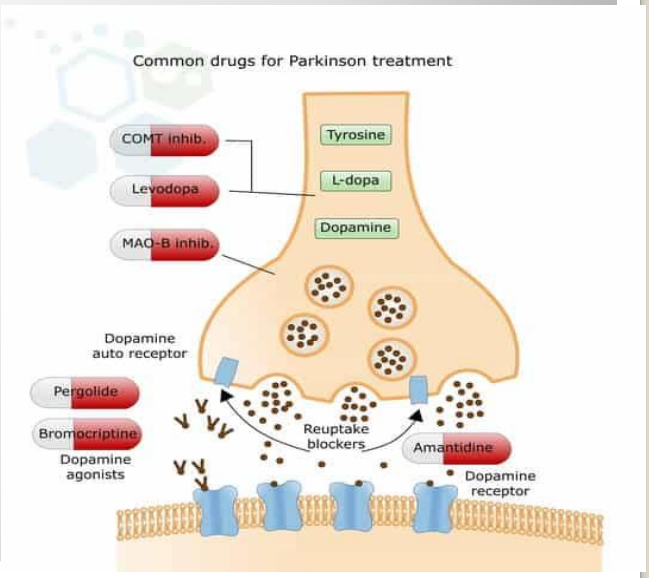
Anticholinergic SE



Dopamine agonists

- Directly act on dopamine *receptors*
- Need no enzymatic conversion
- *No active or toxic metabolites*
- No competition for transport
- Limited adverse effects than levodopa

(*on-off phenomenon or dyskinesias)*



Bromocriptine Uses: (D2Agonist)

1. In Parkinsonism alone or as an adjunct
2. Hyperprolactinemia (Fibroadenosis of the breast ,supression of lactation ,Infertility, amenorrhoea)
3. Acromegaly
4. Type 2 diabetes

Pergolide (damage to heart valves) D1;D2agonist

Rotigotine, skin patches

Pramipexole

- Non ergot, more effect on D3
- Neuroprotective, scavanger of free radicals
- No adverse effect associated ē ergot.

Ropinirole

- Pure D2 agonist, new non ergot compound
- Restless leg syndrome

Adverse effects of Dopamine Agonists

C.N.S

- Dyskinesias reversed by ↓ing total dose
- Confusion, hallucination, delusions & psychiatric reactions seen more ē dopaminergic agonists.

1. painless digital vasospasm
2. Pulmonary infiltrates
3. Pleural & retroperitoneal fibrosis
4. Erythromelalgia
5. Tendency to fall asleep

GIT, CVS same as Levodopa

Apomorphine (Rescue drug)

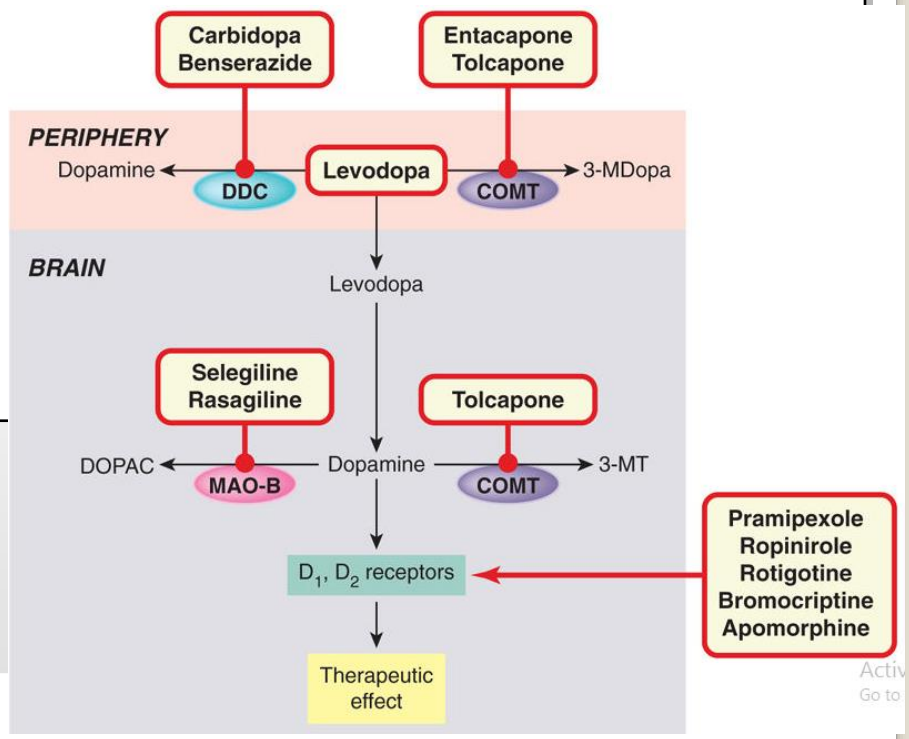
- Given S/C for Off and On phenomenon
- Dopamine agonist
- Onset of action is 10 min, duration of Action 2 hour
- Dyskinesias and nausea(pretreatment with antiemetic)

MAO - Inhibitors

Two types MAO-A & MAO-B Inhibitors

A- inhibitors block *norepinephrine & 5-HT* metabolism

B- inhibitors block *dopamine* metabolism



- Selective MAO-B inhibitor; *retard breakdown of dopamine.*
- Given alone, may reduce disease progression;
- Neuro-protective action of metabolite desmethyl selegiline involve anti-apoptotic action (*antioxidative*).
- Adjunct ē L-dopa *for on-off or wearing off phenomenon*

Selegeline (Deprenyl)

Rasagiline:

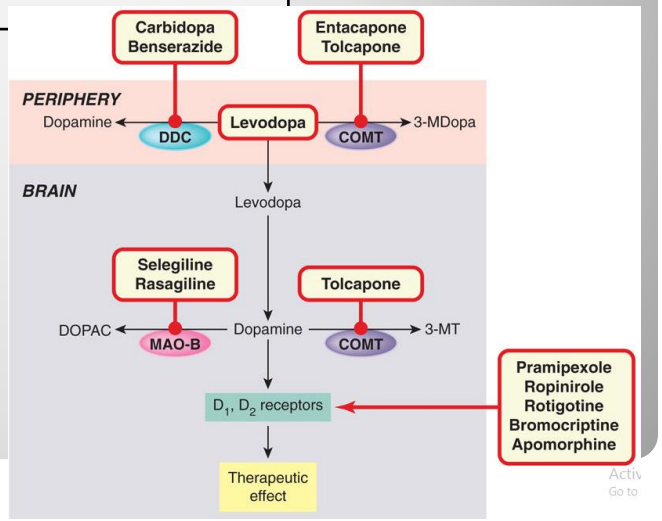
- more potent
- preventing MPTP - induced parkinsonism.

COMT - Inhibitors

- DDCI→ compensatory activation of COMT
- ↑ed level of 3OMD → ↓ L-DOPA response

TOLCAPONE & ENTACAPONE

- ↑Bioavailability & prolong L-DOPA action
- Useful in patients ē response fluctuations
- Smooth response ē ↑on time & ↓ L-DOPA dose.



- Entacapone preferred as no hepatotoxicity
- Has only peripheral effects.
- Tolcapone more potent central & peripheral effects cause fatal hepatotoxicity.
- Used in pts on levodopa with response fluctuations

Adverse effects

- orange coloured urine
- Tolcapone → ↑ liver enzymes & hepatotoxicity

- Combo(L. dopa+carbidopa+entacapone)stalevo
- CVS, CNS, GIT same

Anticholinergics

- Decrease cholinergic excitation
- More effective in ↓ing tremors & rigidity
- Less effective in ↓ing bradykinesia
- Also improve excessive sialorrhea

Uses:

1. In Pts ē minimal symptoms & as adjunct ē L-DOPA
2. Pts intolerant or resistant to L- DOPA
3. Pts ē drug induced parkinsonism

Adverse effects:

CNS:

- Drowsiness, Mental slowness, Inattention, Restlessness, Confusion, Agitation, Delusions.

Antimuscarinic:

- Blurred vision, Urinary retention, Dry mouth

Contraindications:

1. Paralytic ileus
2. Prostatic hyperplasia
3. Narrow Angle Glaucoma
4. Avoid TCA's & Anti-Histamines

Reserpine & Tetrabenazine deplete biogenic amines from storage sites.

Haloperidol & Phenothiazines block dopamine receptors. They Produce a parkinsonism like syndrome within 3 months ē high doses.

DRUG - induced Parkinsonism

Treatment Of drug induced parkinsonism

- If necessary
- Treat ē anticholinergics.
- L-dopa is of no help if antipsychotics are continued,
- It will aggravate the mental disorder for which anti psychotics were given originally.

Tremors

- Bronchodilators and tricyclic anti depressant and Li can produce tremors.
- T/m: beta blocker,s essential tremors are mediated by beta 1 receptor. While physiological tremors are due to beta 2.
- Alprazolam
- Topiramate, Gabapentin
- Primidone

Huntingtons disease

- Excessive dopaminergic activity
- Deficient Ach and GABA
- Anti psychotics(Haloperidol) can be given
- GABA enhancers ..BZD
- Tetrabenazine; reserpine (inhibits VMAT2) amine depleting drugs

- Restless leg syndrome…BZD, opioids, Dopamine agonist
- Wilson disease…. Penicillamine


KEEP
CALM
IT'S
THE END OF
PRESENTATION