COMT inhibitors prolong the periods of levodopa effectiveness ("on" time) with shorter periods of unresponsiveness ("off" time)

COMT Inhibitors

These are the new drugs used for treatment of Parkinsonism

Tolcapone and Entacapone peripherally inhibit the metabolism of Levodopa by into 3-O-Methyl-DOPA. and increase the concentration of Levodopa to cross the BBB.

COMT enzyme cause methylation of Levodopa and prevent/ decrease the concentration of Levodopa to cross BBB

When Levodopa is used alone it is most available for methylation

So, Tolcapone and Entacapone prevent the methylation of Levodopa,

In the CNS Levodopa is converted into dopamine and dopamine is again converted into 3-Methoxytyramine by COMT.

Tolcapone inhibits the COMT enzyme in brain. and ultimately increase the concentration of Dopamine

So these drugs are used to reduce wearing off symptoms of Levodopa.

Tolcapone and Entacapone are similar in their mechanism of action but differ in their pharmacokinetics and adverse effect.

Tolcapone have long half life and cause hepatotoxicity and can act centrally as well peripherally

Entacapone that have short half life that act on the periphery but do not cause hepatotoxicity.

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⇒ Dopamine Receptor Agonists

including

- Bromocriptine
- Pergolide
- Ropinirole
- Pramipexole

These drugs are used for treatment of Parkinsonism or

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alternative drug to Levodopa.

Advantages of DRA Over Levodopa ---

1. Enzymatic conversion is not required for the action of dopamine agonist.
2. These drugs do not depend on the functional capacity of Nigrostriatal neurons.
3. These drugs have longer duration of action and more effective in late parkinson's diseases.
4. These drugs have selectivity in their action as compared to the Levodopa that activate all types of dopaminergic receptor.

These drugs are used to prevent On/off phenomenon of Parkinson's disease patient.

It is hypothesis that Free radicles that are formed by Dopamine metabolism cause neuronal cell death, so Dopamine receptor agonist has potential to modify the course of disease by Endogenous release of Dopamine.

or by Exogenous administration of Levodopa.

Some drugs for example Bromocriptine and pergolide are the older ergot derivative. and Ropinirole and pramipexole are the newer drugs. These drugs are similar in their action and therapeutic effect. but differ in their;

*- Adverse effect

the older drugs;

*- Bromocriptine and

*- Pergolide

have a action as agonist on D_2 receptor and also have some activity on D_1 receptor. whereas the newer drugs Ropirinole and pramipexole have activity only on D_2 receptor

the older ergot derivatives cause

* gastrointenstinal disturbance

↳ Nausea

↳ Vomiting

Whereas in the case of newer drugs there is no evidence of

gastrointestinal disturbance like
- Nausea
- Vomiting

ANTI MUSCARINIC DRUG

* - Benzatropine
* - Trihexyphenydigal

also used for the treatment of Parkinsonism

The biological basis of action of these drugs is not clear, it seems likely that it acts within the Neostriatum through the receptor that normally mediate the response to the intrinsic polynergic innervation arises from cholinergic striatal interneurons.

⇒ Anti muscarinic Adverse Effects
* - Xerostemia (Dry mouth)
* - Urinary retention
* - Blurred vision

D1 receptor Family
↑ cAMP, ↑ PIP_2 hydrolysis
- Ca^{2+} mobilization
- PKC activation

D2 receptor Family
↓ cAMP ↑ K^+ currents
↓ voltage gated Ca^{2+} currents

D_1	D_5	D_2	D_3	D_4
• Striatum	• hippocampus	• Striatum	• olf. tubercle	• frontal cortex
• neocortex	• hypothalamus	• SNPC	• n. accumbens	• medulla
		• Pituitary	• hypothalamus	• retina

Preliminary evidence suggests that this drug may help reduce dyskinesias and other motor complications, associated with levodopa therapy

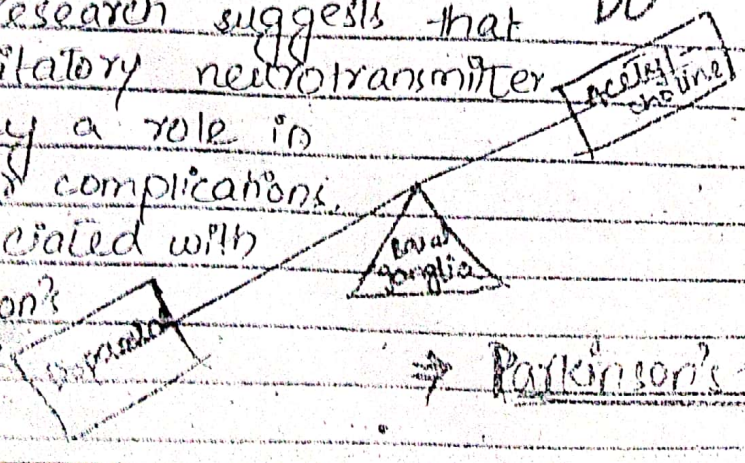
ANTI-VIRAL

Amantadine → Antiviral

use for the prophylactic treatment of influenza virus.
also used for the treatment of Parkinsonism
It may;
⇒ Interrupt dopamine release and reuptake and its anti-muscarinic effect may contribute its anti-parkinson effect but the exact mechanism in parkinson disease treatment is not clear.

Amantadine also have activity on NMDA (glutamate) receptor that may be involved in the treatment of parkinsonism
Amatadine develop some anti-muscarinic adverse effect.

→ Research suggests that excitatory neurotransmitter play a role in motor complications associated with Parkinson's disease



⇒ Parkinson's Disease

MAO Inhibitors

There are two types.

1- MAO A

2- MAO B

Both enzymes types inhibit the metabolism of monoamines (serotonin and NE) in periphery.

whereas MAO B is responsible for metabolism of monoamines (Dopamine) in brain.

So, MAO B is dominant in Neostriatum.

Selegiline at low to moderat dose for example 10mg/day is used to prevent metabolism of dopamine in brain but at higher dose it cause non-selective inhibition.

Other than salageline all MAO inhibit are non-selective.

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* In PARKINSON'S DISEASE THERE IS THE DISTURBANACE OF DOPAMINERGIC RECEPTOR.