



# **Drug Therapy of Parkinsonism**

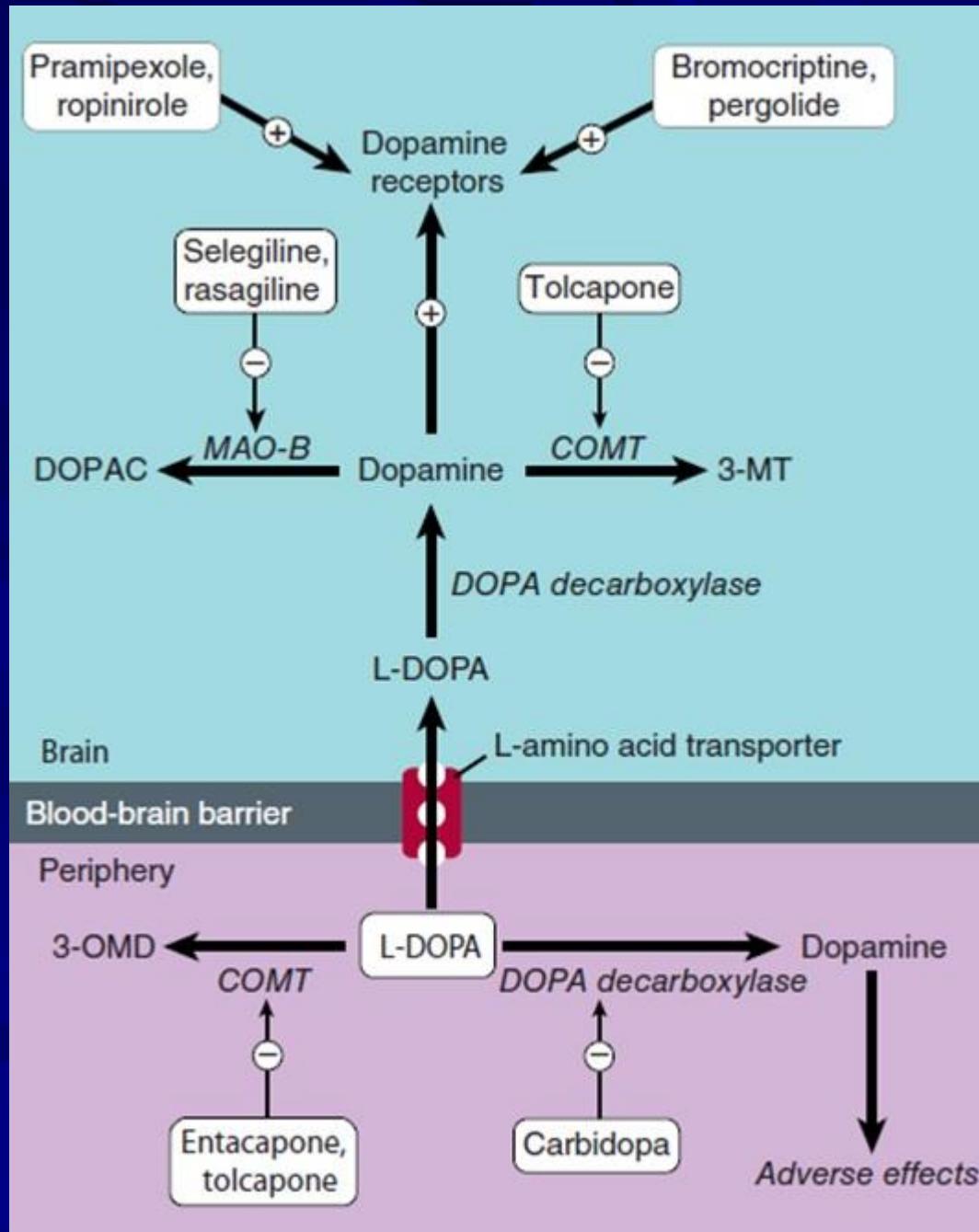
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**Parkinsonism is a progressive neurological disorder of muscle movement, usually affects people over 65Y, characterized by:**

- Tremors
- Muscular rigidity
- Bradykinesia

## Physiology

- Normal muscle movement requires balance of dopamine (inhibitor) and ACh (stimulator)
- In the substantia nigra, enough dopamine is released to counteract the effects of Ach
- In Parkinson's disease destruction of cells in the substantia nigra results in the degeneration of the nerve terminals that secrete dopamine in the neostriatum
- This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.



## **Drug used in parkinson's disease**

### **Dopamine precursor (levodopa)**

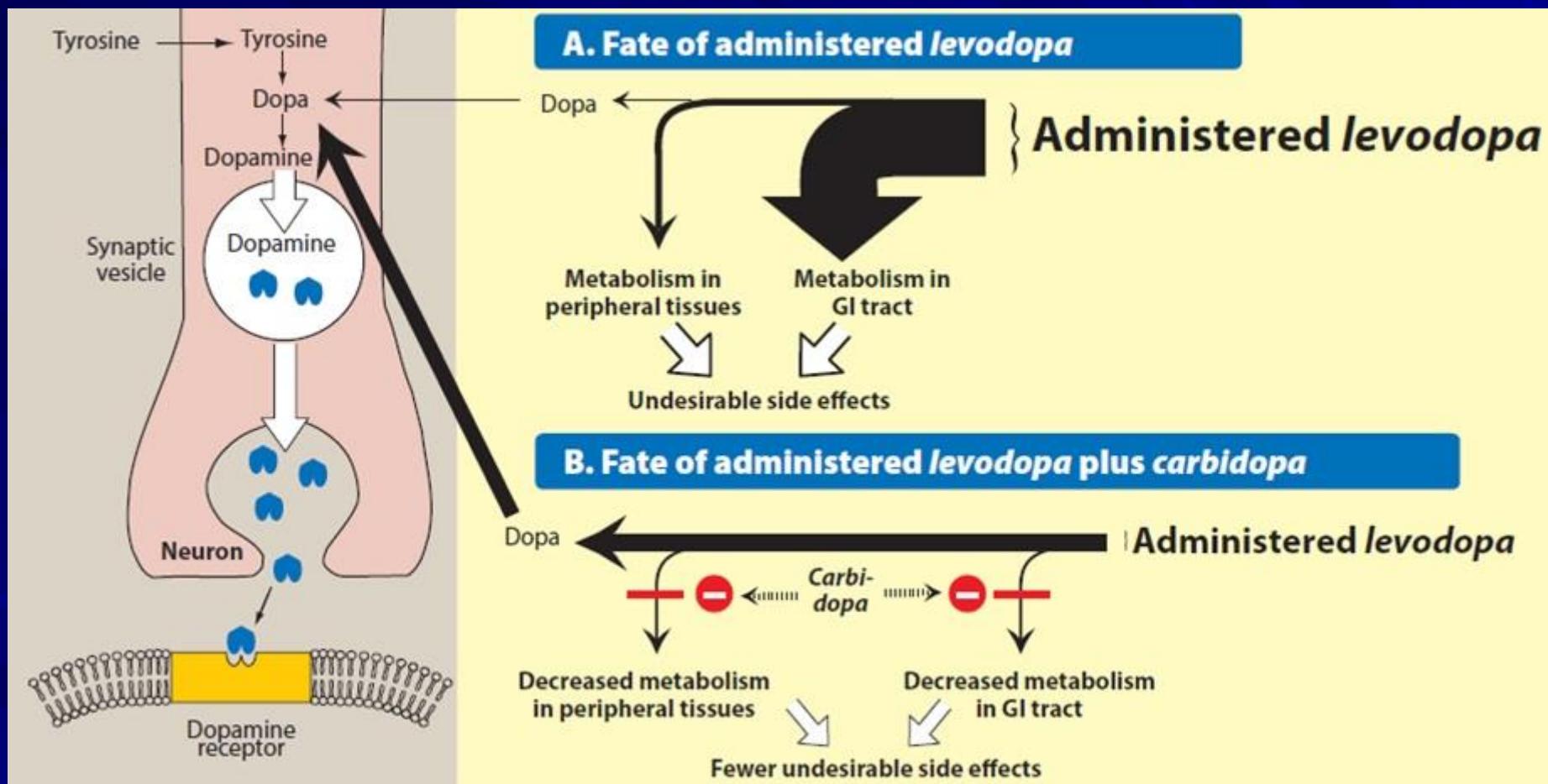
- Dopamine does not cross the blood–brain barrier, but its precursor, levodopa, is actively transported into the CNS and converted to dopamine.
- Levodopa must be administered with carbidopa. Without carbidopa, much of the drug is decarboxylated to dopamine in the periphery, resulting in nausea, vomiting, cardiac arrhythmias and hypotension.

# **Carbidopa**

## **(A dopamine decarboxylase inhibitor)**

- Decrease the metabolism of levodopa in the periphery
- Increasing the availability of levodopa to the CNS.
- Lowers the dose of levodopa needed & decreases the side effects arising from peripherally formed dopamine.

# Synthesis of dopamine from levodopa in the absence and presence of carbidopa



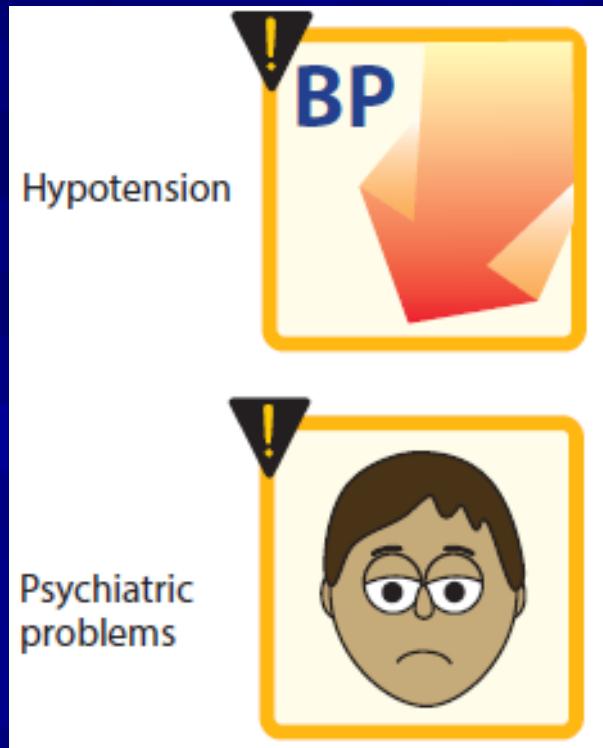
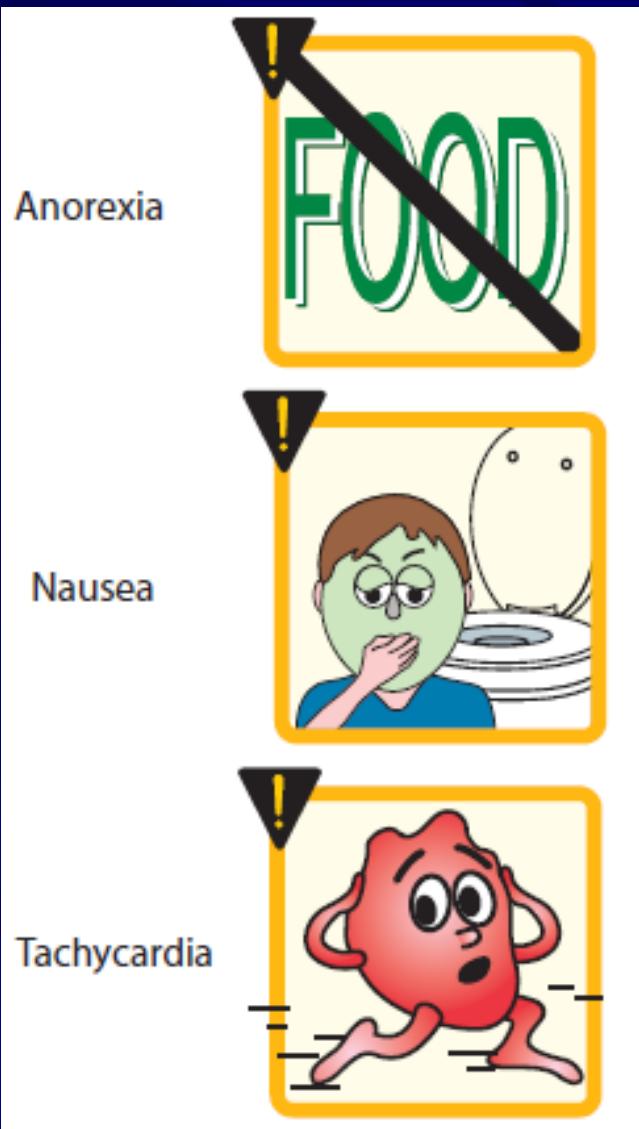
## **Therapeutic Uses**

- Levodopa used in combination with carbidopa
- Reduces the severity of symptom of parkinsonism for the first few years of treatment. but decline in response during the 3rd to 5th year of therapy occurs.
- Withdrawal from the drug must be gradual.

## Parmacokinetic

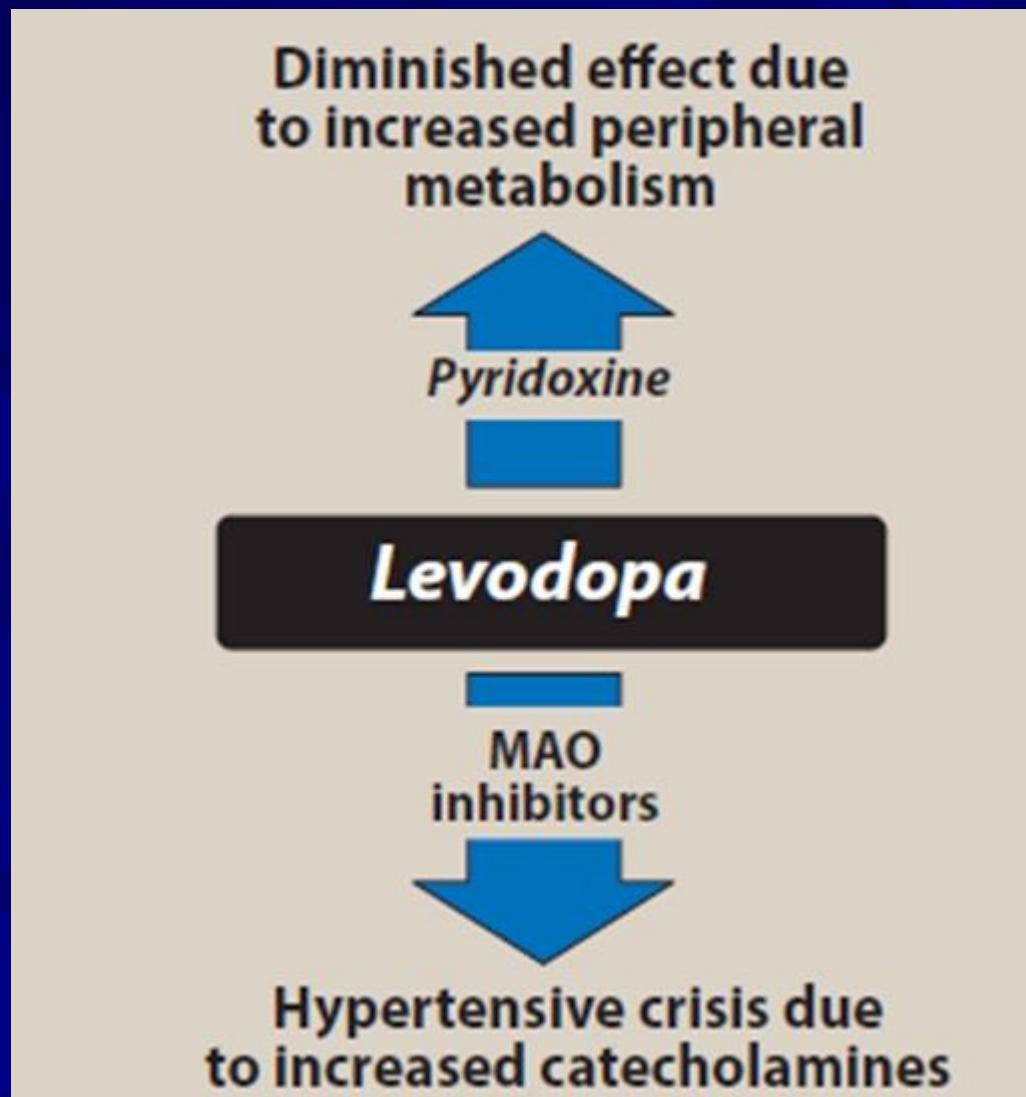
- Levodopa should be taken on an empty stomach  
(30 minutes before a meal)
- Levodopa half-life (1 to 2 hours)

# Adverse Effects of Levodopa



# Some drug interactions observed with levodopa.

MAO = monoamine oxidase

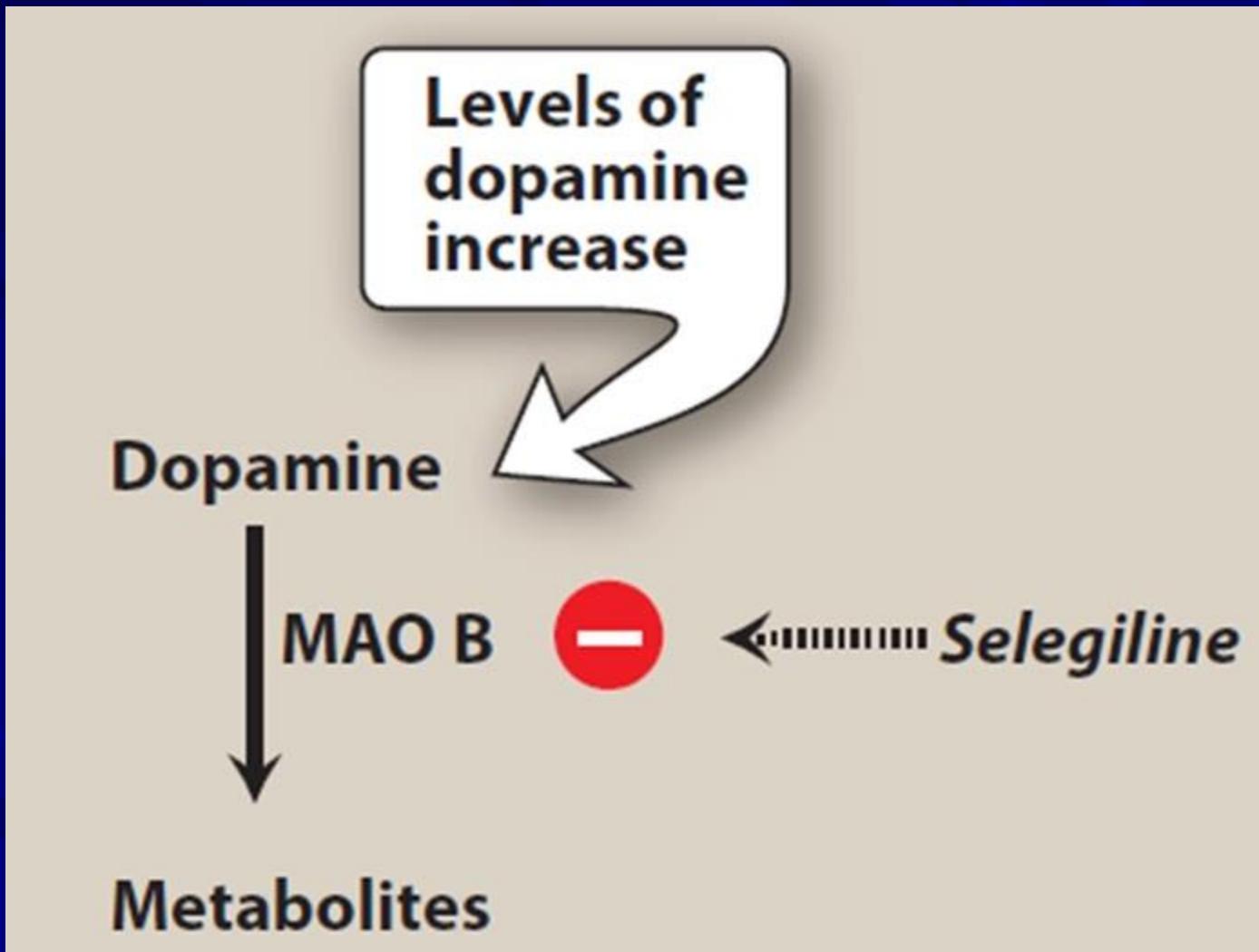


# **MAO inhibitors**

## **Selegiline**

- At low to moderate doses. Selectively inhibits monoamine oxidase (MAO) type B (which metabolizes Dopamine), this lead to increases dopamine levels in the Brain
- At high doses it loses its selectivity, selegiline (inhibit MAO type A (which metabolizes norepinephrine and serotonin))
- Selegiline is metabolized to methamphetamine and amphetamine, whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon.
- It has little potential for causing hypertensive crises

## Action of selegiline in dopamine metabolism.



## **Catechol-O-methyltransferase inhibitors Entacapone and tolcapone**

- Selectively and reversibly inhibit COMT (the enzyme in both the CNS and peripheral tissues, converts levodopa to 3-O-methyldopa)
- Inhibition of COMT by these agents leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine
- Entacapone acts only in the periphery.
- Tolcapone is taken 3 times daily
- Entacapone 5 times daily

## **Adverse Effects of Entacapone and Tolcapone**

- Diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations and sleep disorders
- Hepatic necrosis (tolcapone )

# Dopamine-receptor Agonists

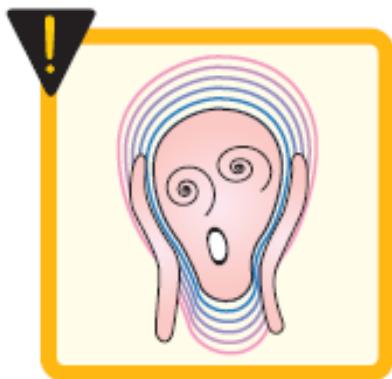
## Bromocriptine

- An ergot alkaloid
- Acts as a partial agonist at dopamine D2 receptors in the brain.
- The drug increases the functional activity of dopamine neurotransmitter
- Used as individual therapy or in combinations with levodopa (and with anticholinergic drugs)

# Some adverse effects of dopamine agonists



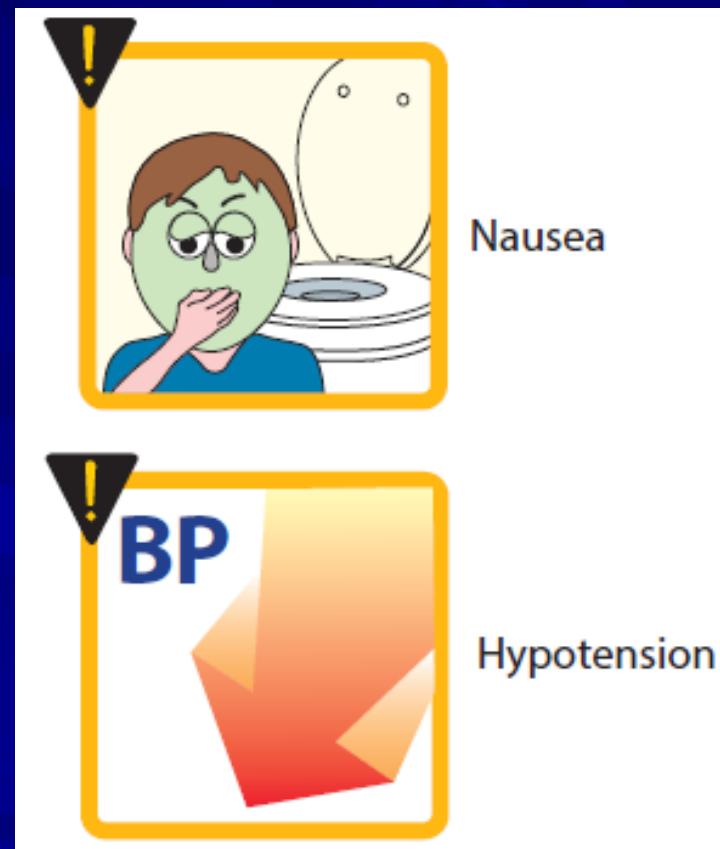
Sedation



Hallucinations



Confusion



Nausea

Hypotension

## **Adverse Effects of Bromocriptine**

- Anorexia, nausea and vomiting
- Dyskinesias, and postural hypotension
- Behavioral effects, confusion and hallucinations

**Note:** Its use decrease with the introduction of non-ergot dopamine receptor agonists.

## **Pramipexole**

- Non-ergot has high affinity for the dopamine D3 receptor.
- Used as monotherapy or with levodopa in advanced disease.
- Pramipexole is administered orally 3 times daily

## **Adverse Effects of Pramipexole**

- Anorexia, nausea and vomiting, postural hypotension and dyskinesias.
- Mental disturbances (confusion, delusions and hallucinations)

**Note:** The drug is contraindicated in patients with active peptic ulcer disease, psychotic illness, or recent myocardial infarction.

## Ropinirole

- Non-ergot, this drug has high affinity for the dopamine D2 receptor.
- Monotherapy or with levodopa
- It is given 3 times daily, but a prolonged release form can be taken once daily.
- Similar adverse effects and contraindications to those of pramipexole.

## **Apomorphine**

- A potent dopamine receptor agonist
- Injected subcutaneously may provide rapid (within 10 min) but temporary relief (1–2 h) of “off-periods” of akinesia in patients on optimized dopaminergic therapy.

## **Adverse Effects of Apomorphine**

- Severe nausea (pretreatment for 3 days with antiemetics is necessary)
- Dyskinesias, hypotension, drowsiness and sweating

## **Amantadine**

- Enhances dopaminergic neurotransmission by unknown mechanisms (increasing synthesis or release of dopamine or inhibition of dopamine reuptake)
- Improve bradykinesia, rigidity, and tremor (for only a few weeks).
- It has muscarinic blocking actions
- Amantadine also has antiviral effects.

## **Adverse Effects of Amantadine**

- Restlessness, agitation, insomnia, confusion, hallucinations and acute toxic psychosis.
- Dermatologic reactions
- Gastrointestinal disturbances
- Urinary retention
- Postural hypotension.
- peripheral edema

# **Acetylcholine-blocking (Antimuscarinic) Drugs**

## **Benztropine**

- Decrease the excitatory actions of cholinergic neurons on cells in the striatum by blocking muscarinic receptors.

## **Adverse Effect**

- Drowsiness, confusion, & hallucinations.
- Peripheral adverse effects are typical of atropine-like drugs.