

# Parkinsonism



# History – Parkinson`s disease

- Parkinson's disease was first formally described in 1817 by a London physician named James Parkinson

# Parkinsonism:

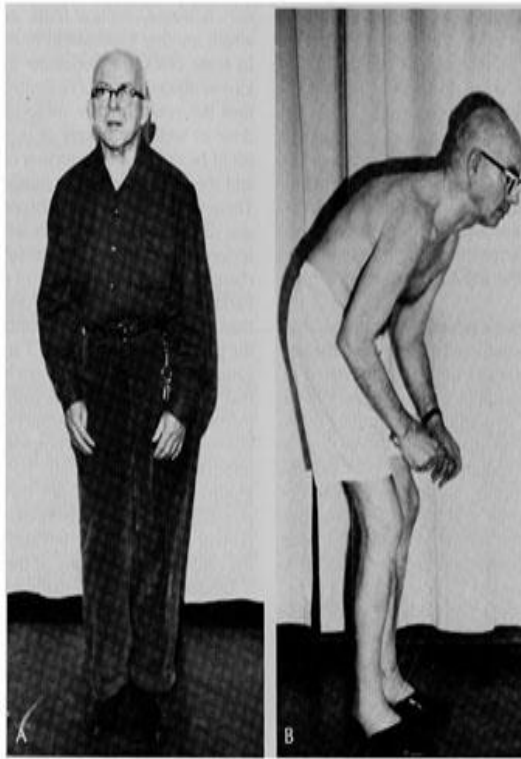
## Definition :

Parkinsonism is a progressive neurological disorder of muscle movement as a clinical syndrome consisting of 4 cardinal features:

- 1) resting tremor (which usually disappears during voluntary movement)
- 2) muscular rigidity
- 3) bradykinesia (slowness of movement) and, in extreme cases, a loss of physical movement (akinesia)
- 4) impairment of postural balance leading to disturbances of gait and falling
- 5) The secondary manifestations are mask-like face, difficulty in speech, slowing of mental process and dementia.

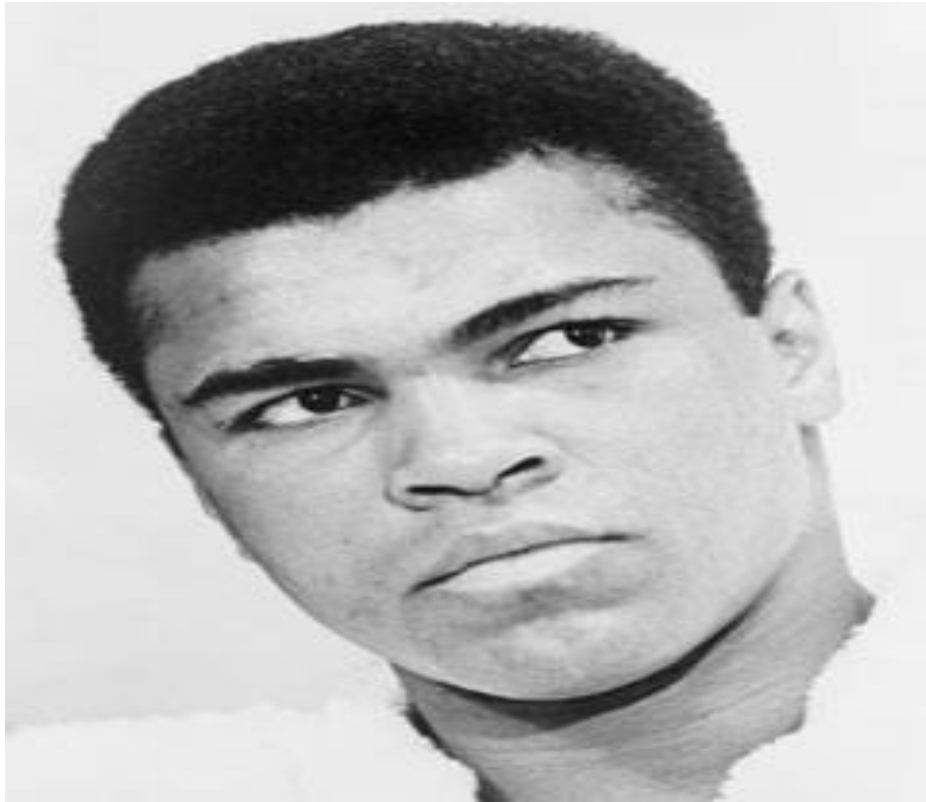
# Parkinsonism (PD) - signs

## Parkinson's Disease





Who is he?



**The main Pathological feature of Parkinson's disease is the loss of the dopaminergic nigrostriatal pathway**

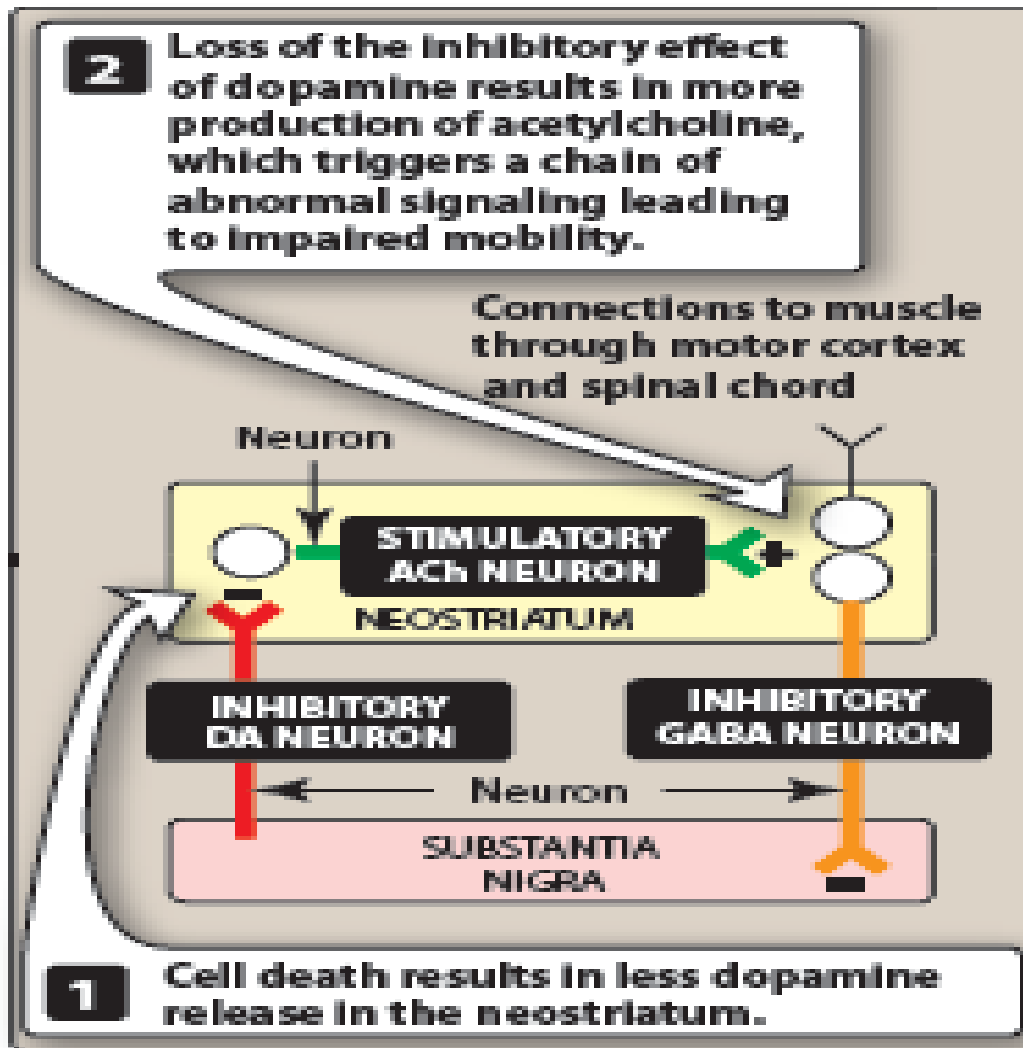
**Dopaminergic neurons in the substantia nigra that normally inhibit the output of GABAergic cells in the striatum are lost**

**80% of the Dopamine producing cells must be lost before symptoms begin to show**

# Etiology

- Nerve fibers from cerebral cortex and thalamus secrete acetylcholine in the neostriatum causing excitatory effects that initiate and regulate gross intentional movements of the body.
- In Parkinson's disease, due to deficiency of dopamine in striatum, an imbalance between dopaminergic (inhibitory) and cholinergic (excitatory) system occurs, leading to excessive excitatory actions of cholinergic neurons on striatal GABAergic neurons.





**Figure 8.5**

Role of substantia nigra in Parkinson disease. DA = dopamine; GABA =  $\gamma$ -aminobutyric acid; ACh = acetylcholine.



Normal  
amount of  
dopamine



Normal  
amount of  
acetylcholine



Decreased  
amount of  
dopamine

Normal  
amount of  
acetylcholine

## **Idiopathic Parkinson's disease**

- Idiopathic Parkinson's disease - or Parkinson's - is the most common type of parkinsonism. Unlike some other forms which have specific causes it is not known why idiopathic Parkinson's occurs.
- The main symptoms of idiopathic Parkinson's are tremor, rigidity and slowness of movement.

# Vascular Parkinsonism:

- Vascular parkinsonism is one of the atypical forms of parkinsonism.
- The most likely causes of vascular parkinsonism are hypertension and diabetes. A stroke (cerebrovascular accident), cardiac disease or carotid artery pathology (another form of stroke) may also be involved.
- Symptoms of vascular parkinsonism may include difficulty speaking, making facial expressions or swallowing.
- Other signs can include problems with memory or confused thought, cognitive problems and incontinence.

# Inherited Parkinson's

- It is thought that although it is not directly inherited, some people may have genes that increase the possibility of developing Parkinson's.
- People who have genes that are prone to Parkinson's may be more likely to develop the condition when combined with other factors, such as environmental toxins or viruses.
- At present, it is estimated that up to 5% of people with Parkinson's may have a genetic cause.

# Drug Induced Parkinsonism:

- Antipsychotics: Chlorpromazine, Fluphenazine and Haloperidol
- Antihypertensive like Reserpine
- Antiemetics: Metochlopramide (Reglan) and Prochlorperazine (Compazine),
- Most people will recover within months, and often within hours or days, of stopping the drug that caused the dopamine block.
- Not associated with loss of nerve cells in the substantia nigra

# PD - Etiology

- Viral encephalitis
- Pesticides, herbicides, industrial chemicals - contain substances that inhibit complex I in the mitochondria



# Drugs used for Parkinsonian Disease:

- Drug therapy is aimed at restoring the balance between the dopaminergic and cholinergic components,

which is achieved by:

– Increasing the central dopaminergic activity

OR

– Decreasing the central cholinergic activity

OR

**BOTH.**

# Classification of antiparkinsonian Drugs:

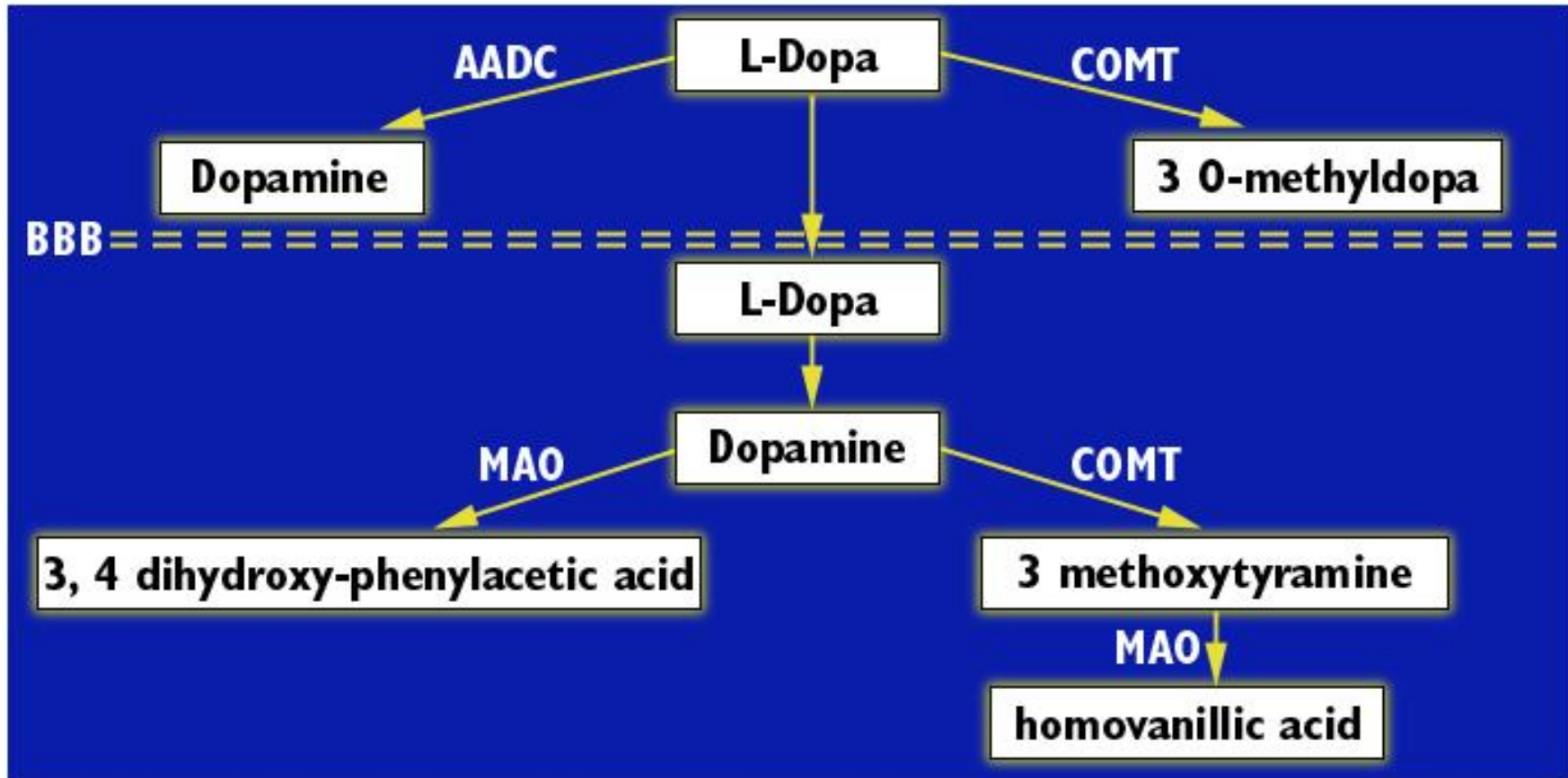
- **Drugs acting on dopaminergic system:**
  - Dopamine precursors – *Levodopa (l-dopa)*
  - Peripheral decarboxylase inhibitors – *carbidopa and benserazide*
  - MAO-B inhibitors – *Selegiline, Rasagiline*
  - COMT inhibitors – *Entacapone, Tolcapone*
  - Dopaminergic agonists: *Bromocriptyne, Ropinirole and Pramipexole*
  - Dopamine facilitator - *Amantadine*
- **Drugs acting on cholinergic system**
  - Central anticholinergics – *Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden*
  - Antihistaminics – *Orphenadrine, Promethazine*

- Dopamine itself does not cross the blood-brain barrier and therefore has no CNS effects. However, levodopa, as an **amino acid**, is transported into the brain by amino acid transport systems, where it is converted to dopamine by the enzyme L-aromatic amino acid decarboxylase, which is stored and released as a transmitter.

# LEVODOPA

- The effect of levodopa may be due to an increased release of dopamine from surviving dopaminergic neurones
- the effectiveness of levodopa decreases as the diseases advances.

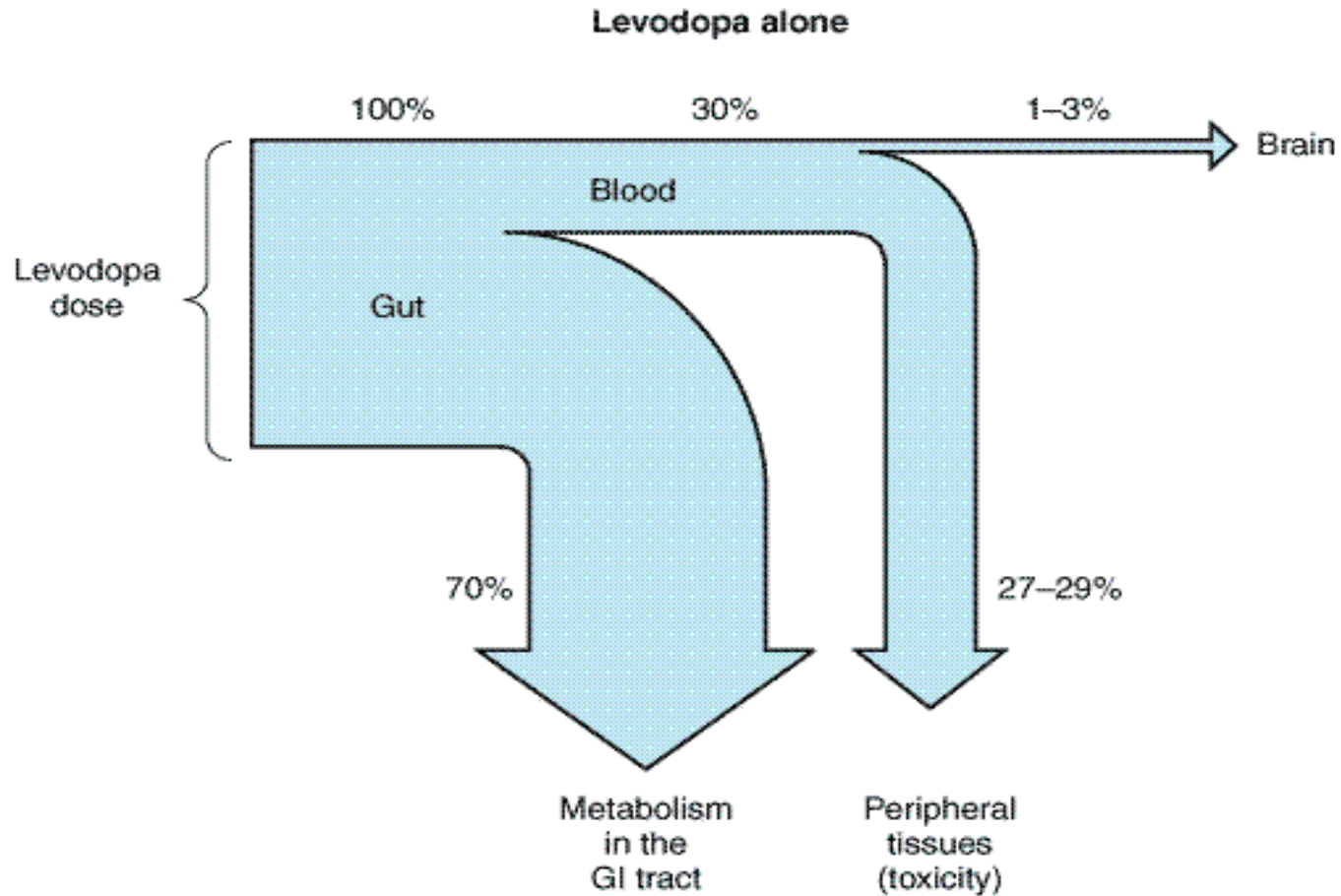
# Diagram of LD Metabolism



# LEVODOPA

- Pharmacokinetics
  - Levodopa, when given without a decarboxylase inhibitor, about 70% of the dose is metabolized in the gut wall and liver, 27-29% goes to peripheral tissues to exert adverse effects and only 1-3% enters the brain.
  - When levodopa is administered with Carbidopa, about 10% of the dose reaches the brain.

# Levodopa (Pharmacokinetics) – contd.



- In practice, levodopa is administered in combination with a peripherally acting inhibitor of aromatic L-amino acid decarboxylase, such as *carbidopa*, that do not penetrate into the CNS.
- Inhibition of peripheral decarboxylase markedly increases the fraction of administered levodopa that crosses the blood-brain barrier and reduces the incidence of peripheral side effects.



# Pharmacological actions:

- CNS

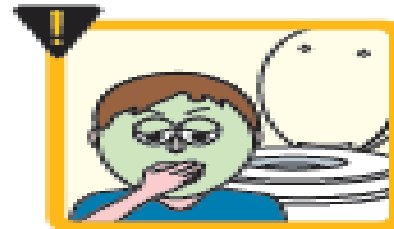
- Levodopa produces marked symptomatic improvement in Parkinsonian patients.

- Hypokinesia and rigidity resolve first, later tremor as well. Secondary symptoms of posture, gait, facial expression and mood are gradually normalized.

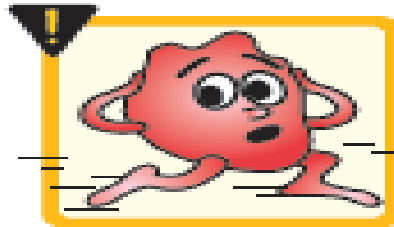
Anorexia



Nausea



Tachycardia



Hypotension



Psychiatric  
problems



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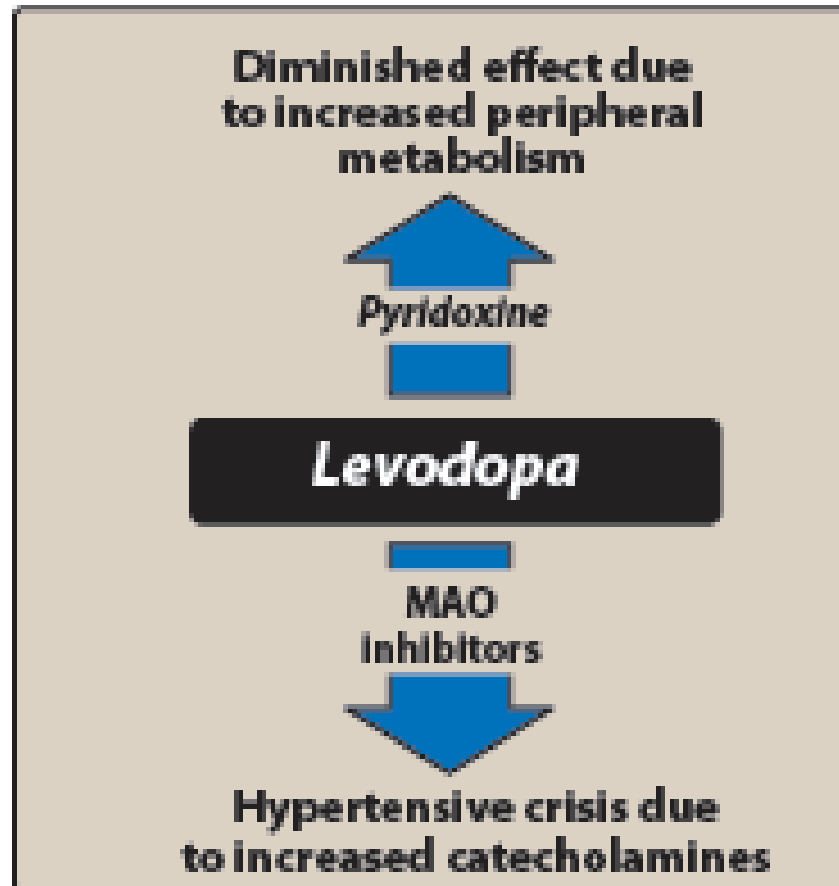
**Figure 8.7**  
*Adverse effects of levodopa.*

# Drugs used in the treatment of parkinsonism

## Levodopa

### Drug Interactions:

1. Pharmacologic doses of **pyridoxine** (vitamin B6) enhance the extracerebral metabolism of levodopa and prevent its therapeutic effect unless a peripheral decarboxylase inhibitor is also taken.
2. Levodopa should not be given to patients taking **monoamine oxidase A inhibitors** or within 2 weeks of their discontinuance, because such a combination can lead to hypertensive crises.



**Figure 8.8**

Some drug interactions observed with *levodopa*. MAO = monoamine oxidase.

# PERIPHERAL DECARBOXYLASE INHIBITORS

- **Carbidopa and Benserazide** are extracerebral (peripheral) decarboxylase inhibitors.
- They do not inhibit conversion of levodopa to dopamine in brain. They increase the half-life of levodopa in the periphery and make more of it available to enter the brain.
- The benefits obtained are:
  - The plasma half-life of levodopa is prolonged and dose is reduced to approximately  $\frac{1}{4}$
  - Due to reduced systemic concentration of dopamine, nausea and vomiting are not prominent
  - Cardiac adverse effects are minimized
  - Pyridoxine reversal of levodopa effect does not occur as the decarboxylase has been inhibited already

# Drugs used in the treatment of parkinsonism

## Monoamine oxidase inhibitors

Two types of monoamine oxidase (MAO) have been distinguished.

Monoamine oxidase (A) metabolizes norepinephrine and serotonin, dopamine; monoamine oxidase (B) metabolizes dopamine selectively.

### **Selegiline (deprenyl) and rasagiline:**

#### **Mechanism of action:**

- Selective irreversible inhibitors of monoamine oxidase B (retards the breakdown of dopamine). Given alone, it has a weak action. It is therefore used as adjunctive therapy for patients with a declining response to levodopa. They allow dose of L-dopa to be reduced.

#### **Side effects:**

- Selegiline is metabolised to methamphetamine and amphetamine thereby producing insomnia when taken later during the day. At high doses, patients are at risk for severe hypertension

#### **Drug interactions:**

- It should not be taken by patients receiving tricyclic antidepressants, or serotonin reuptake inhibitors because of the risk of acute toxic interactions such as serotonin syndrome.
- The adverse effects of levodopa may be increased by selegiline and rasagiline

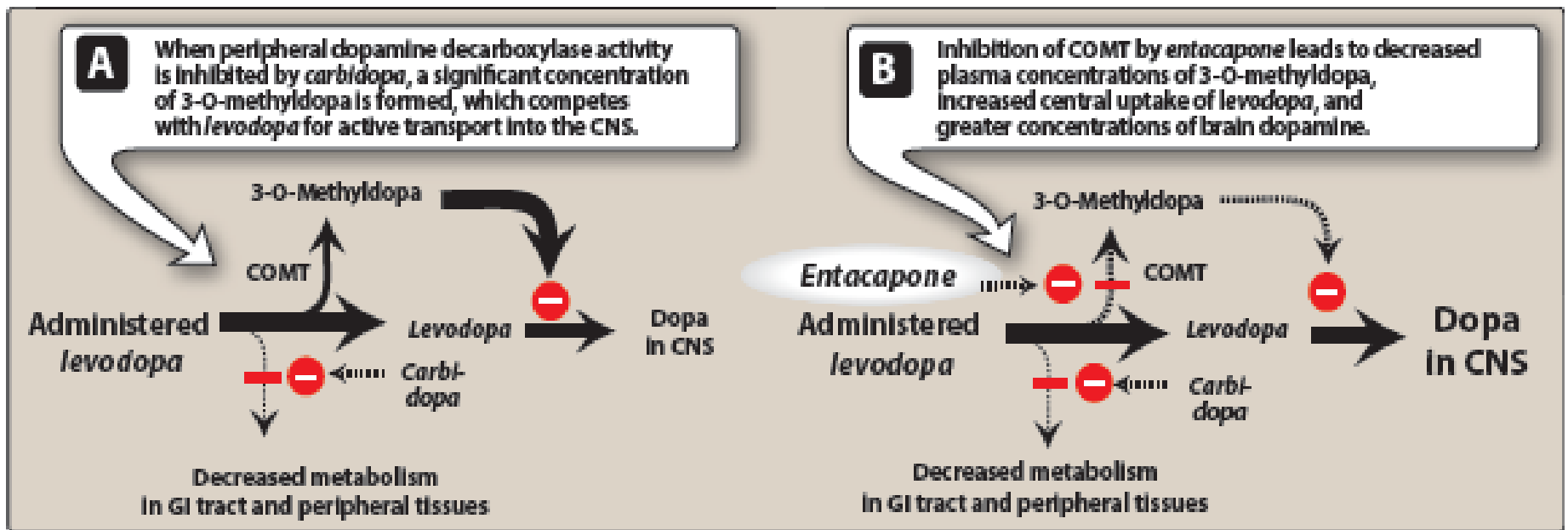
# Drugs used in the treatment of parkinsonism

## **Catechol O methyl transferase inhibitors (1)**

### **Tolcapone and Entacapone**

- **Mechanism of action:**

1. **Inhibit** catechol O methyl transferase (COMT) which is responsible for the conversion of dopa into methyl dopa. Elevated levels of methyl dopa decreases the response to levodopa, because methyl dopa competes with levodopa for an active carrier mechanism that governs its transport across the blood-brain barrier.
2. **prolong the action of** levodopa by diminishing its peripheral metabolism.
  - Tolcapone but not Entacapone penetrates the blood-brain barrier
  - These agents may be helpful in patients receiving levodopa to reduce dose and decrease fluctuations in response



**Figure 8.10**

Effect of *entacapone* on dopa concentration in the central nervous system (CNS). COMT = catechol-O-methyltransferase.

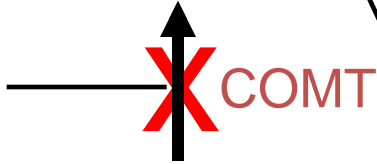


# COMT inhibitors

Periphery

3-O-Methyldopa

tolcapone



L-DOPA

carbidopa



Dopamine



CNS (striatum)

DOPAC

selegiline

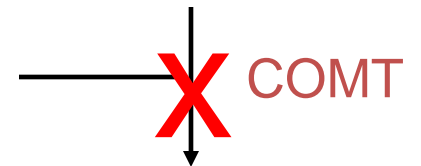


L-DOPA

AAD

Dopamine

tolcapone



3-Methoxy tyramine

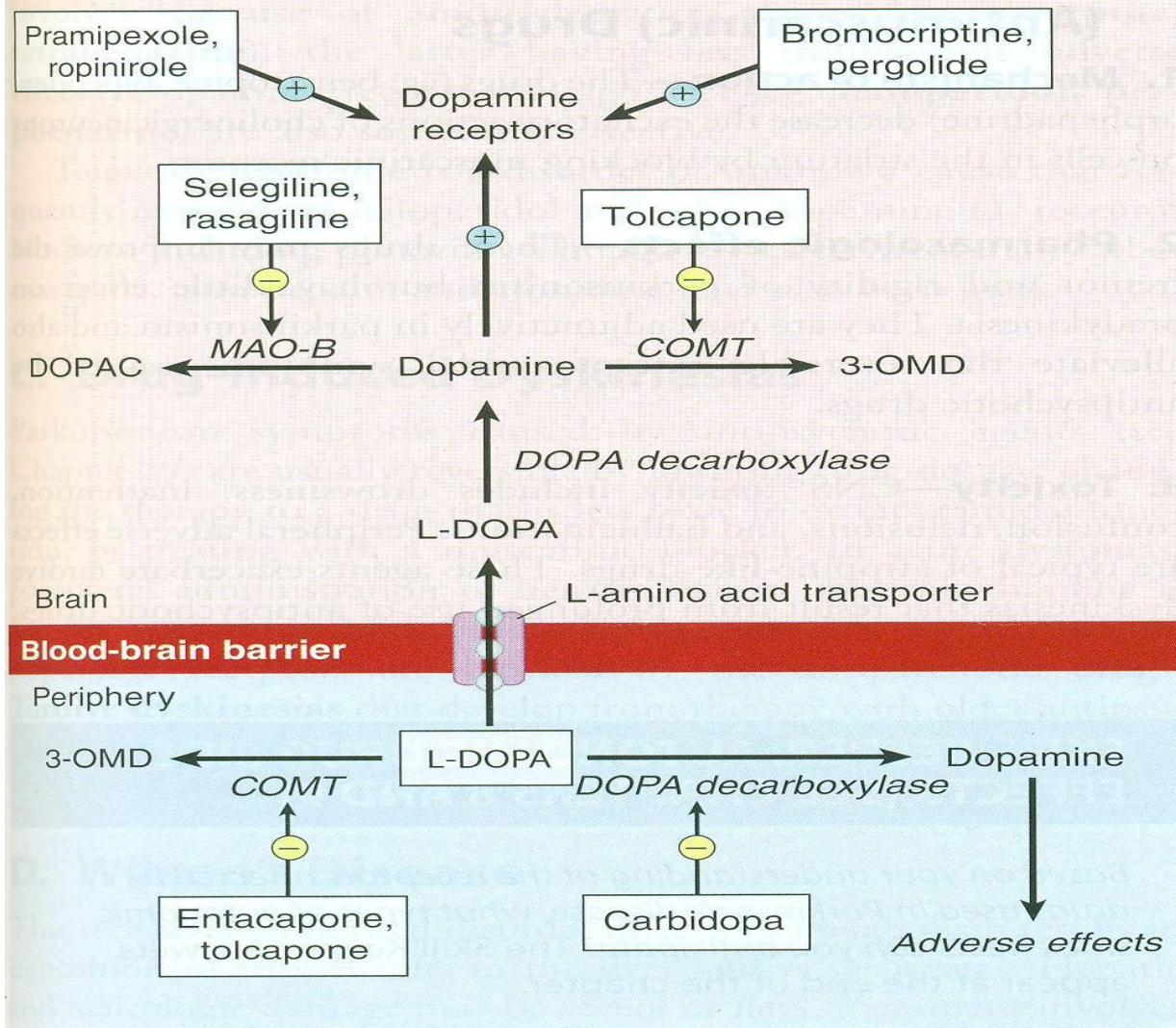


# COMT inhibitors

- Allow more Sinemet (L-DOPA and CARBIDOPA) to pass through the blood brain barrier
- Can only be used in combination with Sinemet
- Side effects are similar to levodopa  
Diarrhea, postural hypotension, nausea, anorexia, dyskinesia, hallucinations and sleep disorders.
- Tolcapone (Tasmar) → hepatic toxicity  
mandatory monitoring of liver function enzymes with Tolcapon

# Stalevo

- Triple combination tablet of levodopa/carbidopa/entacapone in PD patients



**FIGURE 28–2** Pharmacologic strategies for dopaminergic therapy of Parkinson's disease. The actions of the drugs are described in the text. MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; DOPAC, dihydroxyphenylacetic acid; L-DOPA, levodopa; 3-OMD, 3-O-methyldopa. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 11th ed. McGraw-Hill, 2009: Fig. 28–5.)

## Drugs used in the treatment of parkinsonism

### **Dopamine receptor agonists (1)**

- Dopamine agonists are first-line drugs for Patients with mild or moderate symptoms.
- Beneficial effects result from direct activation of dopamine receptors in the striatum.
- They are less effective than L-DOPA

# Drugs used in the treatment of parkinsonism

## **Dopamine receptor agonists (1)**

### Advantages of DA

- They are not dependent on enzymatic conversion to become active
- They are not converted to potentially toxic metabolites
- They do not compete with dietary proteins for uptake from intestine and for transport across BBB
- When used long-term, they have a lower incidence of response failures and are less likely to cause dyskinesias

# Drugs used in the treatment of parkinsonism

## **Dopamine receptor agonists (1)**

DAs cause more serious side effects:

- Hallucinations
- Daytime sleepiness
- Postural hypotension
- When used long-term, they have a lower incidence of response failures and are less likely to cause dyskinesias

## Drugs used in the treatment of parkinsonism

### **Dopamine receptor agonists (1)**

- Four orally administered dopamine-receptor agonists are available for treatment of PD:
  - 1) Ergot derivatives: as bromocriptine or pergolide
  - 2) Non ergot derivatives as ropinirole, pramipexole, Apomorphine (injectable), rotigotine (transdermal delivery system)



## Drugs used in the treatment of parkinsonism

### **Dopamine receptor agonists (1)**

- The non-ergot derivatives have fewer side effects than the ergot derivatives because of selectivity for dopamine receptors in contrast to ergot derivatives interacting with alpha-adrenergic and serotonergic receptors in addition to dopamine receptors.
- The non-ergot drugs are generally preferred to ergot derivatives

# Drugs used in the treatment of parkinsonism

## **Dopamine receptor agonists (2)**

### **Adverse effects:**

#### **I. Central:**

- Dyskinesias , mental Disturbances

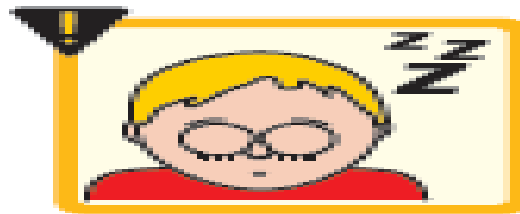
#### **II. Peripheral:**

##### **A) Gastrointestinal Effects:**

- Anorexia and nausea and vomiting

##### **B) Cardiovascular effects:**

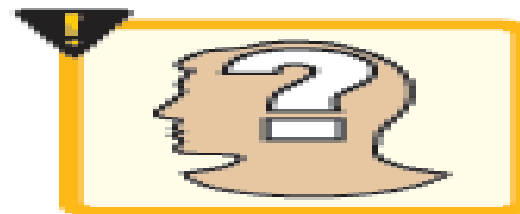
1. postural hypotension
2. cardiac arrhythmias
3. peripheral vasospasm (with ergot derivatives)



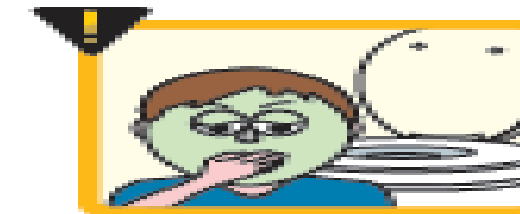
**Sedation**



**Hallucinations**



**Confusion**



**Nausea**



**Hypotension**

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**Figure 8.11**  
Some adverse effects of dopamine agonists.

# Drugs used in the treatment of parkinsonism

## **Amantadine(1)**

Amantadine, an antiviral agent is effective in the treatment of influenza. Its mode of action in parkinsonism is unclear.

### **Possible mechanisms suggested:**

- ✓ Inhibition of dopamine uptake
- ✓ Stimulation of dopamine release
- ✓ Blockade of cholinergic receptors
- ✓ Blockade of glutamate receptors

### **Clinical Use**

- Amantadine is less potent than levodopa and its effects disappear after only a few weeks of treatment. It is considered a second-line drug for PD

# Drugs used in the treatment of parkinsonism

## **Amantadine(1)**

### **Adverse Effects**

1. Central nervous system effects (confusion, anxiety)
2. Peripheral edema
3. headache
4. Heart failure
5. postural hypotension
6. urinary retention
7. gastrointestinal disturbances (eg, anorexia, nausea, constipation, and dry mouth).

### **Contraindications**

- Amantadine should be used with caution in patients with a history of seizures or heart failure.

# Drugs used in the treatment of parkinsonism

## Acetylcholine blocking drugs(1)

- Central anticholinergics:
  - Trihexyphenidyl (Benzhexole),
  - Procyclidine
  - Biperiden
  - Benztropine

# Anticholinergics

- The actions of them are similar.
- Antimuscarinic drugs may improve the tremor and rigidity of parkinsonism but have little effect on bradykinesia.
- They are used for initial or adjunct therapy.
- Individual patients may respond more favorably to one drug.

## **Adverse Effects**

- 1) Central nervous system effects, including drowsiness, restlessness, confusion, agitation, hallucinations, and mood changes. Dyskinesias occur in rare cases
- 2) Atropine – like actions: dryness of the mouth, blurring of vision, urinary retention, nausea and vomiting, constipation, tachycardia, palpitations, and cardiac arrhythmias.

**withdrawal** should be gradual in order to prevent acute exacerbation of parkinsonism.

## **Contraindications**

1. Prostatic hyperplasia,
2. Obstructive gastrointestinal disease (eg, paralytic ileus)
3. Angle-closure glaucoma.





**The net result of all of these medications is ➤  
the balancing out of the  
acetylcholine/dopamine balance and an  
improvement in movement**