

# Anti Parkinsonian Drugs

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## Parkinsonism-

It is a progressive neurodegenerative disorder affecting older people.

It is a extrapyramidal motor disorder characterised by rigidity, tremor and hypokinesia with secondary manifestations like defective posture, gait and mask like face.



## Causes

Degeneration of neurons in dopaminergic Tract due to oxidative metabolism with production of free radicals



Deficiency of dopamine(DA) which controls muscle tone and coordinates movements



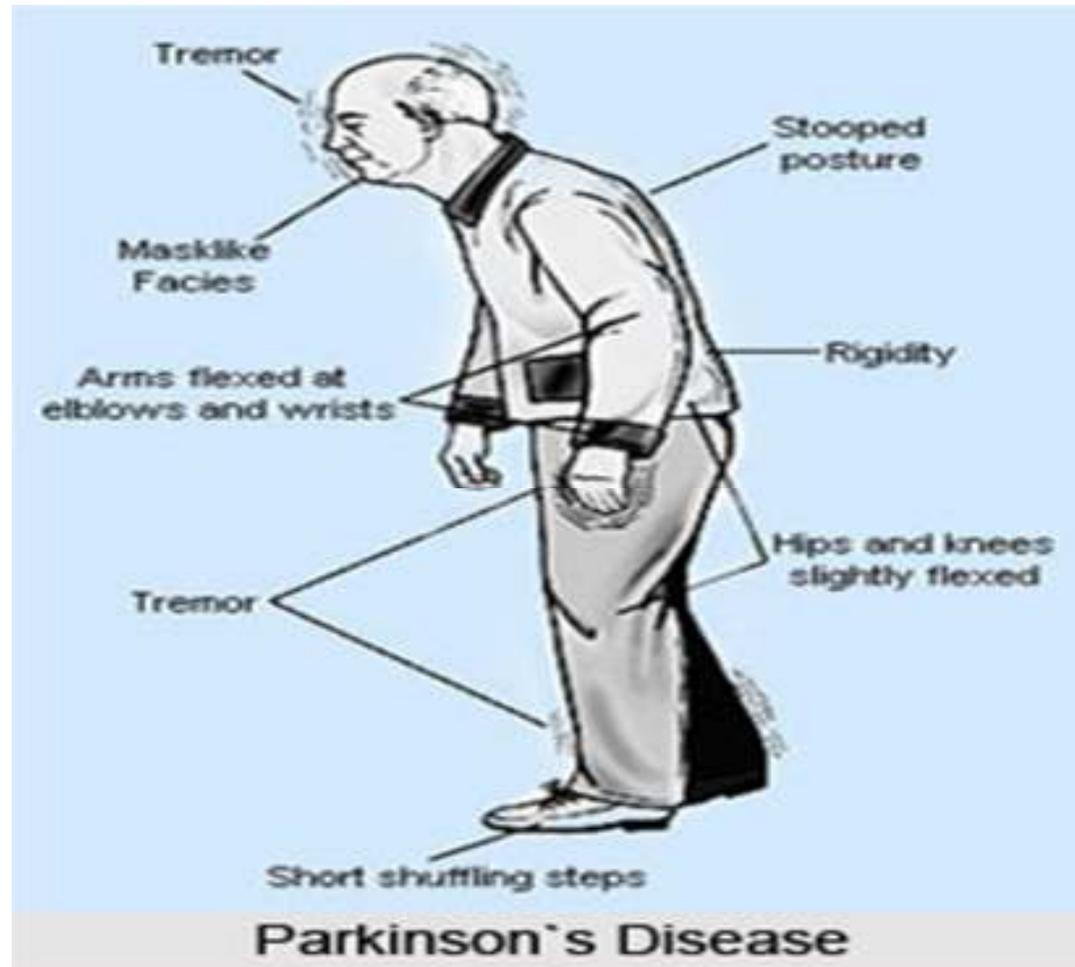
Imbalance between Dopaminergic(Inhibitory)and Cholinergic(Excitatory) system



Motor defect



# Symptoms of Disease



# Classification of Drugs

- I. **Drugs affecting Brain dopaminergic System**
  - a. Dopamine Precursor: Levodopa
  - b. Peripheral Decarboxylase Inhibitors: Carbidopa, Benserazide
  - c. Dopaminergic Agonist: Bromocriptine, Ropinirole, Pergolide
  - d. MAO B Inhibitors: Selegiline
  - e. COMT Inhibitors: Entacapone, Tolcapone
  - f. Dopamine Facilitator: Amantadine



## II. Drugs Affecting Brain Cholinergic System

- a. Central anticholinergics: Trihexyphenidyl, Procyclidine, Biperiden
- b. Antihistaminics: Orphenadrine, Promethazine

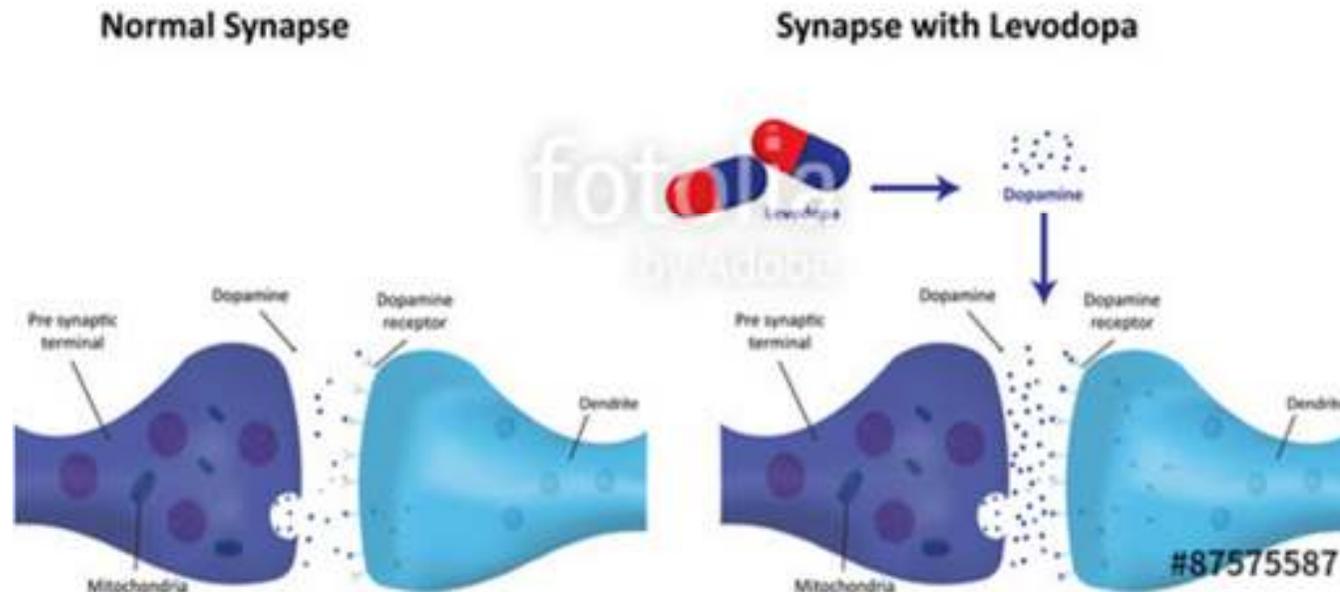


# I. Drugs acting on brain Dopaminergic System

## a. Dopamine Precursor- Levodopa

**Mechanism of Action:** Immediate precursor for transmitter DA which is stored and released as transmitter

### The Mechanism of Action of Levodopa



## Pharmacological Actions:

**1. CNS:** In Parkinsonism Patients- General alerting Response

Hypokinesia and Rigidity resolved

Secondary Symptoms of Posture, Gait, Handwriting, Speech, Facial Expression, Mood, Selfcare and interest in life are generally normalised



**2. CVS:** Acts on  $\beta$  Receptors produces central action.

Postural Hypotension

**3. CTZ:** Triggers the centre leading to nausea and Vomitting

**4. Endocrine : Parkinsonism Patients**

Mammotropes- Inhibit Prolactin Release

Somatotropes- Increase GH Release



## Pharmacokinetics

**A**bsorption from small intestine by Active Transport

**D**istribution enters brain and its capillaries

**M**etabolism in liver ,  $t_{1/2} = 1-2$  hrs.

3-O Methyldopa

↑  
COMT

Levodopa

↓  
Dopa decarboxylase

Dopamine

**E**xcretion in urine



## Adverse Effects

### -At initiation of therapy

- ❖ Nausea & Vomiting
- ❖ Postural Hypotension
- ❖ Cardiac Arrhythmia
- ❖ Exacerbation of Angina
- ❖ Alteration in taste sensation

### -After Prolonged therapy

- ❖ Abnormal movements like Facial tics, Grimacing, movements of Limbs
- ❖ Behavioral effects like mild anxiety, nightmares, Severe depression, Mania, Hallucinations, Mental Confusion like Psychosis.

-Fluctuation in motor performance(After 2-5 Yrs of therapy)  
'End of dose' or 'on-off' effect



## Caution:

Ischaemic heart disease, cerebrovascular, psychiatric, hepatic and renal disease, Peptic Ulcer, Glaucoma and Gout.

**Dose:** 2-3 gm/day (LEVOPA 0.5gm Tablet)

## Drug Interactions:

1. Pyridoxine : reduces availability of levodopa to cross the BBB
2. Antihypertensives drugs causes increase incidences of postural hypotension
3. Atropine – Anticholinergics have additive anti parkinsonism action.



## b. Peripheral decarboxylase inhibitors

**Mechanism of action:** administered along with levodopa and it increase its  $t_{1/2}$  in periphery and make more DA available to cross along the BBB

**Levodopa+ Carbidopa= Co-careldopa**

### Benefits:

- Plasma  $t_{1/2}$   $\uparrow$ , dose is reduced
- Cardiac complications are minimised
- Pyridoxine reversal of Levodopa effect does not occur
- 'On-off' effect is minimised since levels of DA sustained
- Degree of improvement also higher



## Problems not resolved:

- Behavioral movements and abnormal movements are more pronounced and appear earlier
- Postural hypotension

**Dose:** TIDOMET-LS : 10mg Carbidopa +100mg Levodopa



## c. Dopaminergic Agonists

**Mechanism of Action:** Selective activation of DA receptors in dopaminergic tract. particularly on D2 receptors.

Eg. Bromocriptine

### Pharmacokinetics:

A - Orally

D- in major organ brain and its capillaries

M- liver ,  $t_{1/2}$  = 6-10hrs.

E- in Urine

### Side effects:

Vomiting, Hallucinations, Hypotension, Nasal Stiffness, Conjunctival infection, Fall in BP

**Dose:** 5-10mg thrice daily smoothens 'on-off' Fluctuations



## d. MAO B Inhibitor

**Mechanism of action:** Selectively inhibit the mono amine oxidase present in peripheral adrenergic structures and intestinal mucosa, particularly on MAO-B

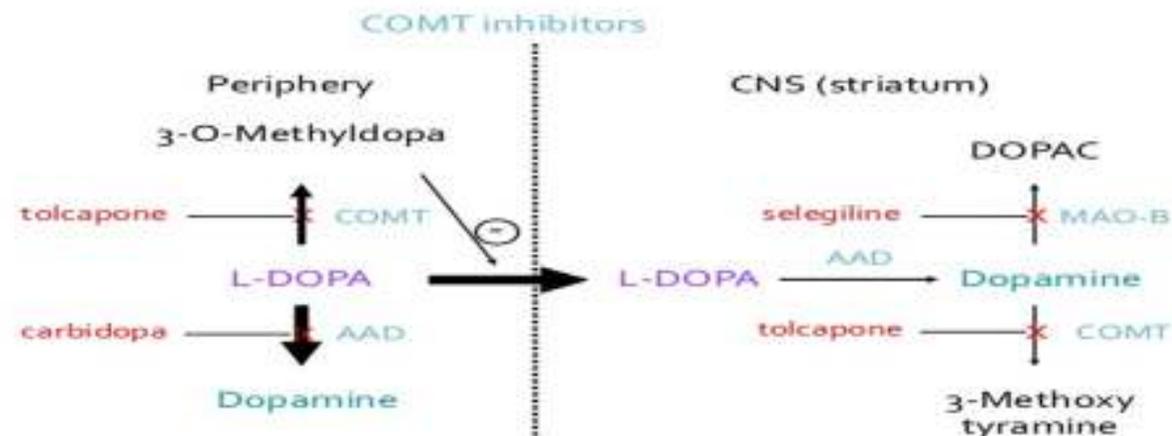
**Side effects:** Postural hypotension, nausea, confusion, accentuation of levodopa induced involuntary movements and psychosis

**Dose:** Selegiline: 10mg/day



## e. COMT Inhibitors

**Mechanism of action:** COMT plays a role in the degradation of DA in brain as well, COMT INHIBITORS could preserve DA formed in the striatum and supplement the peripheral effect eg: entacapone acts only in the periphery (due to short duration of action) , For tolcapone also the central action is less important.



## e. Pharmacokinetics:

**A-** Orally

**D-** By binding with plasma albumin

**M-** in liver by cytochrome P450

**E-** in Faeces and Urine

**Side effects:** Nausea, Vomitting, Dyskinesia, Hallucination

**Dose:** Entacapone: 200mg with each dose of levedopa and carbidopa  
Tolcapone: 100-200mg BD or TDS



## f. Dopamine facilitator

**Mechanism of action:** It appears to act by promoting presynaptic synthesis and release of DA in brain . Action on glutamate receptors through which the striatal dopaminergic system exerts its influence has also been suggested eg: AMANTADINE

**Side effects:** These are not generally serious : insomnia , dizziness,confusion, nightmares, rarely hallucination.

**Dose:** Fixed doses 100mg BD is used



## II. Drugs acting on brain Cholinergic System

### a. Central acting anticholinergics

**Mechanism of action:** They act by reducing the unbalanced cholinergic activity in striatum of parkinsonian patients , similiarly H1 antagonist to act as central acting anticholinergics

**Side effects:** Impariment of memory and organic confusional states are more common in elders

**Dose:** Trihexyphenidyl : 2-10 mg/day  
Procyclidine : 5-20mg/day  
Promethazine : 25-75mg/day



## General Points to Remember

- ✓ No drug alters the pathology of parkinsons disease
- ✓ Drugs provide symptomatic releif and give happy life for additional 3-6 yrs
- ✓ Initial therapy- anticholinergic monotherapy with selegeline is sufficient
- ✓ Combination of Levodopa with Decarboxylase inhibitor is the standard treatment for most of the patients
- ✓ Combination of drugs with decarboxylase inhibitors reduces the early but not late complications
- ✓ In advanced cases COMT inhibitors can be added along with Levodopa and carbidopa to prolong action and subdue 'on-off' Fluctuations



# Thank You

