PARKINSONISM

- characterized by tremor, hypokinesia, rigidity, and abnormal gait and posture.
- occurs in all ethnic groups.
- prevalence of 1 to 2 per 1,000 population
- approximately equal sex distribution.

ETIOLOGY

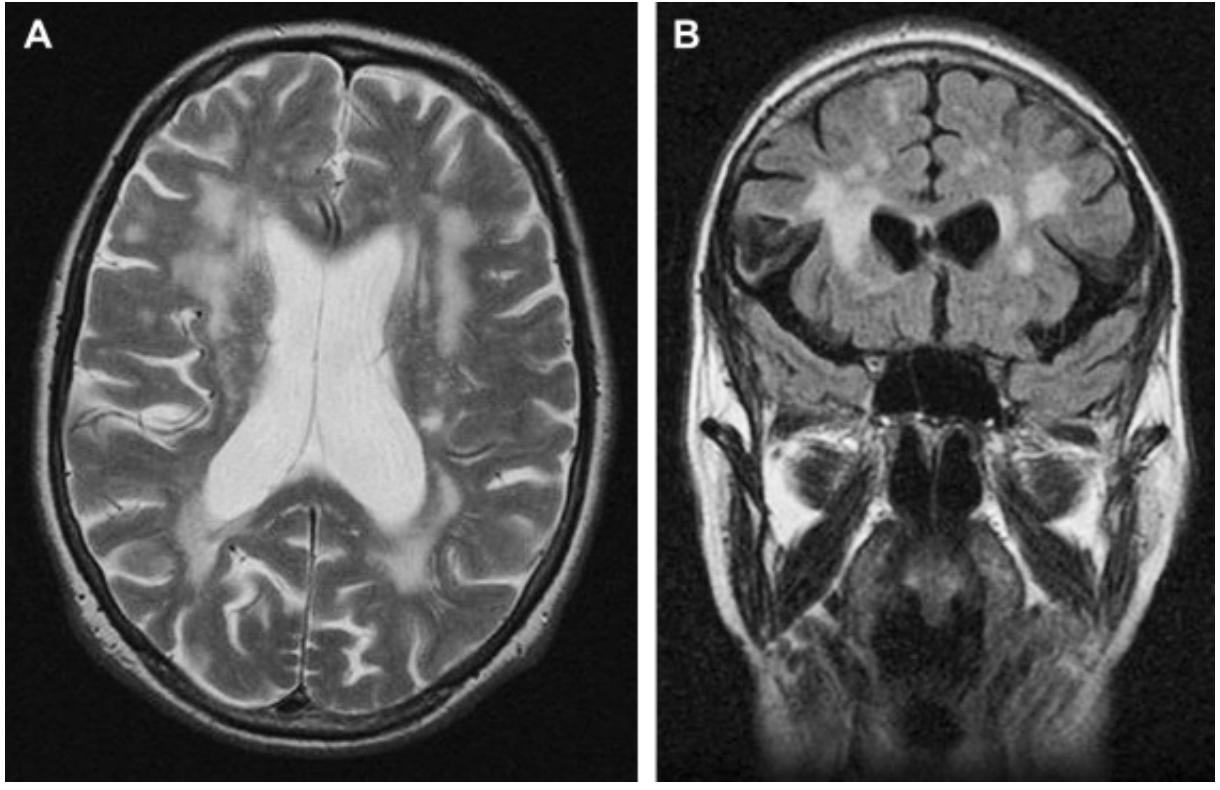
- *Idiopathic* (called Parkinson's disease or paralysis agitans):
  - The most common variety (up to 80%) of parkinsonism
  - occurs without obvious cause (not secondary to some known cause).
  - there is a sustained response to treatment with dopaminergic medication.
  - Mean age of onset is 56 years.
  - Male to female ratio *within same age group* is 2 : 1

- *Encephalitis:*
  - Postencephalitic parkinsonism occasionally follows encephalitic illnesses.
- *Toxin-Induced:*
  - manganese dust
  - carbon disulfide
  - severe carbon monoxide poisoning
  - rarely after exposure to pesticides or fumes during welding.

- *Drug-Induced:*
  - Phenothiazines,
  - Butyrophenones,
  - Metoclopramide,
  - Reserpine,
  - Tetrabenazine
  - MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), a meperidine analogue

- *Vascular Parkinsonism:*
  - multiple subcortical white-matter infarcts (MRI help in diagnosis)
  - brisk tendon reflexes and extensor plantar responses.
  - tremor is often relatively inconspicuous
  - in some patients, abnormalities of gait are especially evident (“lower-body parkinsonism”).
  - the response to antiparkinsonian medication is usually disappointing.
  - management is focused on preventing stroke.

Brain MRI in vascular parkinsonism



▶ *Familial & Genetic:*

- rarely, parkinsonism occurs on a familial basis.
- approximately 3% of cases arise from a single genetic cause.
- it is often not possible to distinguish these from the idiopathic disorder.
- early onset and a familial incidence favor a genetic cause.

▶ *Post-traumatic:*

- Boxers and those in certain other contact sports, such as football

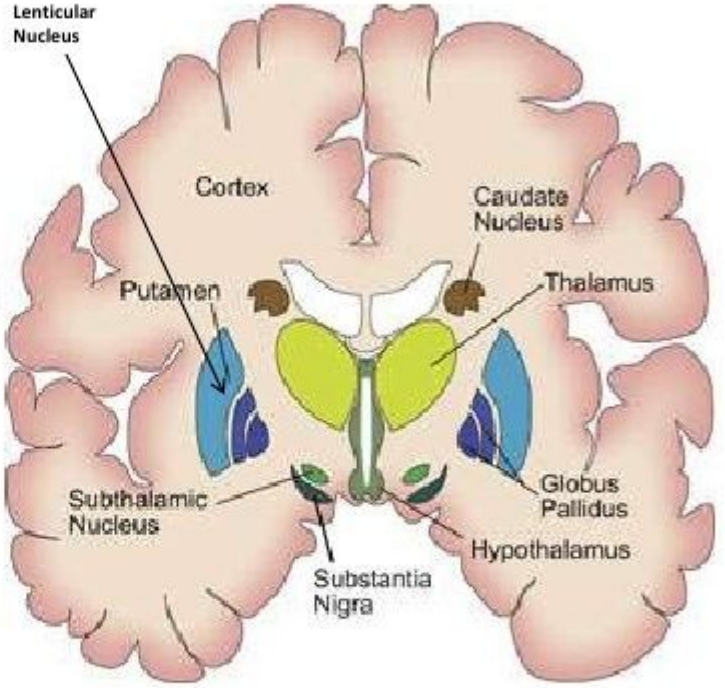
▶ *Parkinsonism Associated With Other Neurologic Diseases* – see differential diagnosis bellow.

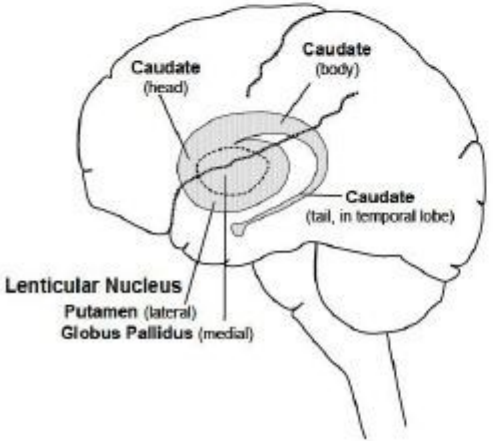
PATHOLOGY & PATHOGENESIS:

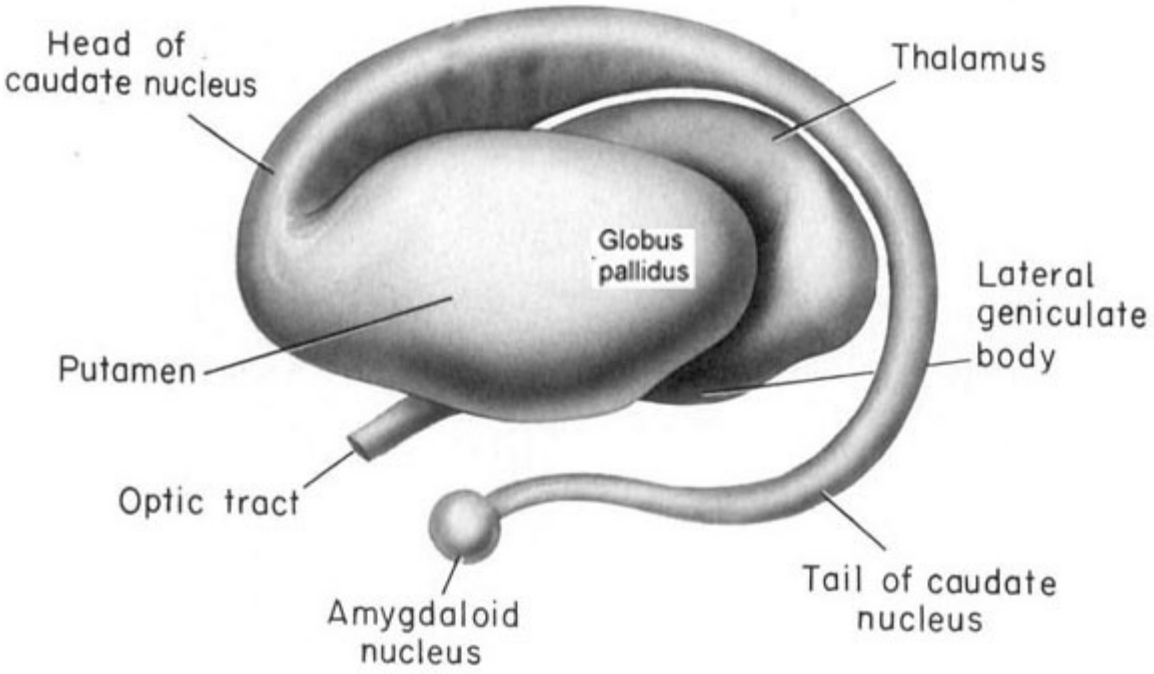
- loss of pigmentation and cells in the substantia nigra and other brainstem centers.
- cell loss in the lenticular nucleus (globus pallidus and putamen).
- filamentous eosinophilic intraneural inclusion granules (Lewy bodies) containing α-synuclein in the basal ganglia, brainstem, spinal cord [early involvement of the lower brainstem (eg, dorsal motor nucleus of the vagus [X] nerve) *causing dysphagia*, olfactory bulb, and enteric nervous system, and subsequent spread to the locus ceruleus, substantia nigra, transentorhinal cortex, hippocampus, and neocortex]
- *Note: Lewy bodies are not seen in postencephalitic parkinsonism*

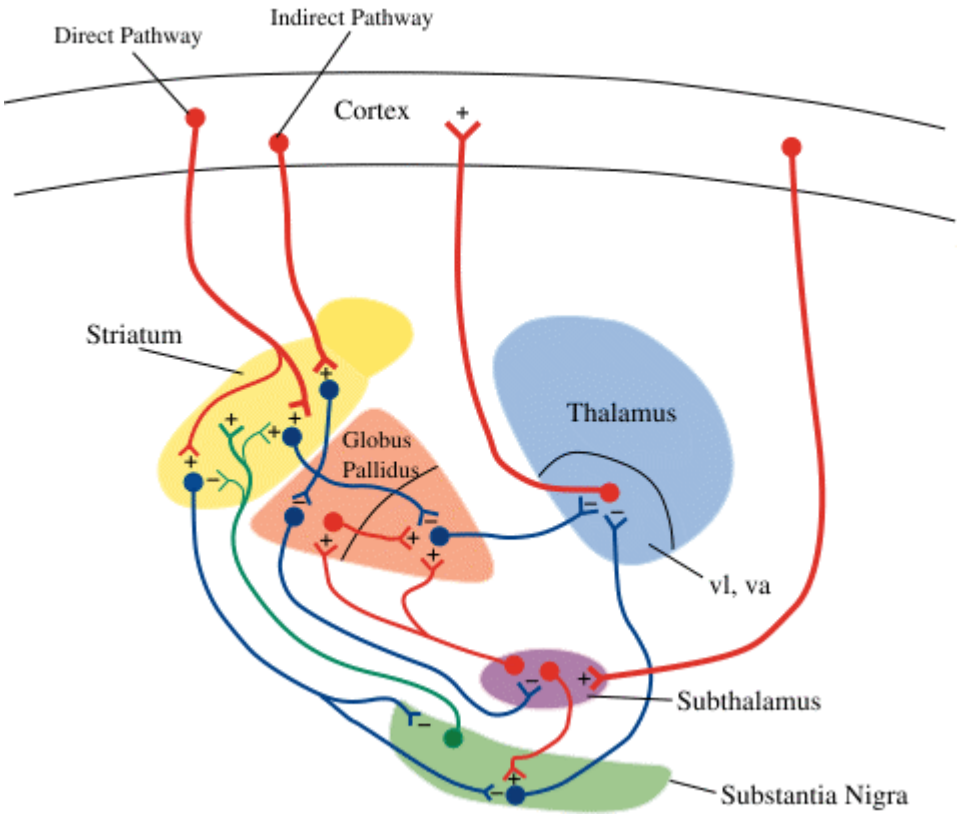
FUNCTIONAL DIVISIONS

1. **Striatum**
   a. caudate nucleus
   b. putamen
2. **Pallidum**
   a. Globus Pallidus Interna (Gpi)
   b. Globus Pallidus Externa (Gpe)
3. **Thalamus**
4. **Subthalamic Nucleus**
5. **Substantia Nigra**






Head of
caudate nucleus
Thalamus
Globus
pallidus
Lateral
geniculate
body
Putamen
Optic tract
Amygdaloid
nucleus
Tail of caudate
nucleus


Direct Pathway
Indirect Pathway
Cortex
Striatum
Globus
Pallidus
Thalamus
vl, va
Subthalamus
Substantia Nigra

- It triggered by α-synuclein protein misfolding and aggregation (a synucleinopathy).
- linked to the microbiome, ie, the bacterial content of the gut.
- abnormalities of mitochondrial function.
- inappropriate production of reactive oxygen species.
- occurrence of an inflammatory response in the absence of infection.
- depletion in the dopaminergic nigrostriatal system.
- norepinephrine, are also depleted in brain of patients.

- *In idiopathic parkinsonism, the normal balance between dopamine and acetylcholinethese (two antagonistic neurotransmitters in basal ganglia) is disturbed because of dopamine depletion in the dopaminergic nigrostriatal system*

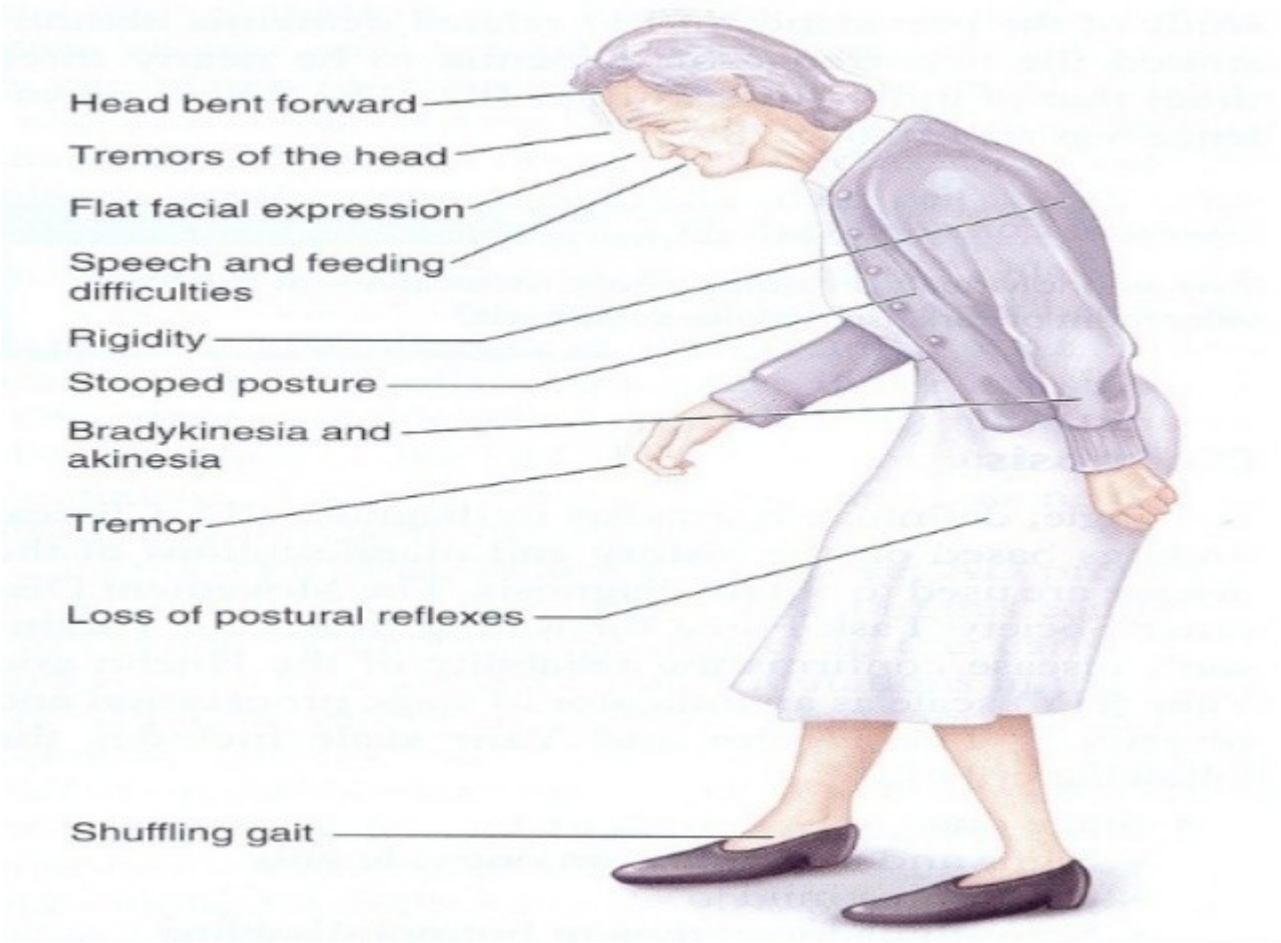
CLINICAL FINDINGS

► *preclinical phase:*

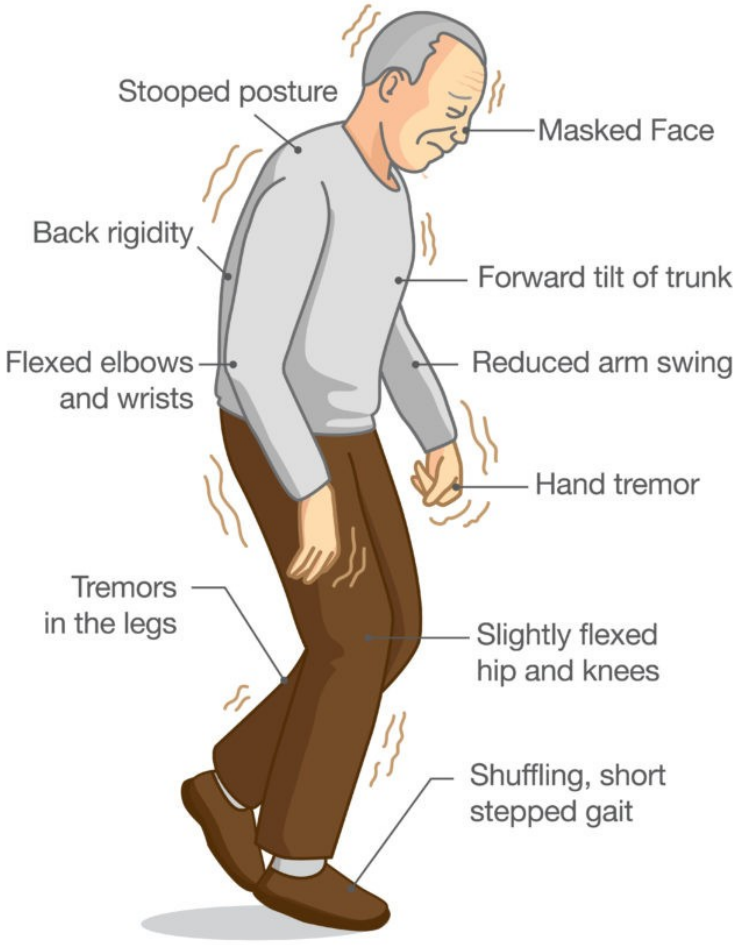
- extending back for several years before the development of the motor deficit,
- During which, hyposmia, constipation, anxiety, depression, and rapid-eye-movement (REM) sleep behavior disorder may be present.

► *clinical phase:*

- 4 to 6 Hz *resting* tremor. Commonly begins as (“pill-rolling”) on one side, then spreed on that side, then become generalized, but *remain asymmetrical in idiopathic disease*. It frequently involves the lower jaw and chin as well.
- led pipe rigidity. It lead to flexed posture of body. When tremor superimposed on this rigidity, it become of cogwheel character.


Head bent forward
Tremors of the head
Flat facial expression
Speech and feeding difficulties
Rigidity
Stooped posture
Bradykinesia and akinesia
Tremor
Loss of postural reflexes
Shuffling gait

Parkinson's Disease Symptoms



- slowness of voluntary movement and a reduction in automatic movement, such as swinging the arms while walking (hypokinesia sometimes called bradykinesia or akinesia). It is the most disabling feature.
- face is relatively immobile (hypomimia or mask like facies), with widened palpebral fissures, infrequent blinking.
- speech become slow & monotonous.
- the handwriting is small (micrographia), tremulous, and hard to read.

- difficult to get up from bed or an easy chair.
- difficult to start walking.
- gait is characterized by small, shuffling steps.
- In advanced cases, the patient tends to walk with increasing speed to prevent a fall (festinating gait) because of the altered center of gravity that results from the abnormal posture.

- positive glabellar tap reflex.
- cognitive decline (about 25% develop dementia)
- personality changes.
- depression, anxiety & apathy.
- fatigue may be prominent.
- some patients complain of pain or sensory disturbances.
- dysautonomic symptoms include urinary urgency and urge incontinence, and constipation & postural hypotension.
- greasy skin.

DIFFERENTIAL DIAGNOSIS:

- Depression
- Essential (Benign Familial) Tremor
- Parkinson-Plus Syndromes (Lewy body disease, multisystem atrophy, progressive supranuclear palsy [a tauopathy with extended posture & late impairment of vertical up & down gaze eye movements], and corticobasal degeneration): poor response to dopaminergic drugs & of poorer prognosis than idiopathic Parkinson disease.
- Dystonia
- Wilson Disease
- Huntington Disease
- Creutzfeldt–Jakob Disease
- Normal Pressure Hydrocephalus (robot gait)

TREATMENT:

- early parkinsonism requires no drug treatment.
- physiotherapy, occupational & speech therapies are useful during all stages of disease.
- treatment of the motor symptoms, when symptoms become more sever, is directed toward *restoring the dopaminergic–cholinergic balance in the striatum by blocking the effect of acetylcholine with anticholinergic drugs or by enhancing dopaminergic transmission.*

► *Anticholinergic Drugs:*

- they are more helpful in alleviating tremor and rigidity than in ameliorating hypokinesia, but are generally less effective than dopaminergic drugs.
- trihexyphenidyl (Artane)® 5mg tab or procyclidine (Kemadrine)® 5mg tab; ½ tab X 3 for 7 days then increased to 1 tab X 3

▶ *Amantadine:*

- for *mild* parkinsonism 100 mg X 2, either alone or in combination with an anticholinergic agent.
- block glutamate and muscarinic cholinergic receptors and stimulate dopamine release.
- improves all the motor features.
- side effects: restlessness, confusion, skin rashes, edema, disturbances of cardiac rhythm
- Useful for depression in Parkinson disease.
- However, its benefit is short-lived.

► *Levodopa/Carbidopa (Sinemet)®:*

- Levodopa, which is converted in the body to dopamine, ameliorates all the major clinical features of parkinsonism and, unlike the anticholinergic drugs, is often particularly helpful against hypokinesia.
- Carbidopa is a drug that reduces the extracerebral metabolism of levodopa to dopamine by inhibiting dopa decarboxylase, but it does not cross the blood–brain barrier.
- Ex: Sinemet® (25 mg carbidopa / 250 mg L-dopa): ½ tab X 2 for 7 days, then increases to 1 tab X 3
- The most common side effects of levodopa are nausea, vomiting, hypotension, abnormal movements (dyskinesias & chorea), restlessness, and confusion. Cardiac arrhythmias and sleep disturbances occur occasionally.

► *Dopamine Agonists:*

- Bromocriptine (ergot derivative) 15-30 mg/day
- Pramipexole (non-ergot derivative) 1.5-4.5 mg/day
- Ropinirole (non-ergot derivative) 8-24 mg/day

- Adverse effects: fatigue, somnolence, nausea, peripheral edema, dyskinesias, confusion, hallucinations, and orthostatic hypotension. An irresistible urge to sleep at inappropriate times sometimes occurs and may lead to injury. Disorders of impulse control also can occur.

▶ *Catechol-O-Methyltransferase Inhibitors:*

- Catechol-O-methyltransferase (COMT) is one of two principal enzymes involved in the metabolic breakdown of dopamine; the other is monoamine oxidase. COMT inhibitors may be used to reduce the dose requirements of and any response fluctuations to levodopa. Their use improves levodopa transport into the blood and across the blood–brain barrier and thus leads to more sustained plasma levels of levodopa.
- Tolcapone 100 mg X 1 or 200 mg X 3 & *entacapone* (200 mg up to 5 time daily), are widely used from this group.

- A commercial preparation named ***Stalevo*** is now available that combines levodopa with both carbidopa and entacapone. It provides the convenience of simplifying the drug regime and requiring the consumption of fewer tablets.
- is available in several combinations, like:

- Stalevo 50 (50 mg levodopa plus 12.5 mg carbidopa and 200 mg entacapone)
- Stalevo 100 (100 mg, 25 mg, and 200 mg, respectively)
- Stalevo 150 (150 mg, 37.5 mg, and 200 mg, respectively)

- Entacapone reduce the risk of response fluctuations to L-dopa.

▶ *Monoamine Oxidase Inhibitors:*

- they inhibits the metabolic breakdown of dopamine, thus enhances the antiparkinsonian effect of levodopa and may reduce mild on–off fluctuations in responsiveness.
- ex: Selegiline 5 mg X 2 taken early in the day to avoid insomnia; &
- Rasagiline, a more potent and selective & well tolerated, 0.5 or 1 mg X 1 as initial treatment for early disease & adjunctive drug for more advanced disease.
- some clinical studies suggest that these 2 drugs may also delay the progression of Parkinson disease, although the evidence is incomplete. In this regard, as neuroprotective agent, Selegiline should kept for mild cases.

▶ *Deep Brain Stimulation (D.B.S):*

- High-frequency stimulation of the globus pallidus internus or subthalamic nucleus may help all the cardinal motor features of parkinsonism, and it reduces the time spent in the off-state in patients with response fluctuations.
- should reserved for individuals with classic Parkinson disease (rather than atypical parkinsonism) who: 1) become refractory to drugs & was previously responded well to them or 2) who have response fluctuations with a significant amount of off-time.