Parkinsonism

Definition:

→ A disorder that can effects movement, often including tremors.

→ long term degenerative (→ loss of function in the organs & tissues) disease of the CNS that mainly affects the motor system.

→ Presence of tremor at rest.
- Bradykinesia (Slowness of movement)
- Postural instability (instability of balance).

Hallmark motor features of Idiopathic Parkinson's disease (IPD)

(→ Reward & movement - Substantia nigra. located in the basal ganglia structure. midbrain. SNs → functions. Eye movement, motor planning, learning, addiction.)

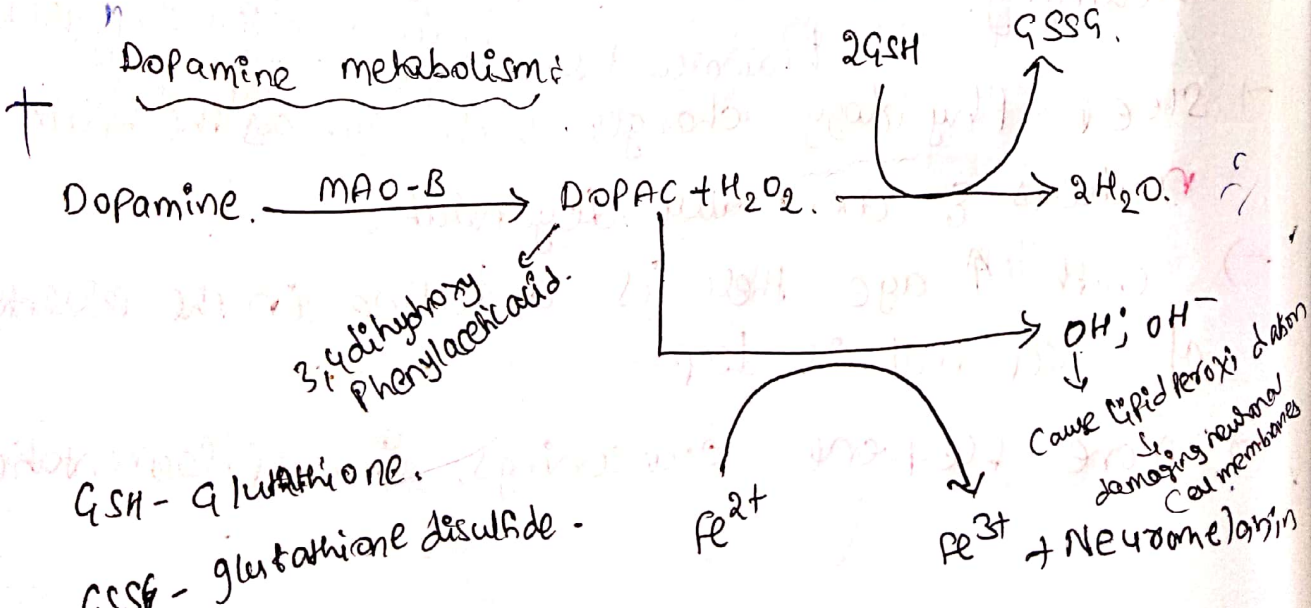
Etiology:

→ age.

→ genetic constitution.

→ Environmental factors (Chronic exposure to pesticides. Heavy metals. Rural living. drinking well water.

Dopamine metabolism:



GSH - Glutathione.

GSSG - glutathione disulfide.

Dopamine metabolism results in hydrogenperoxide (H_2O_2) formation.

Substantia nigra pars compacta (SNc) is a region charcterized by high levels of oxidative stress.

↓

free radicals are generated from dopamine autooxidation mediated by MAO

several antioxidative molecules (eg: glutathione) are present in SNC to limit damage produced by free radical attack.

→ MAO: mono amino oxidase.
↳ catalyze the oxidation of monoamines employing oxygen to clipoff their amino group.
→ substrate binding sites.
→ inactivation of neurotransmitters.

Too much (or) too little MAO activity is thought to be responsible for a number of psychiatric & neurological disorders.

→ In humans & primates adminstration of the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) results in a form of parkinsonism.

MPTP is converted by MAO-B to 1-methyl 4-Phenyl Pyridinium

MPTP $\xrightarrow{MAO\text{-}B}$ MPP^+ (potent neurotoxin)
↓ progresses.
Toxic by Inhibiting mitochondrial complex I of electron transport chain.
↓
generation of excessive reactive oxygenspecies.
↓
cell death

Pathophysiology: → associated with gradual loss of cells in the Substantia nigra of the brain.

→ Hallmark histopathologic features of IPD are :

1) Depigmentation of dopamine producing neurons. (i.e loss of SNc neurons).

2) Presence of Lewy bodies (Neuronal cytoplasmic filamentous aggregates composed of the presynaptic protein α-Synuclein)
↓
fibrillal aggregates

→ lewy bodies are abnormal clumps of proteins that form in the brain cells.

Premotor stage

→ Lewy body present in medulla oblongata
↓
Locus coeruleus, Raphe nuclei, olfactory bulb.

→ This may correlates with observations that
↓
anxiety, depression & impaired olfaction is detectable.

→ As IPD Progresses. Lewy Pathology ascends to the mid brain. & account for development of motor features.

⇒ In advanced stages. ~~development of~~ spreads to the cortex & this may correlate with cognitive & additional behavioural changes.

→ Dopamine is a chemical messenger that transmits signals between two regions of the brain to coordinate activity..

Eg:- Dopamine connects the substantia nigra and the corpus striatum to regulate muscle activity.

→ If there is deficiency of dopamine in the striatum the nerve cells in this region "fire" out of control.

→ This leaves individual unable to direct (&) control movements.

↓

Initial symptoms of Parkinson's disease.

↓

As disease progresses,

↓

other areas of the brain & nervous system degenerate as well causing a more profound movement disorder.

→ The exact cause for the loss of cells is unknown.

→ Possible causes include both genetic & environmental factors.

Striatum - component of the motor and reward systems.

↳ Receives glutamatergic & dopaminergic inputs from different sources.

Clinical Presentation:

Signs & Symptoms:

→ Resting tremor.
→ Rigidity.
→ Bradykinesia.
→ Postural instability.

Motor symptoms:

→ dysarthria (slurred speech).
→ dysphagia (difficulty c swallowing).
→ hypophonia (used voice volume).

Mental status symptoms.

→ anxiety.
→ bradyphrenia.
→ confusion.
→ dementia
→ depression.
→ hallucinosis.
→ sleep disorders.

Autonomic & sensory symptoms:

→ constipation.
→ fatigue.
→ pain.
→ sexual dysfunction.
→ olfactory disturbance.

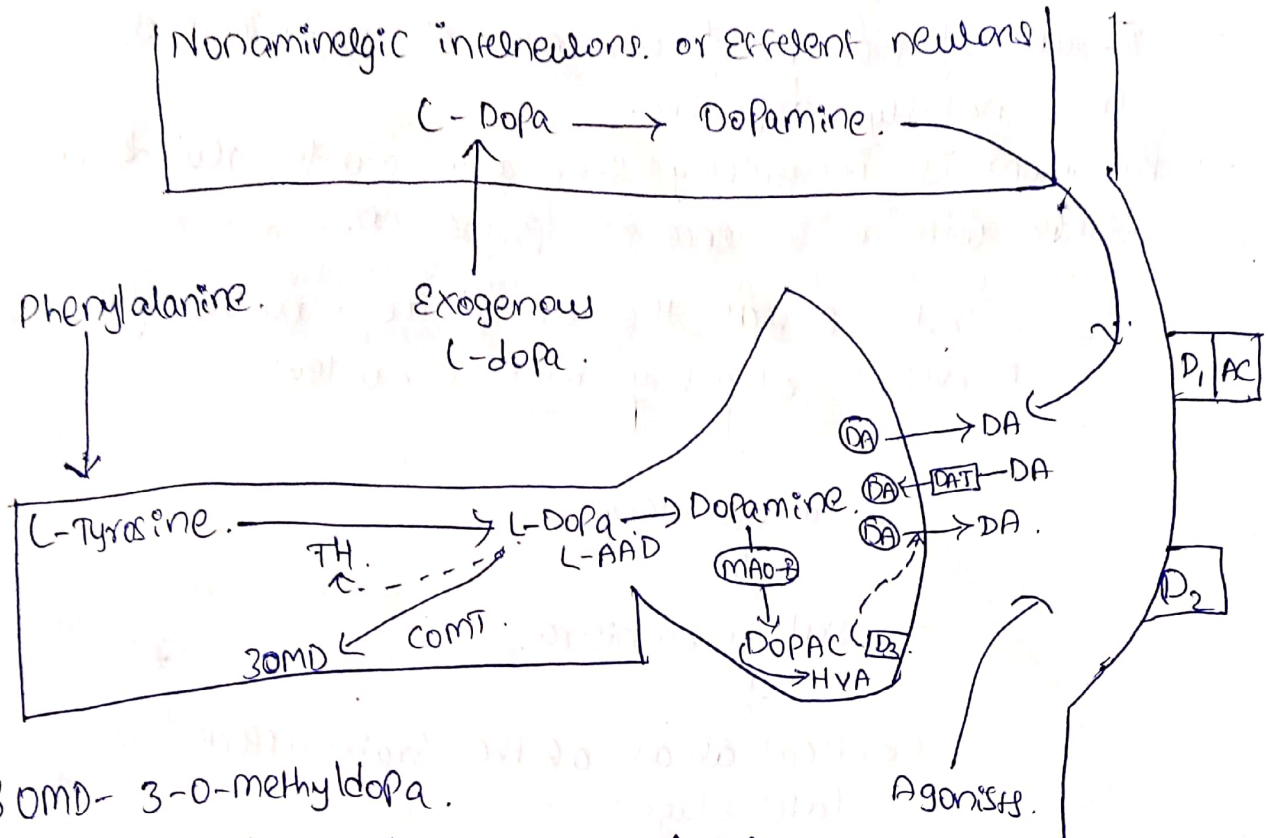
Diagnosis:

- No standard tests to diagnose Parkinson's disease.
- Diagnosis is usually based on symptoms, medical history and results of a clinical Examination.
- symptoms usually do not develop until 80% of the brains dopamine producing neurons are damaged.
- In Early stages the symptoms are milded & diagnosis is difficult.
- History of family members.
- Pt is asked to move around (&) perform a task like write his (&) her name etc.
- Uncontrollable shaking (&) Hemor seen at rest.
- Slowness of movement.
- Rigidity & Used muscle tone.
- CT | MRI brain - Reveals rule secondary causes of PD Blood flow abnormalities in brain.
- PET (Positron Emission tomography) - can localise dopamine deficiency in the basal ganglia.
- Sphincter Electromyography : used to diagnose multiple System atrophy.

Differential diagnosis:

- Several conditions have symptoms & features similar to Parkinson's disease.
  1) Benign Essential Hemor.
  2) Drug (&) toxin induced Hemor.
  3) Wilson's disease: accumulation of copper in the body & damage to brain & liver.
  4) Huntington disease: genetic condition & family history.
  5) Corticobasal degeneration of the brain.
  6) cerebellar Hemor that may be caused by a stroke, brainstem tumour.
  7) Psychogenic Hemor.

Dopamine metabolism in presynaptic dopamine neuron:



3OMD - 3-O-methyldopa.

AC - Adenylate cyclase.

AD - Aldehyde dehydrogenase.

COMT - Catechol-O methyltransferase. TH - Tyrosine hydroxylase.

D_1-D_2 - Dopamine Receptors.

HVA - Homovallillic acid.

C-AAD - L-aromatic aminoacid decarboxylase.

Management of Parkinsonism:

→ Goal in the management of IPD is to improve motor & non motor symptoms → mood disorders. (depression, anxiety, & irritability) (personality changes).

→ so that PTs are able to maintain the best possible quality of life.

Non Pharmacological therapy:

→ Exercise & Physical therapy → Uses cognitive function. → Reduces constipation.

→ Speech therapy.

→ Mindfulness & meditation.

→ Nutrition. [Coenzyme Q, vit E, vit C].

→ Occupational therapy.

→ Diet. (when using levodopa. Protein rich foods taken use absorption of L-dopa).

→ Balance
→ Stooped posture.
→ Bradykinesia

1) Pathophysiology of Parkinson's disease:

→ Pathophysiology of Parkinson's is idiopathic (unknown cause)

→ Result of the loss of a number of neurotransmitters most notably dopamine.

→ Parkinsons is increasingly seen as a complex neurodegenerative disease with a sequence of progression.

→ First effects the dorsal motor nucleus of the vagus nerves & olfactory bulbs & nucleus

↓

Locus coeruleus

↓

Substantia nigra.

↓

Cortical areas of the brain affected at a later stage.

→ Damage to these various neuronal systems account for the multifaceted pathophysiological changes that cause impairments not just to motor system but also to the cognitive & neuropsychological systems.

Role of dopamine:

→ transmits chemical messages from one nerve cell to another across the synapse, a space blw presynaptic & post-synaptic receptor.

→ Dopamine is secreted into the synapse from membrane storage vesicles in the presynaptic membrane.

→ It crosses the synapse & binds to the postsynaptic membrane. While it activates dopamine receptors.

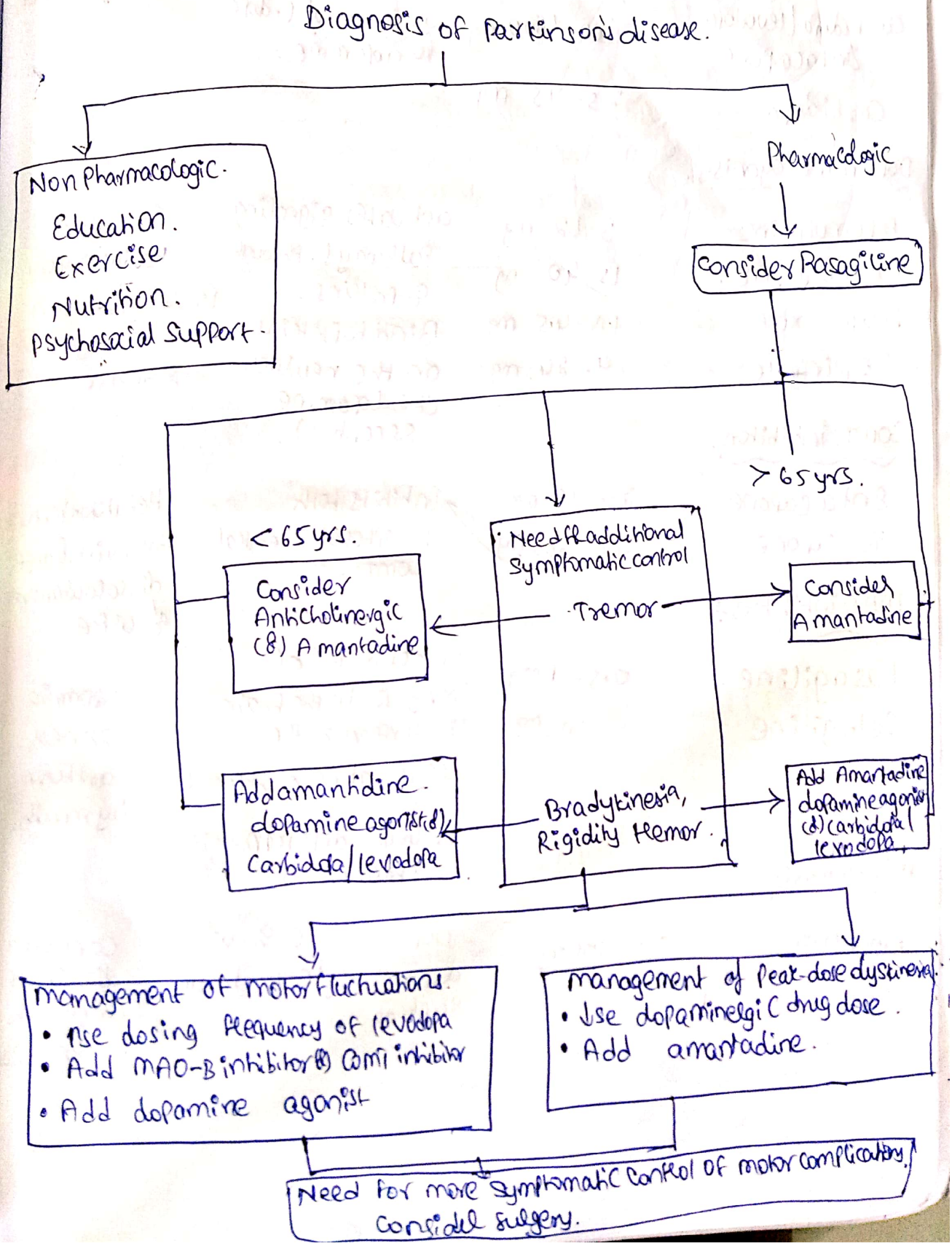
→ Unused dopamine remaining in the synapse is absorbed back into the presynaptic cell.

→ once back in the presynaptic cell the excess dopamine is repackaged into storage vesicles & released once more into the synapse.

→ within the synapse as dopamine travels from one cell to another it can be broken down & rendered inactive by two Enzymes.

MAO - monoamino oxidase.
COMT - Catechol-o-methyl-transferase.

Pharmacological Treatment: Algorithm



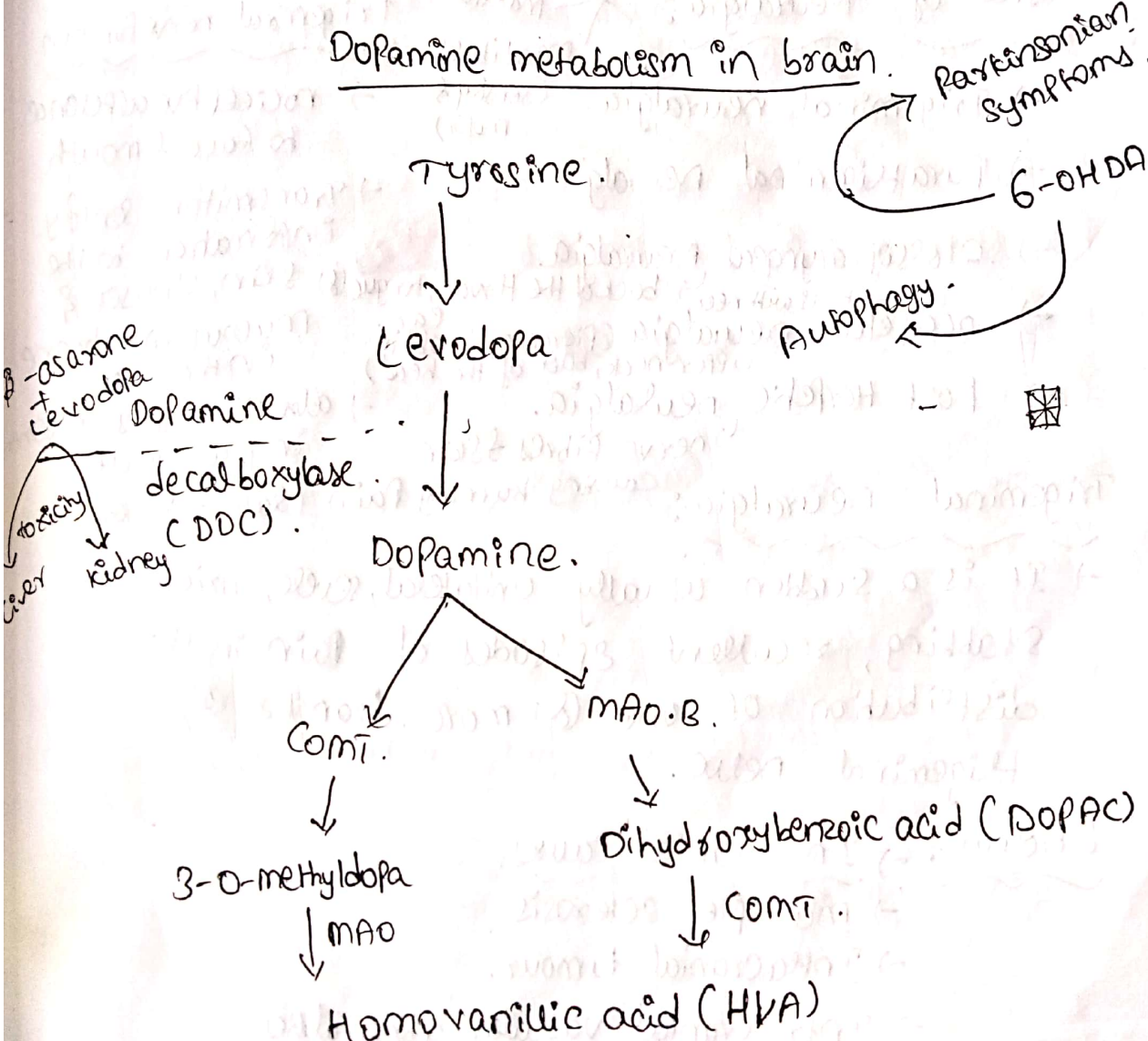
Name of drugs	Dose mg/day	MOA	Adverse effects
Anticholinergic drugs			
Benztropine	0.5-4		Blurred vision, Confusion, dry mouth, memory difficulty, sedation, urinary retention
Trihexyphenidyl	1-6 mg		
Carbidopa/levodopa	300-1000 mg	L-dopa crosses the BBB. Uses the unwanted peripheral conversion of L-dopa to dopamine.	
Carbidopa/levodopa Entacapone	600-1600 mg		
Carbidopa	25-75 mg		
Dopamine agonists			
Apomorphine	3-12 mg	activates signaling pathways through G-proteins. Bind to proteins on the neurons (i.e dopamine receptors).	Confusion, Hallucinations, Postural hypotension, sedation, Edema
Bromocriptine	15-40 mg		
Pramipexole	1.5-4.5 mg		
Ropinirole	9-24 mg		
COMT inhibitors			
Entacapone	200-1600 mg	inhibits both peripheral & central COMT	Hepatotoxicity, Brownish, Orange discoloulation of urine
Tolcapone	300-600 mg		
MAO inhibitors			
Rasagiline	0.5-1 mg	Selective On of MAO-B in the brain interferes the degradation of dopamine. ↓ Prolonged dopaminergic activity.	Insomnia, Dizziness, Heartburn, dry mouth
Selegiline	5-10 mg		
Miscellaneous			
Amantadine	200-300 mg	Dopaminergic & non dopaminergic mechanisms, Such as.	Confusion, dizziness, dry mouth, Hallucinations

Motor complications of L-DOPA:

Long term L-dopa therapy is associated with a variety of motor complications of which.

End-of-dose "wearing off" (motor fluctuations).

Dopamine metabolism in brain.



Levodopa converted to dopamine via the action of a naturally occuring enzyme called dopa decarboxylase (carbidopa)

Carbidopa- decarboxylase inhibitors.