★Neurodegerative diseases

- Drugs that affect CNS act by altering in the neurotransmission process
  - presynaptically :- production, storage, relase ..... .
  - postsynaptically :- activate / Block.

- **Neurodegerative diseases**:- progressive Loss of selcted neurons in Brain.
  - Alzheimer's disease :- Loss of cholinergic neurons in Maynert nucleus.(↓Ach).
  - Parkinson's disease :- Loss of dopaminergic neurons in substantia nigra (↓Dopamine).

- **Parkinson's disease**
  - signs & symptoms :- Tremor, Rigidity, bradyKinesia, Balance Abnormalities.
  - Etiology :- ↓dopamine in corpus striatum
  - strategy of Tx :- Dopamine (inhibitory) / AcetylCholine (excitatory) Balance.

1. **Dopaminergics** → Restore dopamine function. (↑dopamine LvL).
   → stimulate dopamine receptors Located within the brain.

   (I) **Levodopa (L-Dopa)**:- metabolic precursor of dopamine.
   - ↓ number of neurons (↓activity by time), Relief is only symptomatic, cross BBB.
   - MoA :- Levodopa ⟶ dopamine (Decarboxylation).
   - SE :- nausea, vomiting, arrhythmias, hypotension, Anorexia, Tachycardia, iris mydriasis.
     Blood dyscrasias (⊕ coomb's test), Brownish color of the melanin pigment in urine & saliva (cetacholamine oxidation ⟶ Homovillinic acid).
     - CNS :- hallucinations, dyskinesias, mood changes, depression, psychosis & anxiety.
   - Absorption & metabolism :- absorbed rapidly (empty stomach), short $t_{1/2}$ = 1-2 hours
   - Interactions
     - Food will decrease the absorption of L-Dopa.
     - Bg ↑ the peripheral breakdown of L-Dopa & diminishes it effect.
     - monoamine oxidase (MAO) inhibitor (phenelzine) :- HTN crisis, ↑Ach.
     - Antipsychotic drug :- Block dopamine receptors.
     - Glaucoma :- ↑ intraocular pressure.
     - cardiac patients :- Cardiac arrhythmias.

   - **Carbidopa** :- A dopa decarboxylase inhibitor, don't cross BBB (+ L-Dopa).
     - effects
       - ↑ availability of L-Dopa in CNS.
       - ↓ doses of L-Dopa (x4-5)
       - ↓ severity of the side effects.

   (II) **MAO-B inhibitors** :- ↓metabolization of dopamine.

   - **Selegiline (deprenyl)**
     - ↑dose
       - inhibit MAO-A (metabolize norepinephrine & serotonin).
       - Loss of sensitivity ⟶ severe HTN.
     - Action
       - ↓Dopamine metabolism
       - ↑dopamine LvL in the brain.
       - enhance the action of L-Dopa (↓dose)
     - ↓ potential of causing HTN crisis (unlike nonselective MAO inhibitors).
     - SE :- insomia :- metabolized to methamphetamine & amphetamine.

- Rasagiline → x5 potency of selegiline.
  → not metabolized to an amphetamine-like substance.

III Catechol-O-methyltransferase inhibitor (COMT inhibitors.):- Po, not influenced by food.
- effects → ↓ plasma concentration of 3-O-methyldopa.
  → ↑ central uptake of Levodopa.
  → ↑ concentration of Brain dopamine.
  → ↓ symptoms of (wearing-off symptoms):- ↑ t½ of L-Dopa.
- Kinetics :- extensively metabolized, eliminated in feces & urine.
- SE → L-Dopa:- Diarrhea, postural hypotension, nausea, anorexia, dyskinesia, hallucinations, sleep disorders.
  → Special:- fulminating hepatic necrosis / cirrhosis. (should be monitored).

- Tolcapone :- cross BBB, Long duration of action (compared with entacapone)
- Entacapone:- no hepatic necrosis.

IV Dopamine-Receptor agonists → Ergot derivative :- Bromocriptine
→ non-Ergot:- ropinirole, pramipexole, rotigotine & Apomorphine
→ ↑ Duration of action, ↓ dyskinesia & motor fluctuations, inactive in patients who have shown no therapeutic response to L-Dopa.

- Bromocriptine :- Long acting, similar actions to L-Dopa (parkinson + dyskenisia / fluctuation)
  - SE → L-Dopa → more:- hallucination, confusion, delirum, nausea, orthostatic hypotension.
    → Less:- Dyskinesia.
    → Special:- pulmonary & retroperitoneal fibrosis (ergot).
  - Contraindications → MI:- cardiac problems.
    → peripheral vascular disease:- vasosperms.
    → peptic ulcer:- worseining of the ulcer.

- Apomorphine:- IV
  - Indications → acute mangment of the hypomobility (off phenomenon).
    → L-Dopa-naive patients
    → advanced parkinson's disease who are taking L-Dopa.
- pramipexole:- (parkinson's + dyskenisia / fluctations), No vasosperms & fibrosis
  the dependence on renal function for its elimination can't be overly stressed.

- ropinirole:- (parkinson's + dyskenisia / fluctations). No vasosperms & fibrosis.
  - Interaction:- fluroquinolone & cyp450-1A2 inhibitors:- ↓ metabolism, ↑ AUC (80%).

- Rotigotine:- early, Transdermal patch (24h).

V Amantadine:- Antiviral (influenza), not active when max dopamine relase, ↓ effect, ↑ Tolerance
- effect → primary:- ↓ NMDA glutamate receptors.
  → ↑ dopamine relase
  → Block cholinergic receptors.
- SE:- restlessness, agitation, confusion, hallucinations, acute toxic psychosis, orthostatic hypotension urinary retention, peripheral edema, dry mouth.

VI Additional
- ropinirole hydrochloride :- x2 effective dyskinesia.
- pramipexole dihydrochloride
- ropinirole hydrochloride

2 Anti-cholinergics (Antimuscarinic) :- ↓Ach in the brain
- Indications
  - early in the course (↓severe)
  - patients who cannot tolerate L-Dopa.
  - combination therapy.
- SE:- Atropine :- Dry mouth, blurred vision, tachycardia, urinary retention, constipation, paralytic ileus & cvs collapse, mood changes, xerostomia, visual problems
- contraindication
  - Glaucoma
  - prostatic hyperplasia
  - pyloric stenosis
- MoA :- Block cholinergic ⟶ ↑ dopaminergic transmission.

- Benztropine mesylate.
- Trihexyphenidyl hydrochloride.
- Biperiden hydrochloride.
- Diphenhydramine hydrochloride.
- procyclidine hydrochloride.

- Alzheimer's disease :- ↓ Ach, ↑glutamate
  - Neuron degeneration :- hippocampus ⟶ Lobes (except occipital) → Loss of basal nuclei of Meynert ⟶ rest of Brain ⟶ Brain shrinks.
  - Amyloid plagues :- β - Amyloid. (secretase enzymes α, β, δ snips APP, if first by β → β-Amyloid
  - Neurofibrillary tangles :- Tau protein (internal transport system, microtubules, if they fail → destroy cells.
  - Signs & symptoms :- memory loss, confusion, personality changes, Difficulty concentrating & carrying out routine or complex tasks, inability to formulate abstract thought, paranoid.

1 Cholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine).
- MoA :- ↑Ach Lvl.

2 NMDA receptor antagonist (Memantine)
- MoA :- ↓ Glutamate Lvl.

- All of the drugs don't Treat the patient but they prevent the disease worseness (Rate of memory Loss).