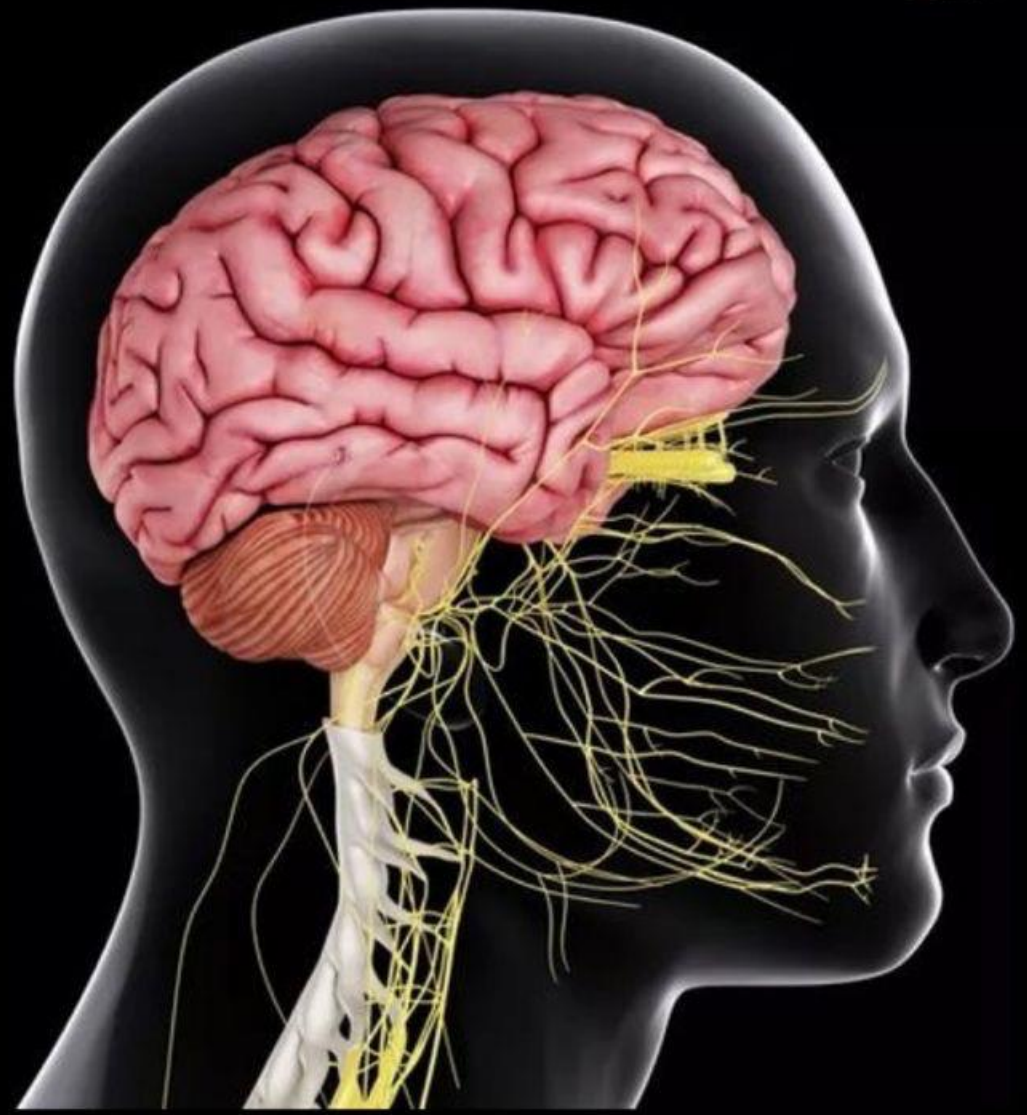
وَقُل رَّبِّ زِدْنِي عِلْمًا



CENTRAL NERVOUS SYSTEM

SUBJECT : Pharma

LEC NO. : Lec 4 nuerodegenerative

DONE BY : Enas wail hantash

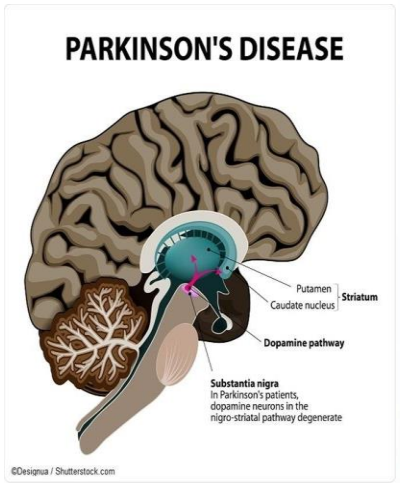
Drugs for Neurodegenerative Diseases

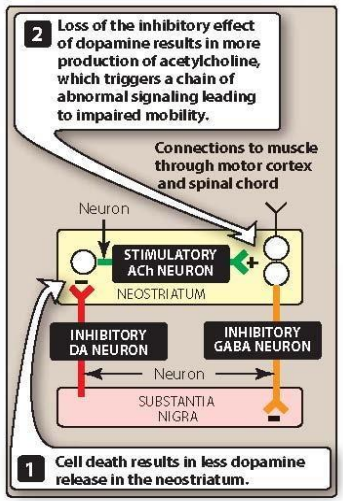
Parkinson's Disease: Pathophysiology

- Destruction of the dopaminergic neurons in the **substantia nigra** → ↓ dopaminergic stimulation in the corpus striatum.
- The dopaminergic neurons fire **tonically** (not in response to certain stimuli).

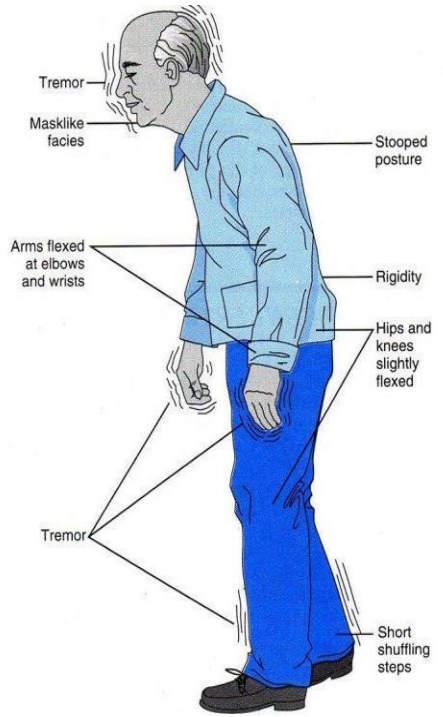
- Parkinson's results from reduced dopaminergic inhibition of the cholinergic neurons in the neostriatum, resulting in overproduction of acetylcholine→ loss of control on muscle movement.

- **Parkinsonism**: is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia and postural and gait abnormalities.

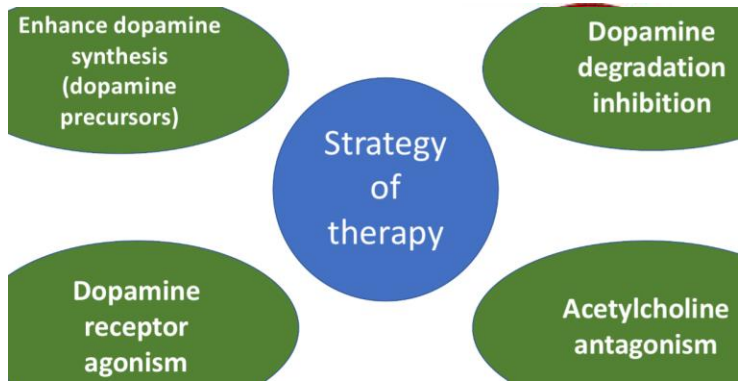




- Etiology
- **Idiopathic (Parkinson's disease)**: primary or idiopathic destruction of dopaminergic neurons in the basal ganglia.
- **Secondary parkinsonism**:
  - ❑ Viral encephalitis
  - ❑ CO or manganese poisoning.
  - ❑ Drug-Induced parkinsonism "pseudoparkinsonism" e.g., *haloperidol*



1. Levodopa and carbidopa
2. Selegiline and rasagiline
3. Catechol-O-methyltransferase inhibitors (COMTis).
4. Dopamine receptor agonist
5. Amantadine
6. Antimuscarinic agents



Antiparkinsonian Drugs aim to restore DA/Ach balance

I. ↓ Cholinergic Activity

Anticholinergics.

Benzhexol - Benztropine

II. ↑ Dopaminergic Activity

Dopaminergic Drugs

1. Levodopa. **(DA precursor)**
2. Bromocriptine- pramipexole- ropinirole. **(D_2 agonists)**
3. Amantadine. **(↑DA release)**
4. Entacapone. **(↓DA degredation)**
5. Selegiline **(↓DA degredation)**

ANTI-PARKINSON DRUGS

Amantadine SYMMETREL
Apomorphine APOKYN
Benztropine COGENTIN
Biperiden AKINETON
Bromocriptine PARLODEL
Carbidopa LODOSYN
Entacapone COMTAN
Levodopa (w/Carbidopa) SINEMET, PARCOPA
Pramipexole MIRAPEX
Procyclidine KEMADRIN
Rasagiline AZILECT
Ropinirole REQUIP
Rotigotine NEUPRO
Selegiline (Deprenyl) ELDEPRYL, ZELAPAR
Tolcapone TASMAR
Trihexyphenidyl ARTANE

1. Levodopa and carbidopa

Mechanism of action:

- **Levodopa:** is metabolic precursor of dopamine.
- Levodopa must be administered with carbidopa.
- **Carbidopa** is a decarboxylase inhibitor, that diminishes the metabolism of levodopa in the periphery → increasing the availability of levodopa at BBB.

Without carbidopa, most of levodopa is metabolized in the periphery.

Therapeutic uses

- Levodopa + carbidopa: the gold standard of symptomatic treatment for Parkinson's disease.
- *(*) "wearing off" phenomenon (symptoms of Parkinson's start to return or worsen with progression of the disease)*

two-thirds of patients respond well to levodopa+carbidopa for the first few years then they experience a decline in response.

Pharmacokinetics

- Levodopa is rapidly absorbed from the gut. -administered on an empty stomach (high-protein diet interferes with its transport to the brain).
- SHORT half-life (1-2 hours). -results in fluctuation in its plasma concentration→ fluctuation in motor function.

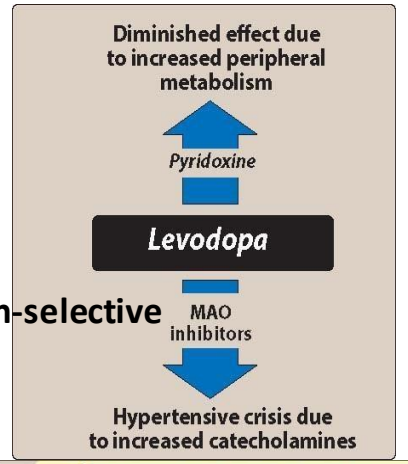
(*) ***"on-off" phenomenon*** *(sudden swings from mobility to bradykinesia that are not related to plasma levels in a simple way)*

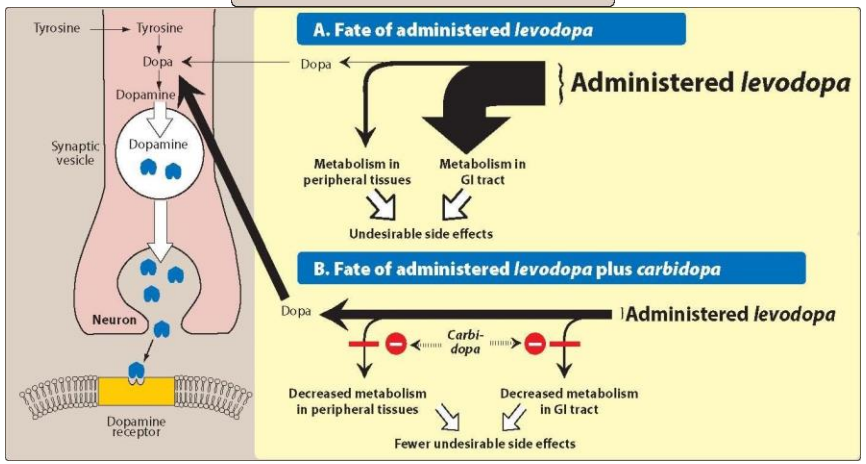
Adverse effects:

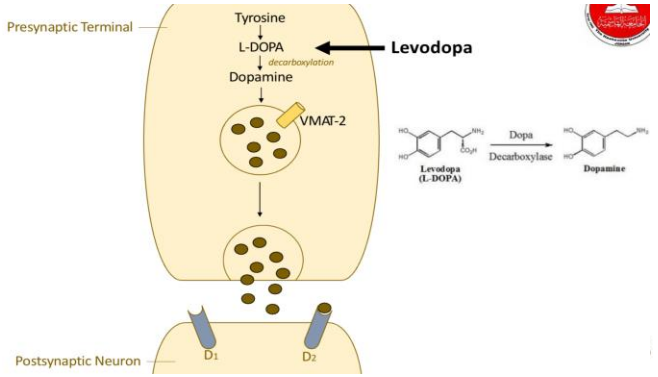
- **Peripheral effects:**
  - ❑ Simulation of chemoreceptor trigger zone: Anorexia, nausea and vomiting
  - ❑ Dopaminergic stimulation of the heart: tachycardia, extrasystole
  - ❑ Adrenergic action on iris: mydriasis
  - ❑ Catecholamines oxidation: melanin pigmentation, brownish saliva and urine.
- **Central effects:**
  - ❑ Visual and auditory hallucinations
  - ❑ Dyskinesia
  - ❑ Mood changes

(These CNS effects are the opposite of parkinsonian symptoms and reflect the overactivity of dopamine at receptors in the basal ganglia)

Drug-drug Interaction







Kluwer

2. Catechol-O-methyltransferase inhibitors (COMTis) Entacapone and tolcapone

Mechanism of action:

- The methylation of levodopa by COMT to 3-*O*-methyldopa is a minor pathway for levodopa metabolism.
- When carbidopa is used→ more 3-*O*-methyldopa is formed by COMT→ 3-*O*-methyldopa competes with levodopa transport to the brain.
- **Entacapone and tolcapone** are selective and reversible inhibitors of COMT → decrease plasma concentration of 3-*O*-methyldopa → enhance levodopa transfer to the brain.

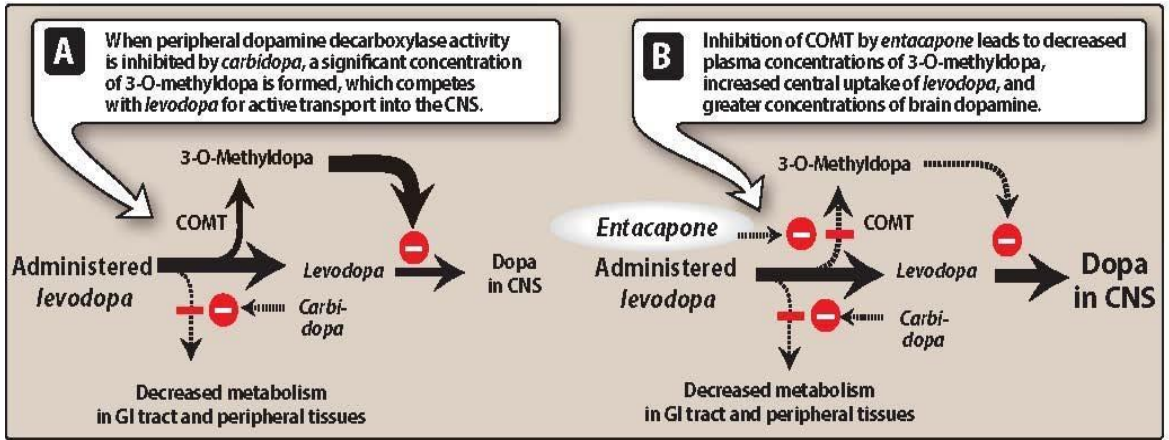
Both drugs decrease "wearing off" phenomenon.

Pharmacokinetics

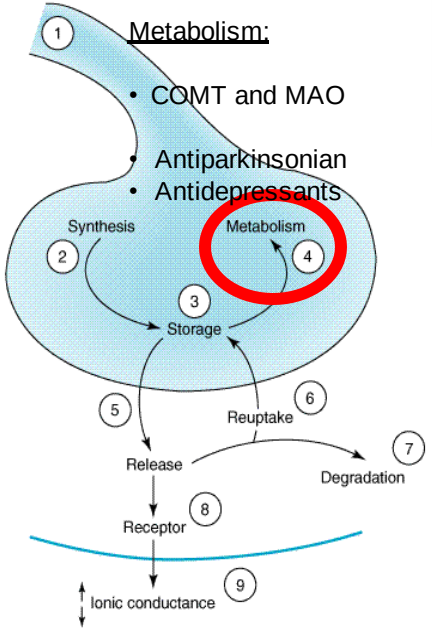
- Both drugs are orally administered.
- Highly bound to plasma albumin.
- Tolcapone has a longer half-life.

Adverse effects:

- Both drugs have similar side effects profile as levodopa+carbidopa
- Tolcapone: fulminating hepatic necrosis (does not occur with entacapone)



3. MAO Inhibitors: Selegiline and Rasagiline



Mechanism of action:

- **Selegiline:** selective MAO B inhibitor → decreases dopamine degradation → increases dopamine levels in the brain.

both MAO A and MAO B efficiently metabolize dopamine however type B degrades dopamine more. (MAO A predominantly metabolizes norepinephrine).

- **Rasagiline** is an irreversible and selective inhibitor of brain MAO B and is **5 times** more potent than selegiline.

Therapeutic uses:

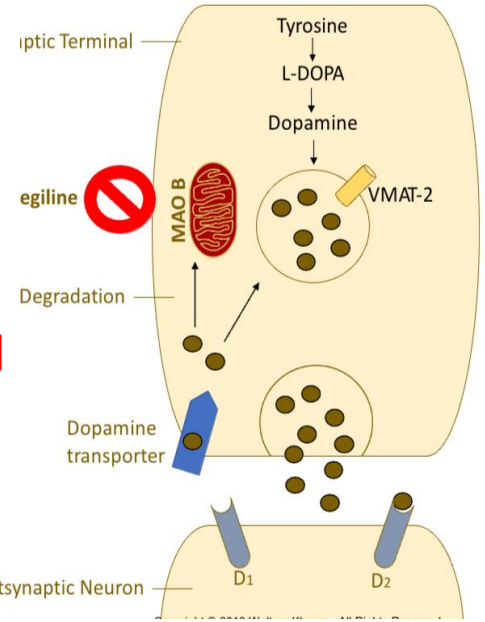
- **Seligiline** is often administered with levodopa:

delays breakdown of nigrostriatal dopamine→ prolongs levodopa action → decreases fluctuation in motor function. "on-off phenomenon"

Adverse effects:

- Insomnia: due to its metabolism to methamphetamine and amphetamine.

Unlike selegiline, rasagiline is not metabolized to amphetamine-like substances → less insomnia.



4. Dopamine Receptor Agonists

Drugs:

- Bromocriptine (ergot derivative)
- Rotigotine, apomorphine, pramipexole and ropinirole (nonergot derivatives).

Mechanism of action

- Direct dopamine receptor 2 (D_2) agonism.

Therapeutic uses:

- Patients exhibiting fluctuation in response to levodopa.
- Parkinson's disease complicated by motor fluctuations and dyskinesia.
- Ineffective in patients who have not responded to levodopa.
- Apomorphine is given by injection to treat severe and advanced stages of Parkinson's disease (also given in emergencies to treat sudden freezing i.e. immobility "off" phenomenon)

Adverse effects

- Similar to levodopa.

Bromocriptine: pulmonary and retroperitoneal fibrosis

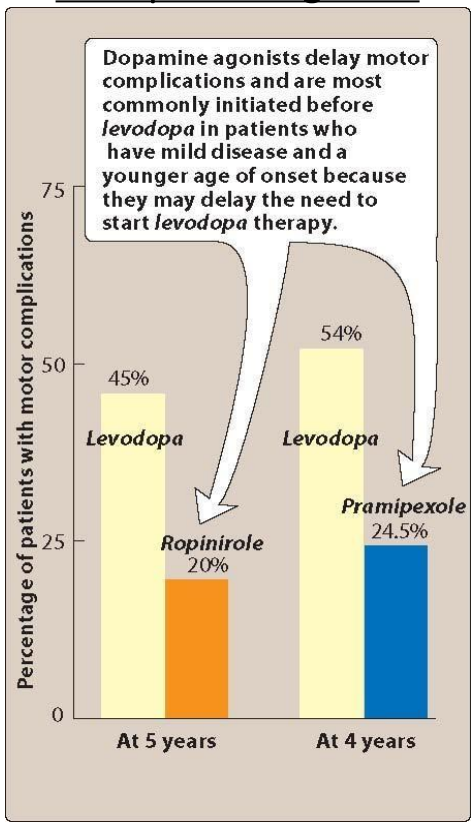
- nonergot derivatives do NOT cause fibrosis.

Pharmacokinetics

Characteristic	Pramipexole	Ropinirole	Rotigotine
Bioavailability	>90%	55%	45%
V_d	7 L/kg	7.5 L/kg	84 L/kg
Half-life	8 hours[1]	6 hours	7 hours[3]
Metabolism	Negligible	Extensive	Extensive
Elimination	Renal	Renal[2]	Renal[2]

Therapeutic advantage

of dopamine agonists



5. Amantadine

Mechanism of action:

- **Antiviral used to treat influenza.**
- **Amantadine increases the release of dopamine, blocks cholinergic receptors and inhibit NMDA glutamate receptors.**

Therapeutic uses:

- **Amantadine is less efficacious than levodopa in the treatment of Parkinson's disease.**
- **Effective against rigidity and bradykinesia**

6. Antimuscarinic agents

Drugs

- Benztropine
- Trihexyphenidyl
- Procyclidine
- Bioperiden

Mechanisms of action

- Blockade of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission → correct the imbalance of dopamine/acetylcholine ratio.

Therapeutic uses

- Much less efficacious than levodopa and always used in adjuvant to other antiparkinsonian therapy.

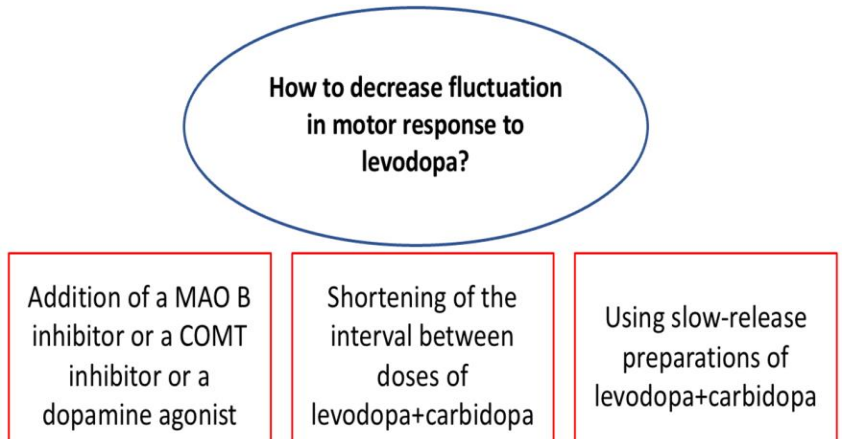
  Anticholinergics are mainly used in antipsychotic-induced parkinsonism.

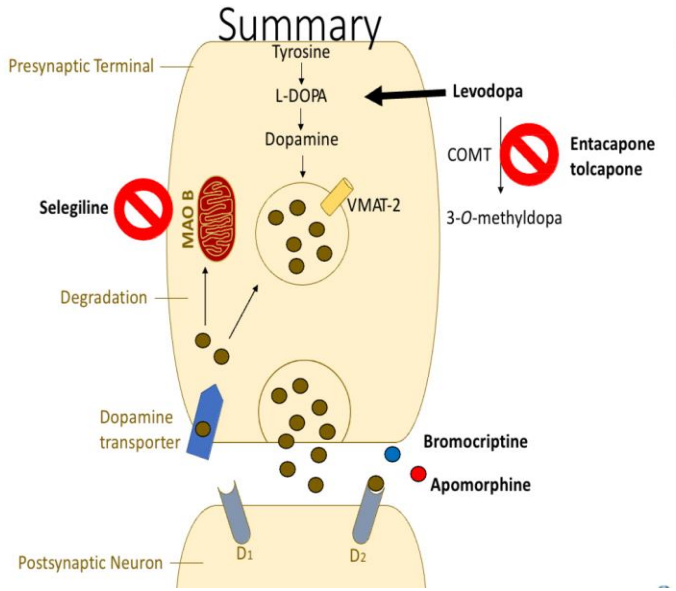
- Levodopa+carbidopa is the mainstay (first-line) therapy of Parkinson's disease (mostly in combination with a MAO B inhibitor or COMT inhibitor).
- MAO B inhibitors and COMT inhibitors are given in adjunct to levodopa+carbidopa therapy.

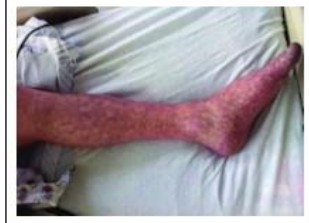
----- MAO B inhibitors increase efficacy of levodopa and decrease fluctuation in motor response

----- COMT inhibitors increase efficacy of levodopa and decrease "wearing off" mechanism.

- Dopamine agonists can be given alone in young and mild parkinsonians (to delay levodopa use) OR in combination with levodopa+carbidopa if disease is in progress.
- Antimuscarinics are used in adjunct with levodopa+carbidopa (or in cases of antipsychotics-induced parkinsonism).





Drug	Mechanism of Action	Adverse Effects
I. Bromocriptine, Pramipexole &Ropinirole (Given alone or with L-dopa). **Apomorphine**	Direct D_2 agonists. (Less fluctuation due to rapid absorption - longer $t_{½}$). is given **SC in emergency** (sudden freezing i.e. immobility) as it is rapid and more effective than L-dopa.	- Similar to L-dopa; with more psychosis. - Vasospasm & cardiac fibrosis **(bromocriptine)**
II. Amantadine (Given alone or with L-dopa).	- ↑ DA release (mild effect) → enhances L-dopa effect. - Blockading cholinergic receptors - Block glutamate receptor (NMDA) → ↓ glutamate excitotoxicity → ↓ neuronal degeneration • **more effective against rigidity and bradykinesia**	- Insomnia. - Hallucination. - Livido reticularis: purple spotting of skin 
III. Selegiline (Adjunct to L-dopa/carbidopa). **Rasagiline**	Selective inhibitor of MAO-B → delays breakdown of nigrostriatal DA → prolongs L-dopa action → ↓ fluctuation **5 times more potent**	- Insomnia (due to its metabolism to methamphetamine and amphetamine) - Hallucination. - Very low risk of cheese reaction. **No Insomnia**
IV. Entacapone (Adjunct to L-dopa/carbidopa). **Tolcapone**	COMT inhibitor → ↓ L-dopa peripheral metabolism → ↑ its bioavailability & **prolongs its action → ↓ fluctuations.** **Relatively longer duration**	- Similar to L-dopa /carbidopa. + **Diarrhea.** **Fulminant hepatic necrosis**

Alzheimer's Disease

- **is a neurodegenerative disorder characterized by impairment of memory and cognitive function together with mood and personality changes.**

  is the most common cause of dementia in the elderly.

- **Pathophysiology**
- **Dementia of Alzheimer's disease has three distinct features:**

1. **Accumulation of senile plaques (β-amyloid accumulations)**
2. **Formation of numerous neurofibrillary tangles**
3. **Loss of cortical neurons (cholinergic neurons)**

- 1. **Acetylcholinesterase inhibitors**

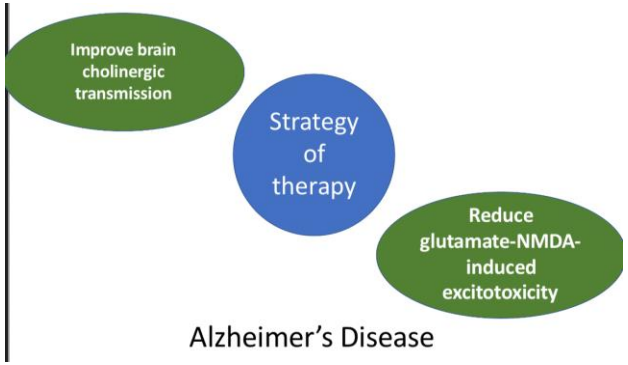
❑ Donepezil

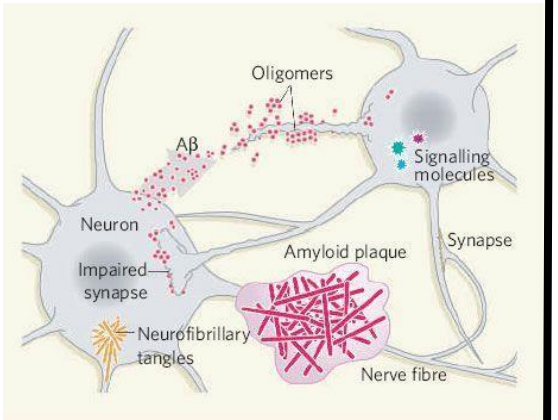
❑ Galantamine

❑ Rivastigmine

- **2. NMDA receptor antagonists**

❑ Memantine





1. Acetylcholinesterase Inhibitors

Mechanism of action:

- hallmark of the disease: Progressive loss of cortical cholinergic transmission participates in Alzheimer's disease-associated dementia.
- Inhibition of acetylecholinesterase (AchE) → improve cholinergic transmission.

Therapeutic uses:

The reversible AchE inhibitors (Donepezil, galantamine and rivastigmine) are approved for the treatment of *mild* to *moderate* Alzheimer's disease.

❑ These drugs provide a modest reduction in rate of loss of cognitive function in Alzheimer patients.

❑ Rivastigmine is the ONLY agent approved for the management of dementia associated with Parkinson's disease.

❑ Rivastigmine is the ONLY agent available as a transdermal patch.

Adverse effects

- Nausea , Diarrhea , Vomiting ,Anorexia , Tremors, Bradycardia , Muscle cramps

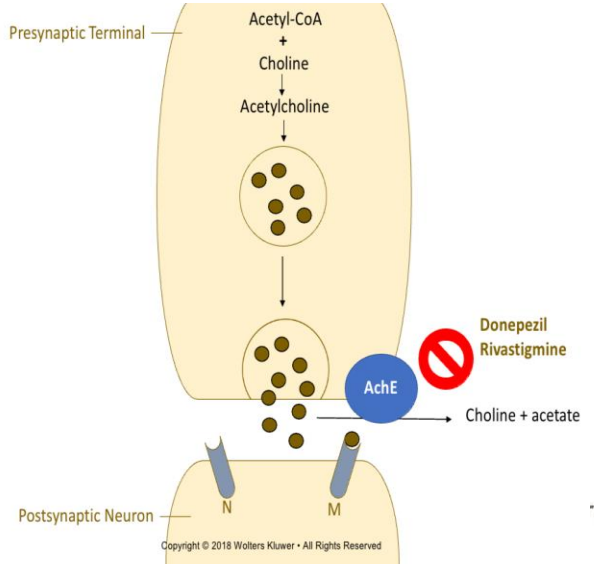
2. NMDA Receptors Antagonists

Mechanism of action:

- Overstimulation of NMDA glutamate receptors in the brain→ increases intracellular calcium → neurodegenerative or apoptotic loss of neurons (excitotoxicity)

Therapeutic uses

- Memantine is an NMDA receptors antagonist approved for the treatment of *moderate* to *severe* Alzheimer's disease.
- Memantine is often given in combination with an AchE inhibitor to treat Alzheimer's disease.



Treatment of Alzheimer's Disease

- Pharmacotherapy of Alzheimer's disease is symptomatic.
- The standard care includes AchE inhibitors + a NMDA antagonist.
- They both provide modest, short-term benefits but do NOT alter the underlying neurodegenerative process.

Future alternatives for the treatment of Alzheimer's Disease

- **Cholesterol-lowering agents**: statins
- **Insulin sensitizers**: PPAR-γ agonists (Rosiglitazone) (it sensitizes tissue to insulin and alters apolipoprotein E gene expression →↑ break- down of β-amyloid).
- **Intranasal insulin** (insulin crosses BBB from the nasal mucosa via transport from the olfactory receptor cells in the roof of the nasal cavity as patients with AD have lower insulin levels in CSF and higher plasma insulin levels)
- **NSAIDs**: low dose aspirin, celecoxib

Experimental disease-modifying drugs:

- Amyloid lowering agents: Semagacestat (failed)
- Drugs interfering with amyloid-β deposition: Tramiprosate
- Drugs increasing amyloid-β clearance: anti-amyloid antibodies
- Drugs interfering with tau deposition: Li+ small dose, valproate, methylene blue