Drugs for Neurodegenerative Diseases

Pharmacology and Toxicology

Central Nervous System Module

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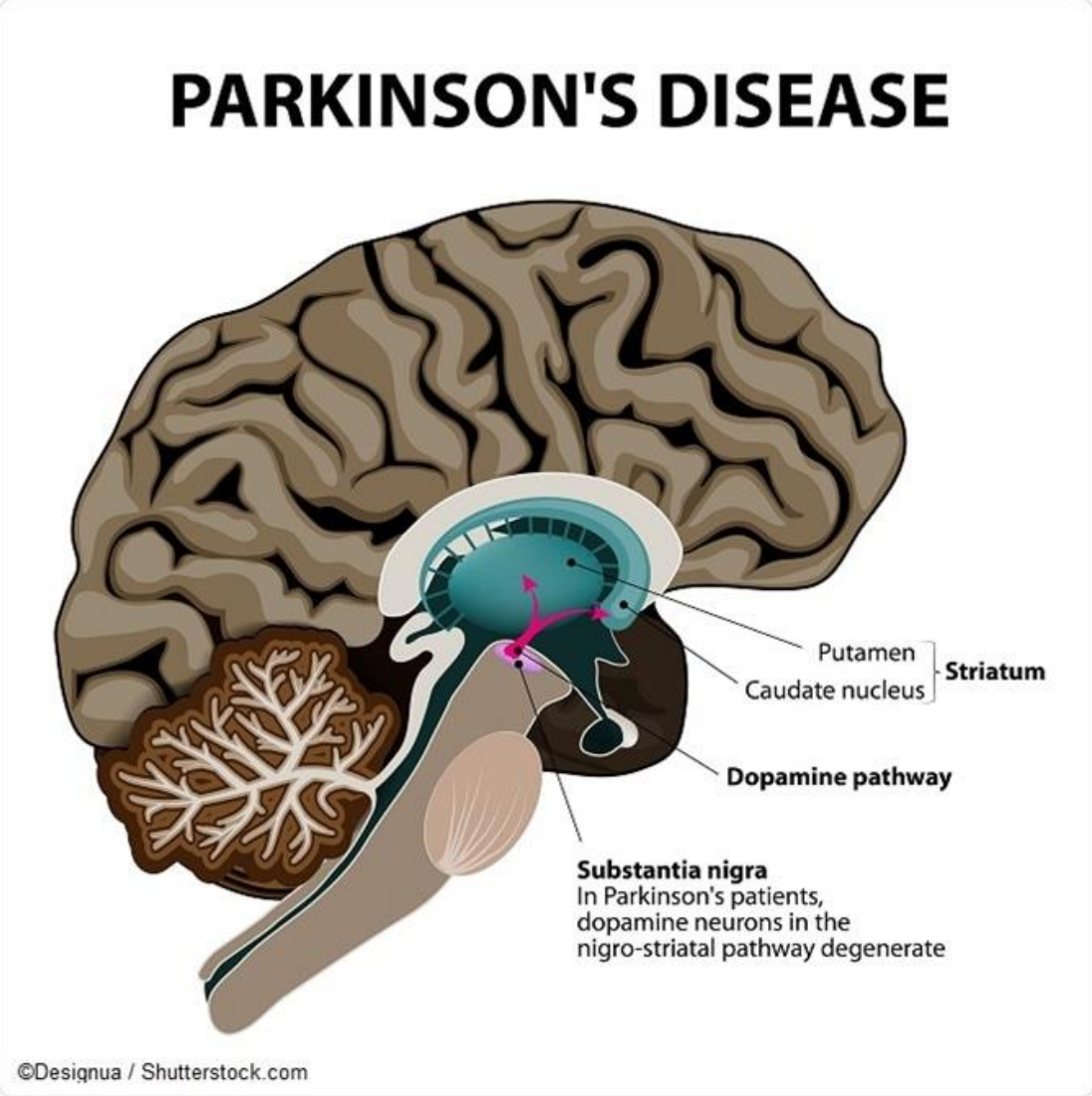
Parkinson's Disease: Pathophysiology

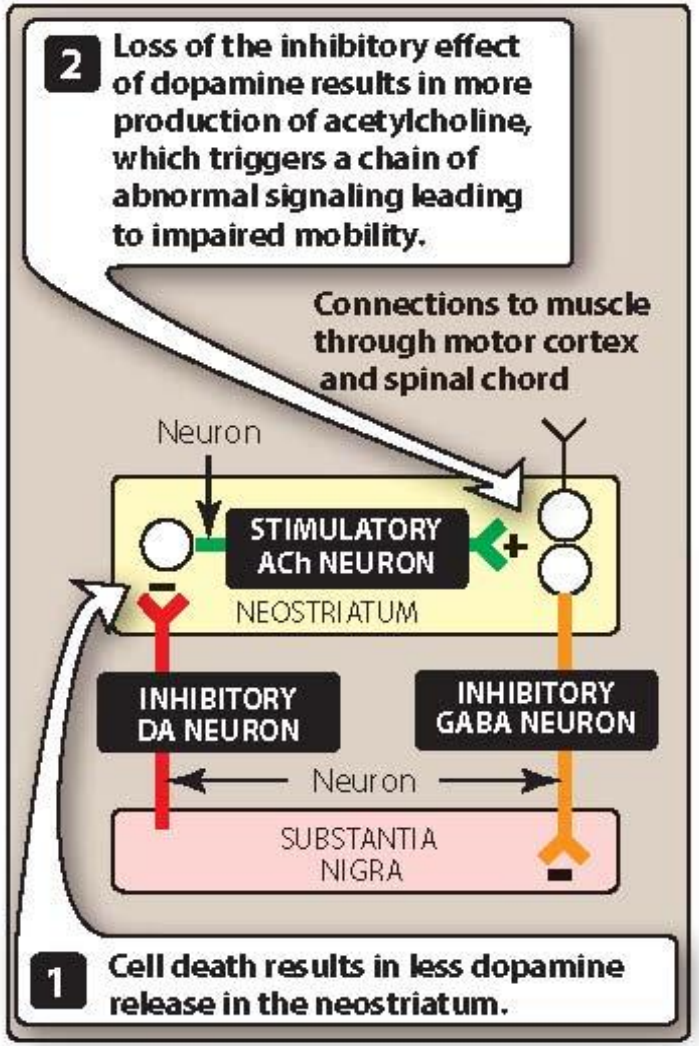
- Destruction of the dopaminergic neurons in the **substantia nigra** → ↓ dopaminergic stimulation in the corpus striatum.

- 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.

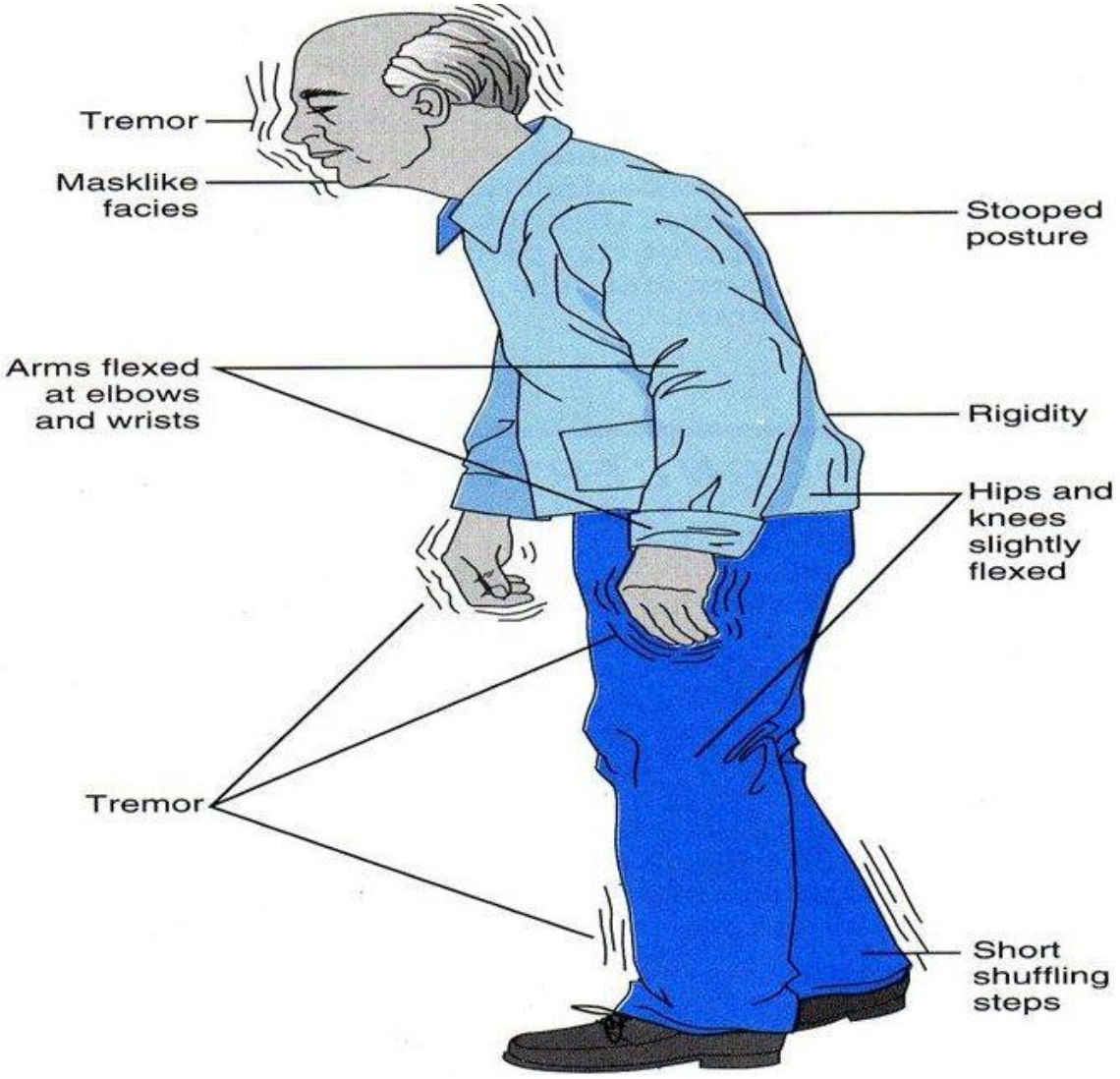
Parkinson's Disease: Pathophysiology





Parkinson's Disease

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



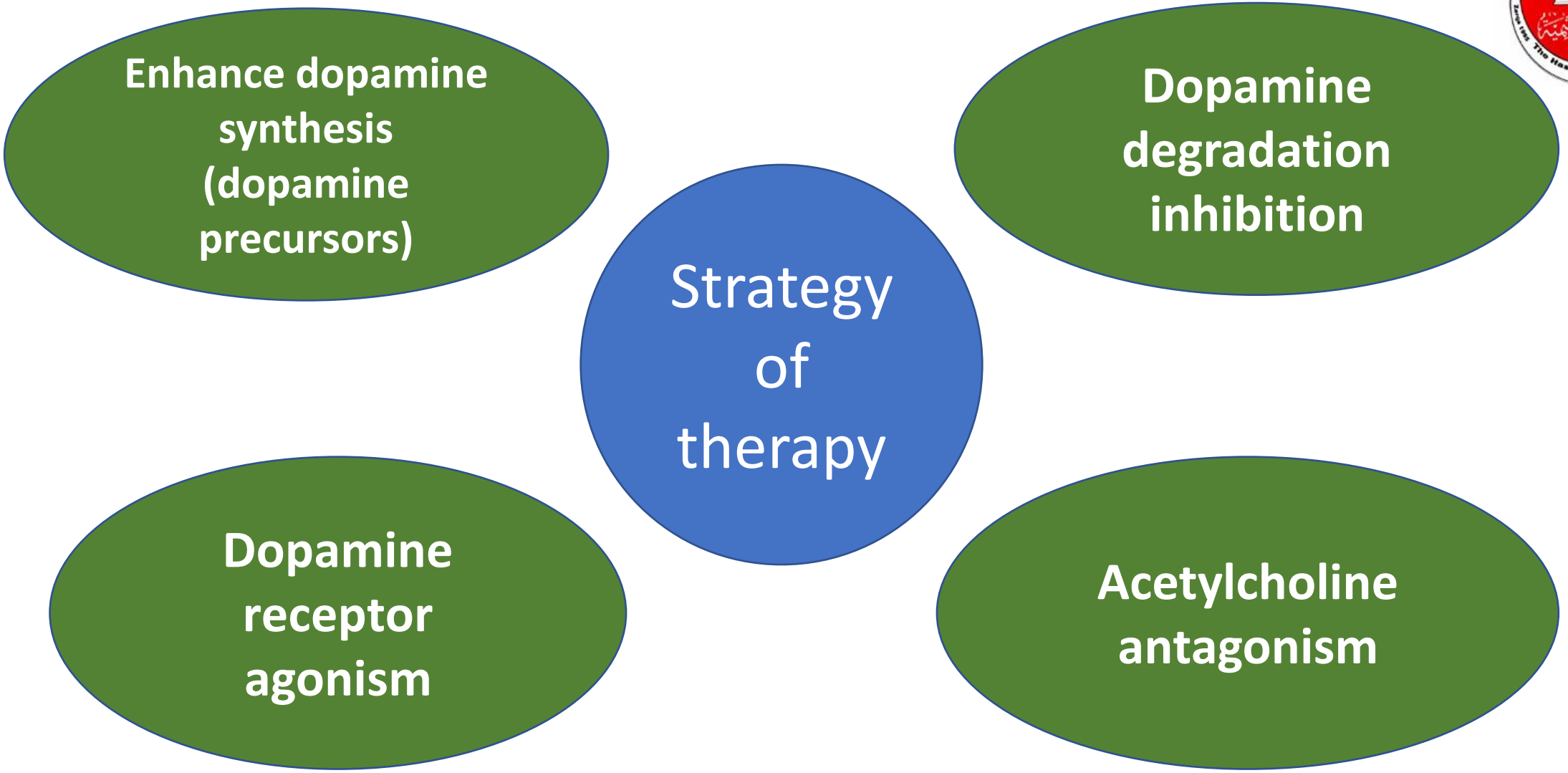
Parkinsonism: Etiology

- **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*



Parkinsonism

Strategy of treatment

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)**

Drugs Used in Parkinson's Disease

- Levodopa and carbidopa
- Selegiline and rasagiline
- Catechol-O-methyltransferase inhibitors (COMTis).
- Dopamine receptor agonist
- Amantadine
- Antimuscarinic agents

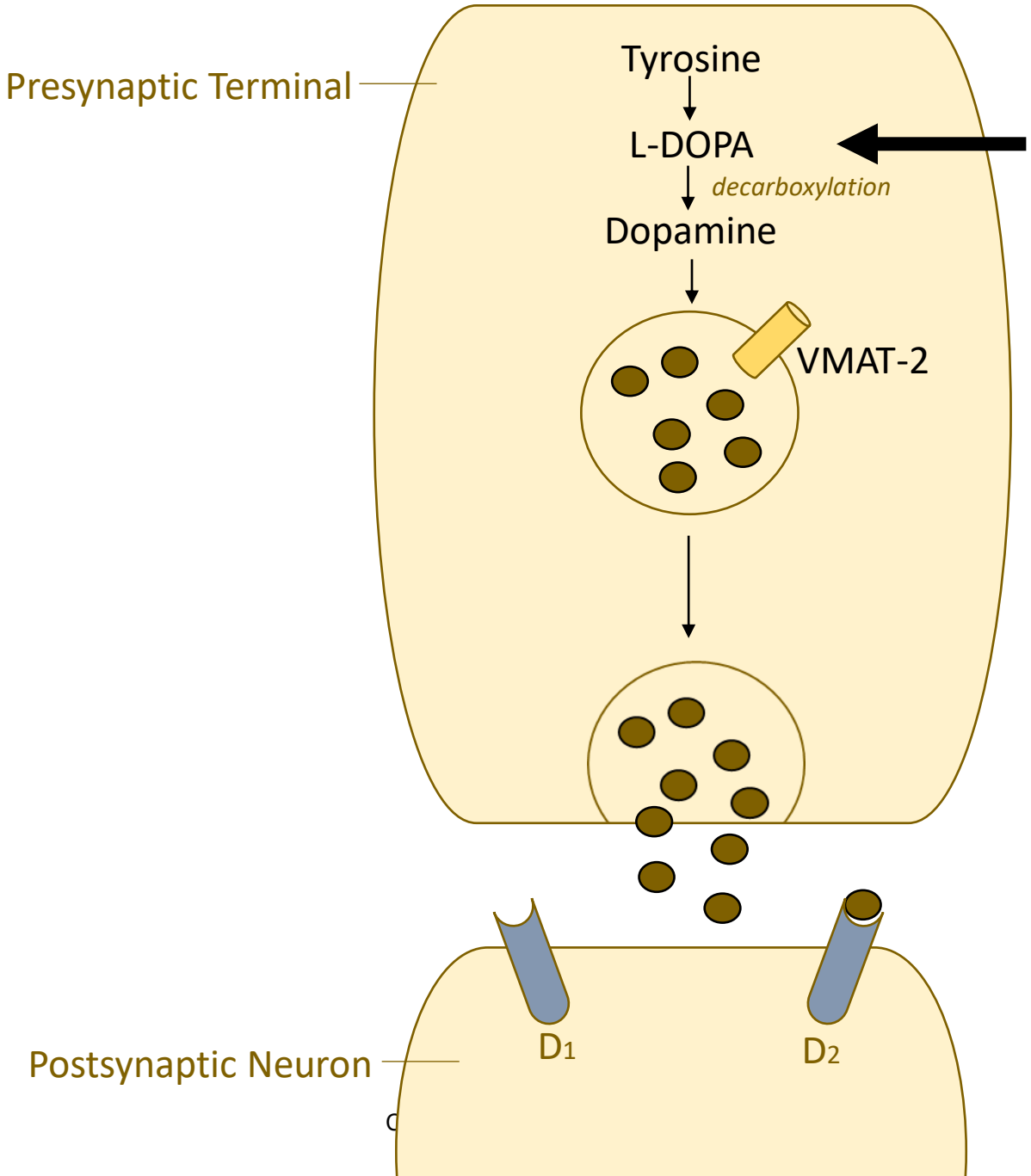
ANTI-PARKINSON DRUGS
Amantadine SYMMETREL
Apomorphine APOKYN
Benztropine COGENTIN
Biperiden AKINETON
Bromocriptine PARLODEL
Carbidopa LODOSYN
Entacapone COMTAN
Levodopa (w/Carbidopa) SINEMET, PARCOPA
Pramipexole MIRAPEX
Procyclidine KEMADRIN
Rasagiline AZILECT
Ropinirole REQUIP
Rotigotine NEUPRO
Selegiline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

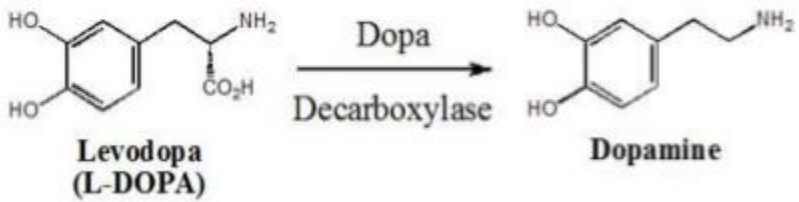
Levodopa and carbidopa

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.

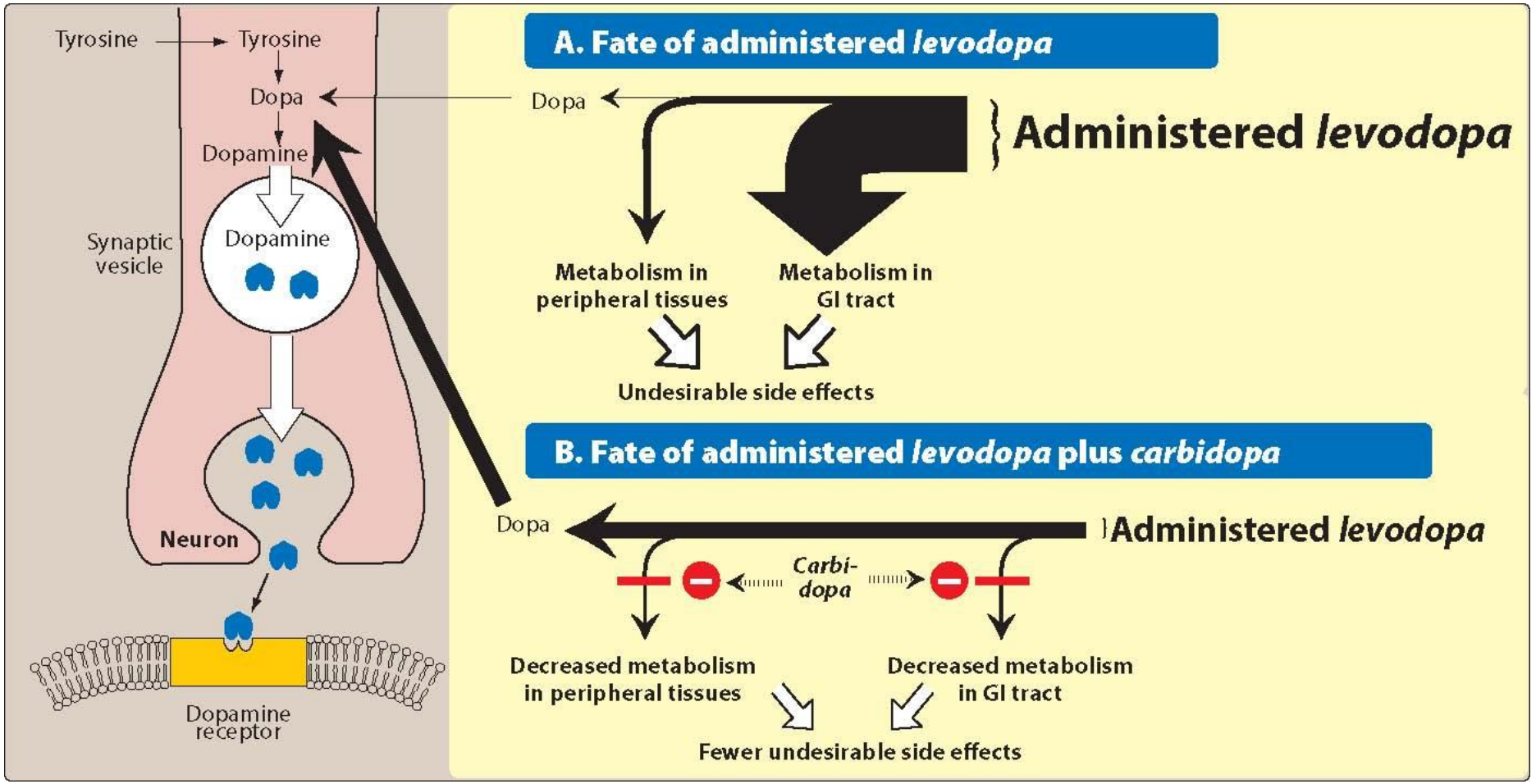
Without carbidopa, most of levodopa is metabolized in the periphery.





Levodopa (L-DOPA) **Dopamine**

Levodopa and carbidopa



Levodopa and carbidopa

Therapeutic uses

- Levodopa + carbidopa: the gold standard of symptomatic treatment for Parkinson's disease.

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

*(*) "**wearing off" phenomenon** (symptoms of Parkinson's start to return or worsen with progression of the disease)*

Levodopa and carbidopa

Pharmacokinetics

- Levodopa is rapidly absorbed from the gut.

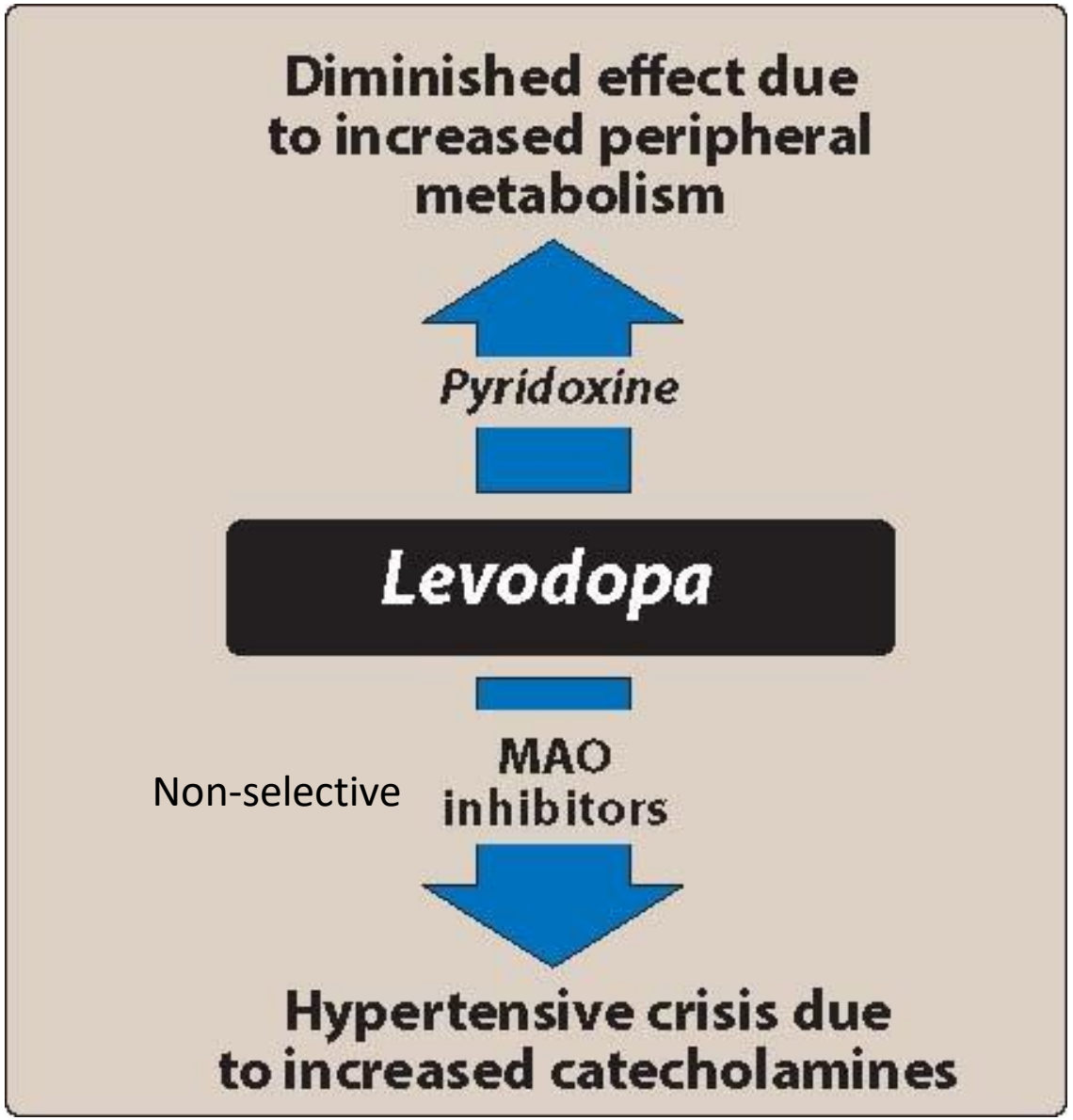
  -administered on an empty stomach (high-protein diet interferes with its transport to the brain).

- 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)*

Drug-drug Interaction



Levodopa and carbidopa

Adverse effects:

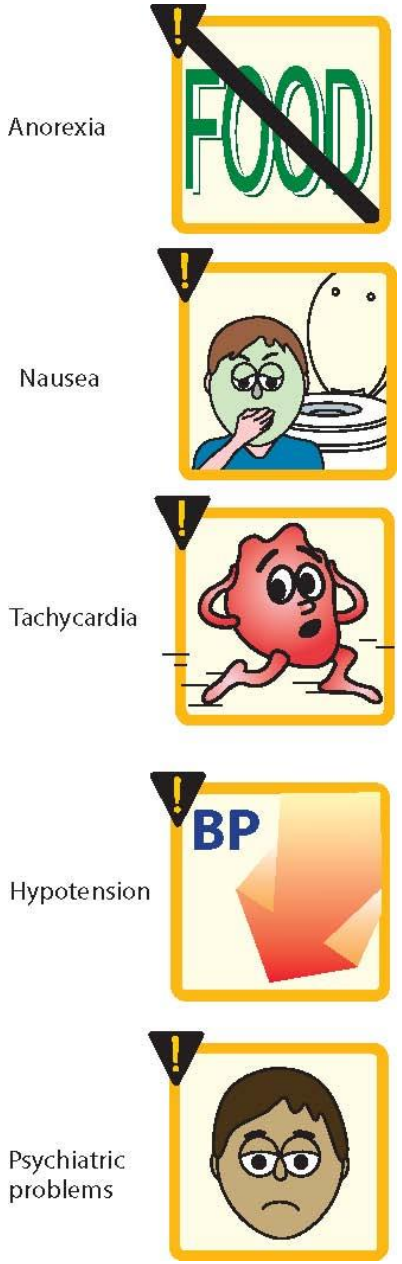
- **Peripheral effects:**

❑ 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.



Levodopa and carbidopa

Adverse effects:

- **Central effects:**

❑ Visual and auditory hallucinations

❑ Dyskinesia

❑ Mood changes

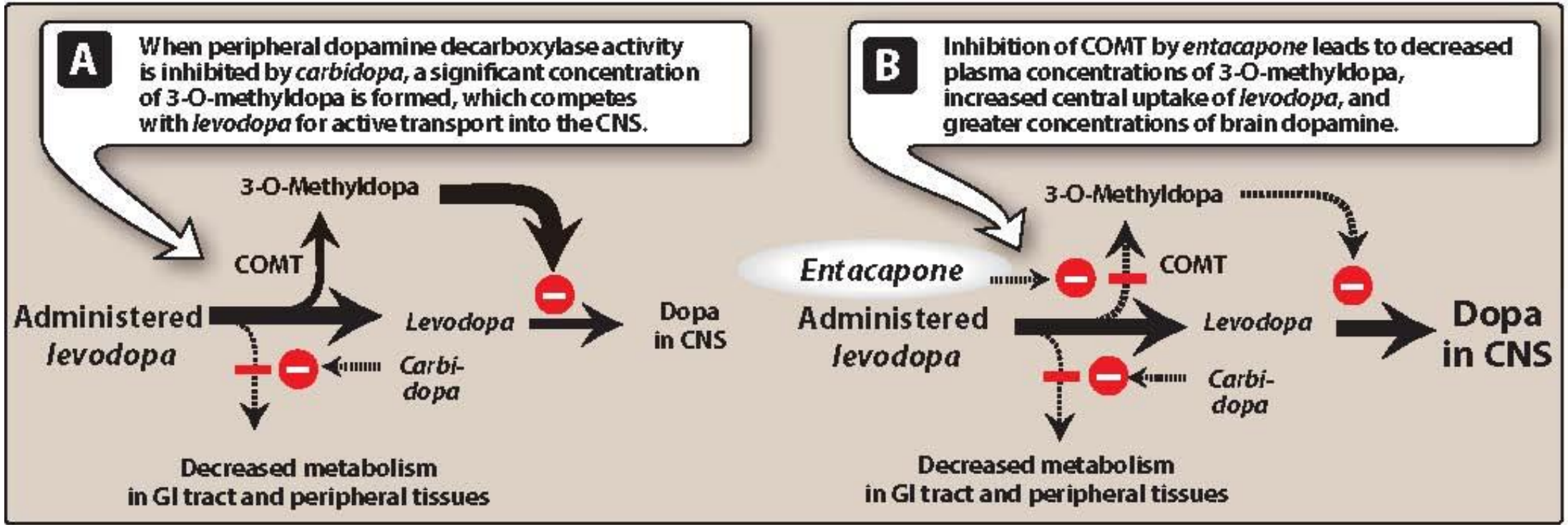
(These CNS effects are the opposite of parkinsonian symptoms and reflect the overactivity of dopamine at receptors in the basal ganglia)

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.



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

Pharmacokinetics

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

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

Adverse effects:

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

MAO Inhibitors: Selegiline and Rasagiline

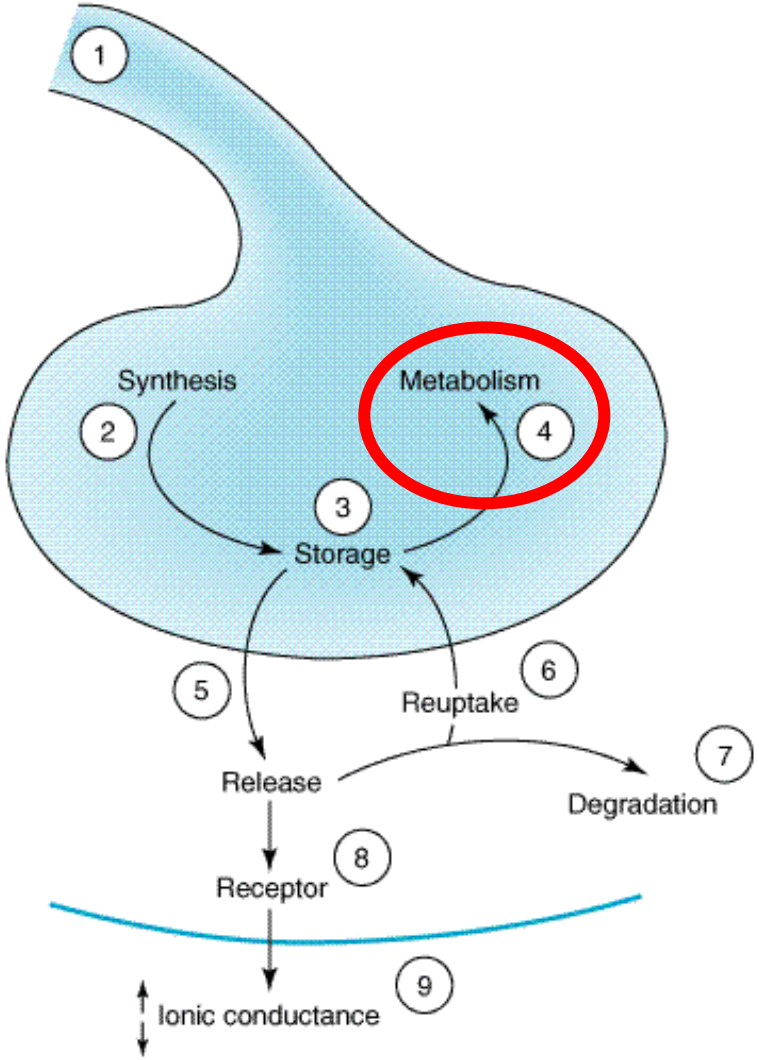
Mechanism of action:

- **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.

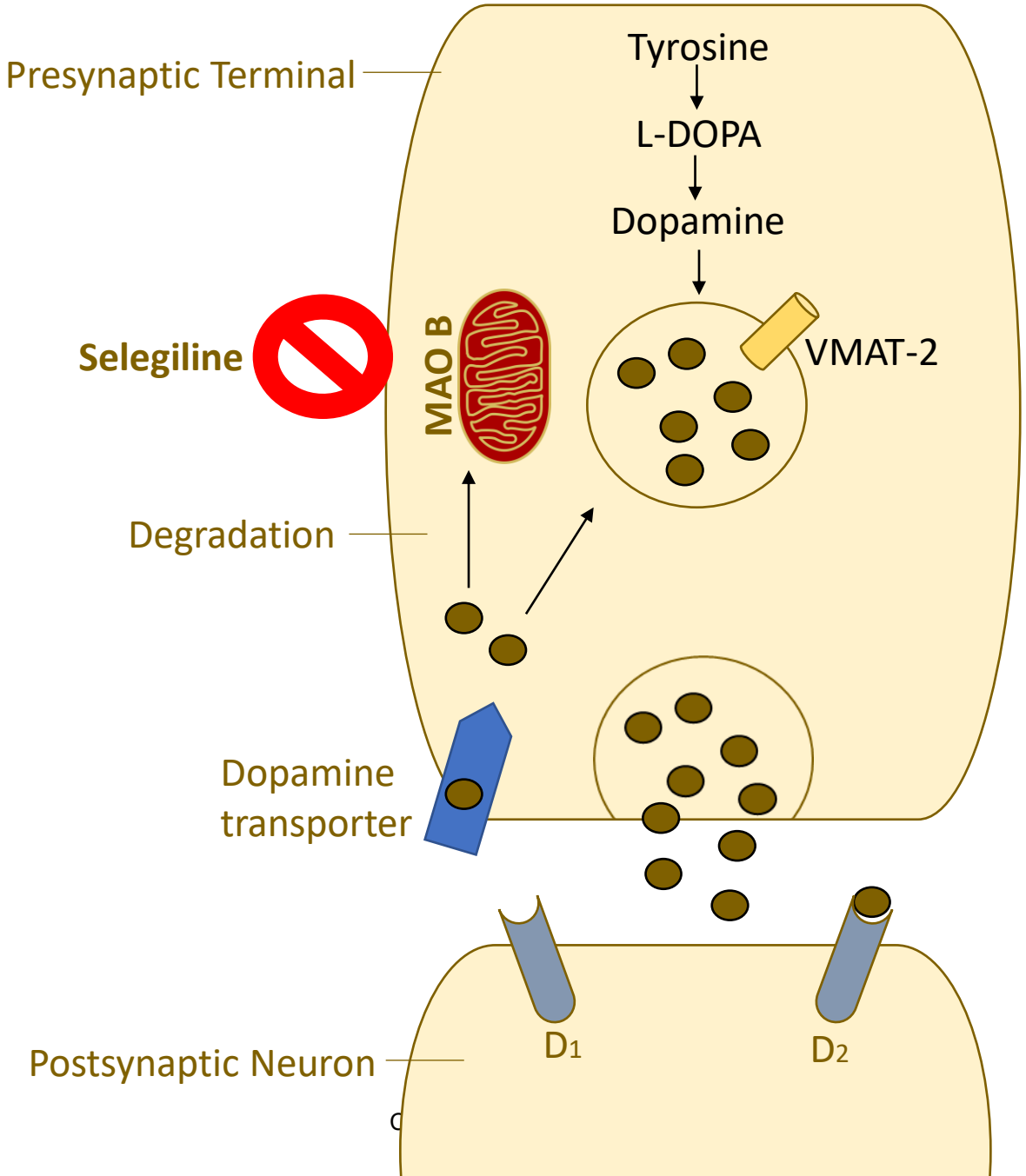
Sites and Mechanisms of CNS Drug Action



Metabolism:

- COMT and MAO

- Antiparkinsonian
- Antidepressants



MAO Inhibitors: Selegiline and Rasagiline

Therapeutic uses:

- **Seligiline** is <u>often administered with levodopa</u>:

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

MAO Inhibitors: Selegiline and Rasagiline

Adverse effects:

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

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

Dopamine Receptor Agonists

Drugs:

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

Dopamine Receptor Agonists

Mechanism of action

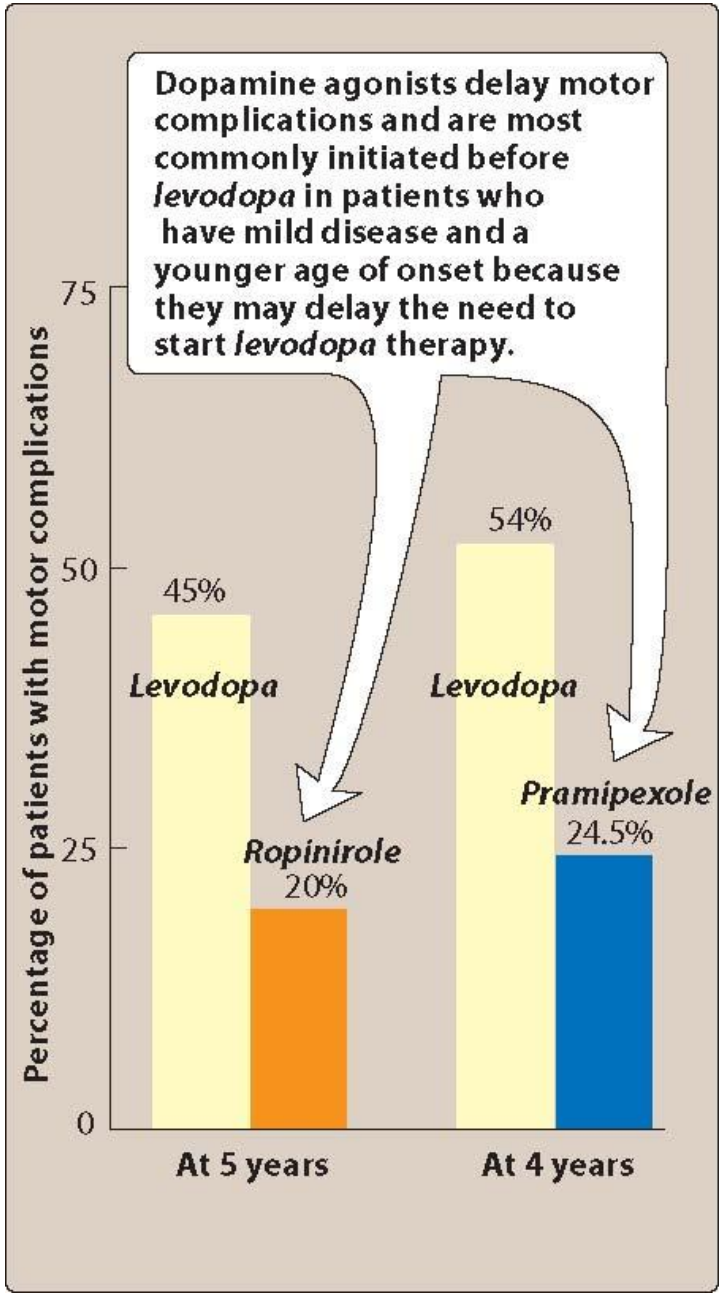
- Direct dopamine receptor 2 (D_2) agonism.

Dopamine Receptor Agonists

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)

Therapeutic advantage of dopamine agonists



Dopamine Receptor Agonists

Pharmacokinetics

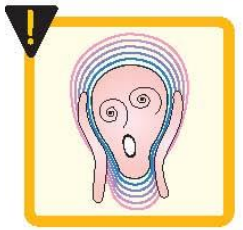
Characteristic	*Pramipexole*	*Ropinirole*	*Rotigotine*
Bioavailability	>90%	55%	45%
V_d	7 L/kg	7.5 L/kg	84 L/kg
Half-life	8 hours[1]	6 hours	7 hours[3]
Metabolism	Negligible	Extensive	Extensive
Elimination	Renal	Renal[2]	Renal[2]

Dopamine Receptor Agonists

Adverse effects

- Similar to levodopa.
- Bromocriptine: pulmonary and retroperitoneal fibrosis
- nonergot derivatives do NOT cause fibrosis.

Sedation


Hallucinations


Confusion


Nausea

Hypotension

Amantadine

Mechanism of action:

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

Amantadine

Therapeutic uses:

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

Antimuscarinic agents

Drugs

- Benztropine
- Trihexyphenidyl
- Procyclidine
- Bioperiden

Antimuscarinic agents

Mechanisms of action

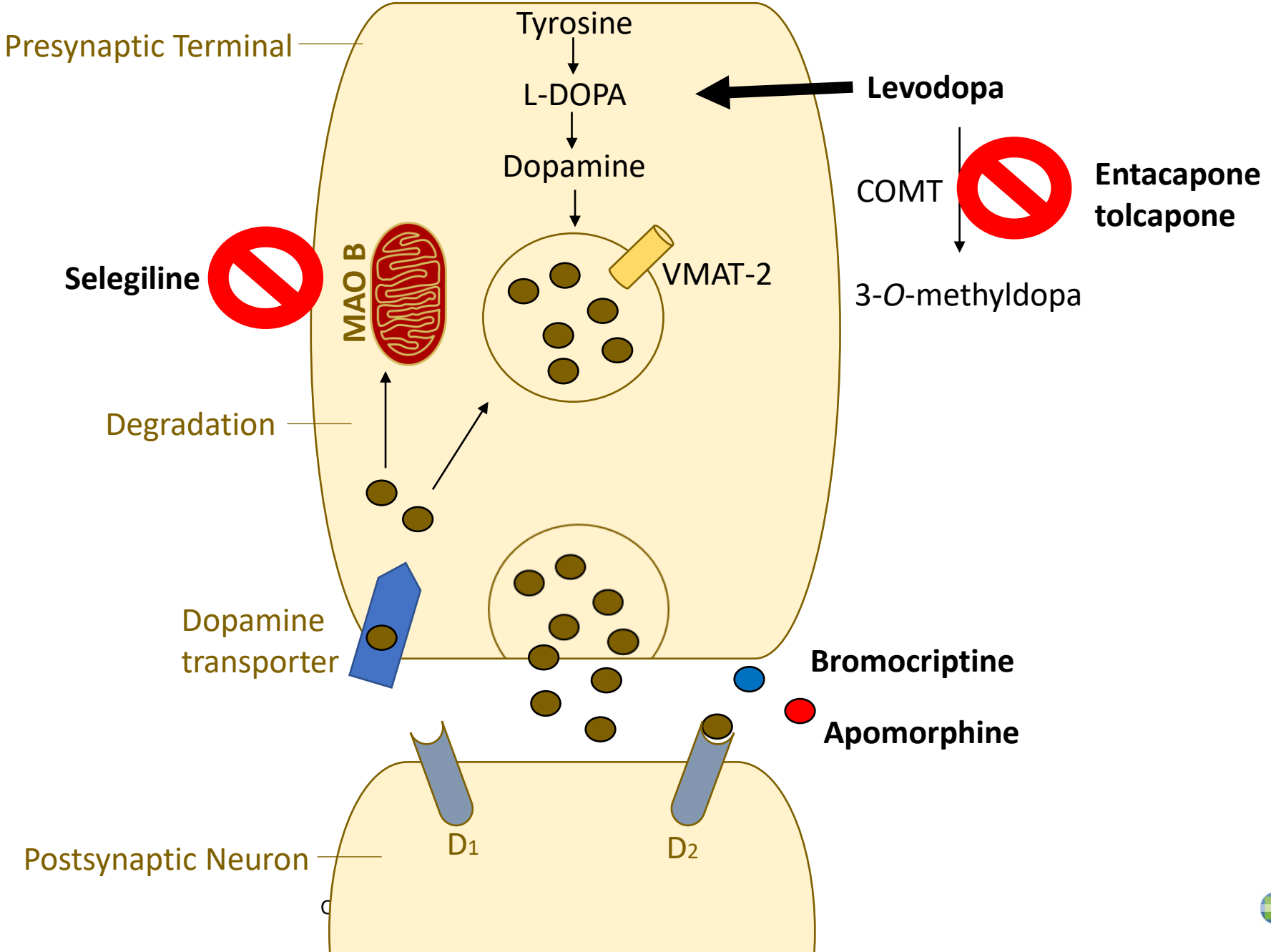
- Blockade of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission → correct the imbalance of dopamine/acetylcholine ratio.

Antimuscarinic agents

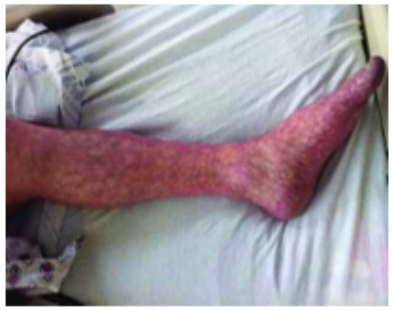
Therapeutic uses

- Much less efficacious than levodopa and always used in adjuvant to other antiparkinsonian therapy.
- Anticholinergics are mainly used in antipsychotic-induced parkinsonism.

Summary



Summary

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 

Summary

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**

Summary Of The Therapeutic Strategy

- 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).

Summary of the therapeutic strategy

How to decrease fluctuation in motor response to levodopa?

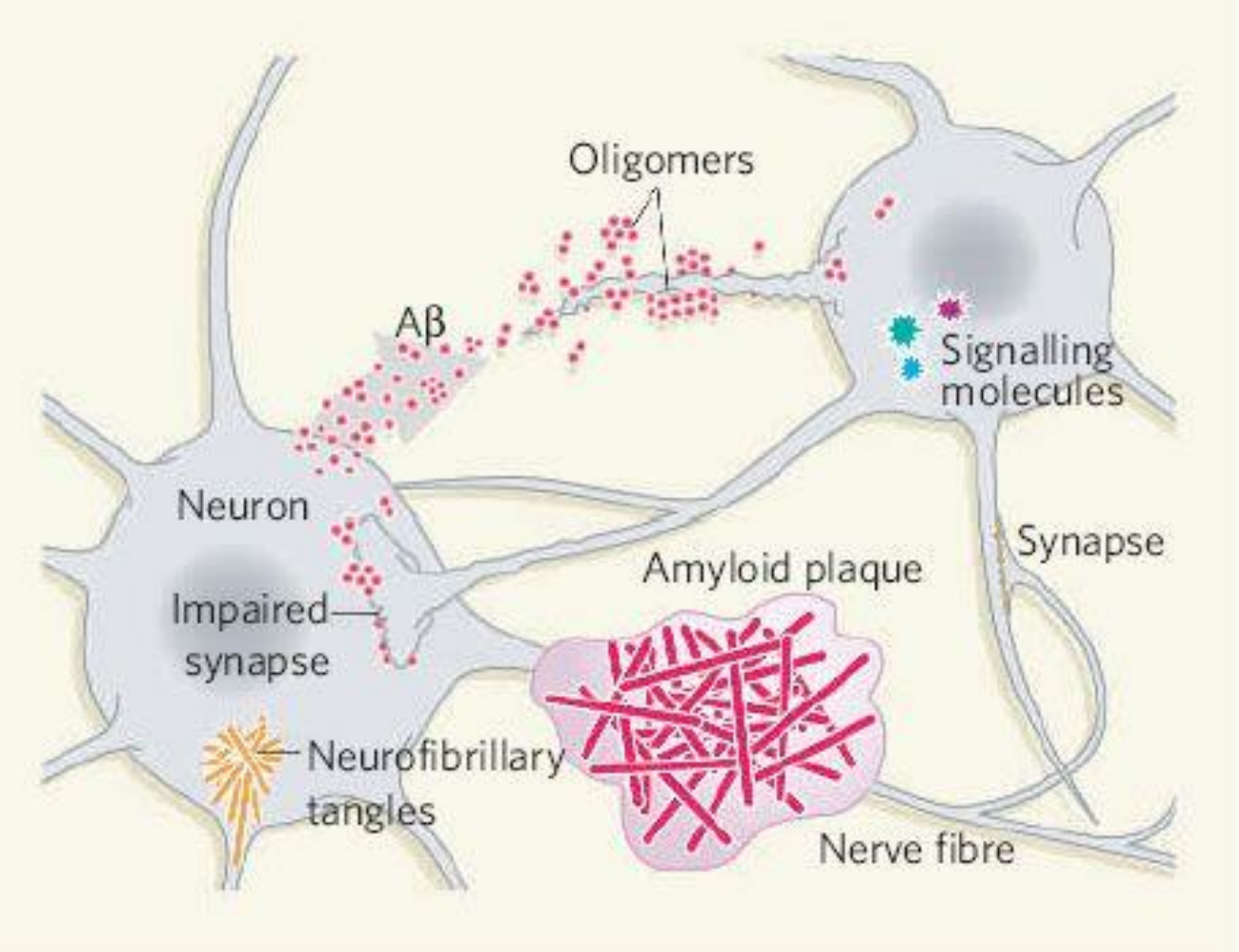
Addition of a MAO B inhibitor or a COMT inhibitor or a dopamine agonist

Shortening of the interval between doses of levodopa+carbidopa

Using slow-release preparations of levodopa+carbidopa

Overview: 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.



Alzheimer's Disease: 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)

Improve brain cholinergic transmission

Strategy of therapy

Reduce glutamate-NMDA-induced excitotoxicity

Alzheimer's Disease

Drugs Used in Alzheimer's Disease

- Acetylcholinesterase inhibitors

❑Donepezil

❑Galantamine

❑Rivastigmine

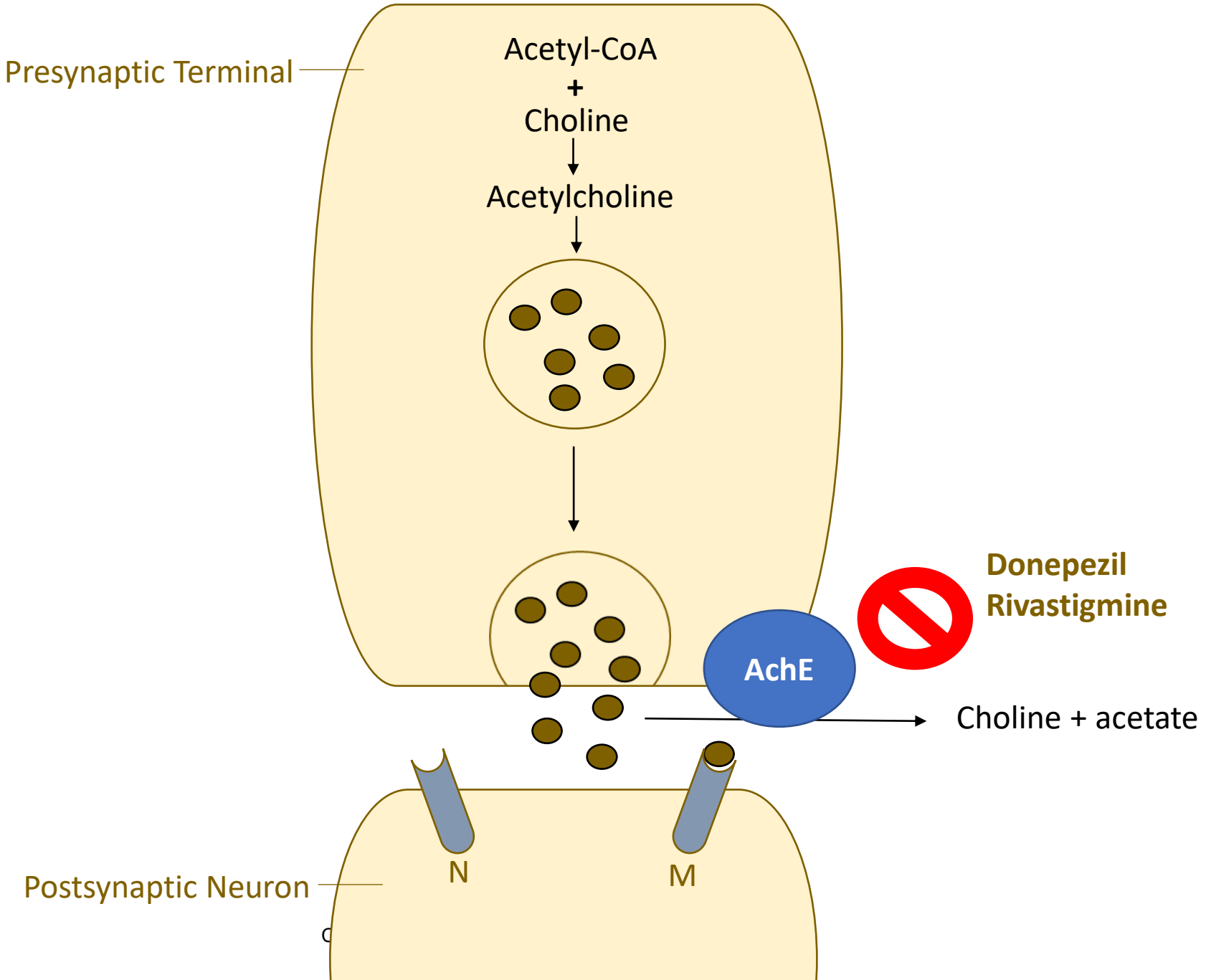
- NMDA receptor antagonists

❑Memantine

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.



Acetylcholinesterase Inhibitors

Therapeutic uses:

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

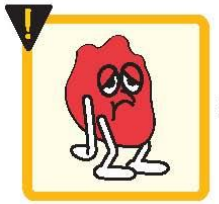
- These drugs provide a modest reduction in rate of loss of cognitive function in Alzheimer patients.
- Rivastigmine is the ONLY agent approved for the management of dementia associated with Parkinson's disease.
- Rivastigmine is the ONLY agent available as a transdermal patch.

Acetylcholinesterase Inhibitors

Adverse effects

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


Tremors


Bradycardia


Nausea


Diarrhea

Anorexia


Myalgia

NMDA Receptors Antagonists

Mechanism of action:

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

NMDA Receptors Antagonists

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

Future alternatives for the treatment of Alzheimer's Disease

Experimental disease-modifying drugs:

- Amyloid lowering agents: Semagacestat
- 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