Al-Mustaqbal University College
Department of Pharmacy
4th stage
Pharmacology II
Lecture: 6

Drugs for Neurodegenerative Diseases

Dr Qassim A zigam

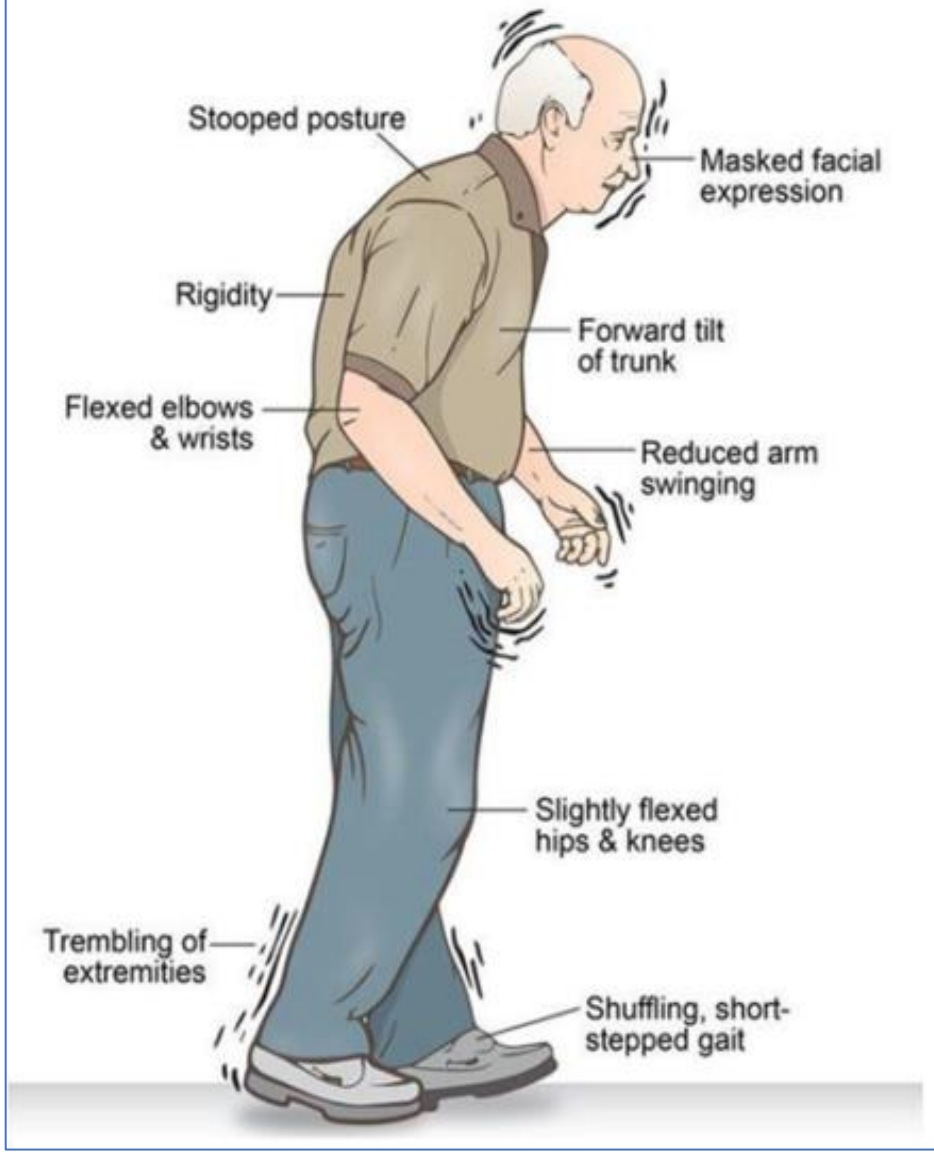
PARKINSON'S DISEASE

- Parkinsonism is a **progressive neurological** disorder of **muscle** movement, characterized by:

1. Tremor
2. Muscular rigidity
3. Bradykinesia (slowness in initiating and carrying out voluntary movements)
4. Postural and gait abnormalities

- PD affects **1-2 per 1000** of the population at any time.
- PD **prevalence** is increasing with age and PD affects **1%** of the population above **60 years**.

PARKINSON'S DISEASE



T Tremor: shaking, usually starting on one side

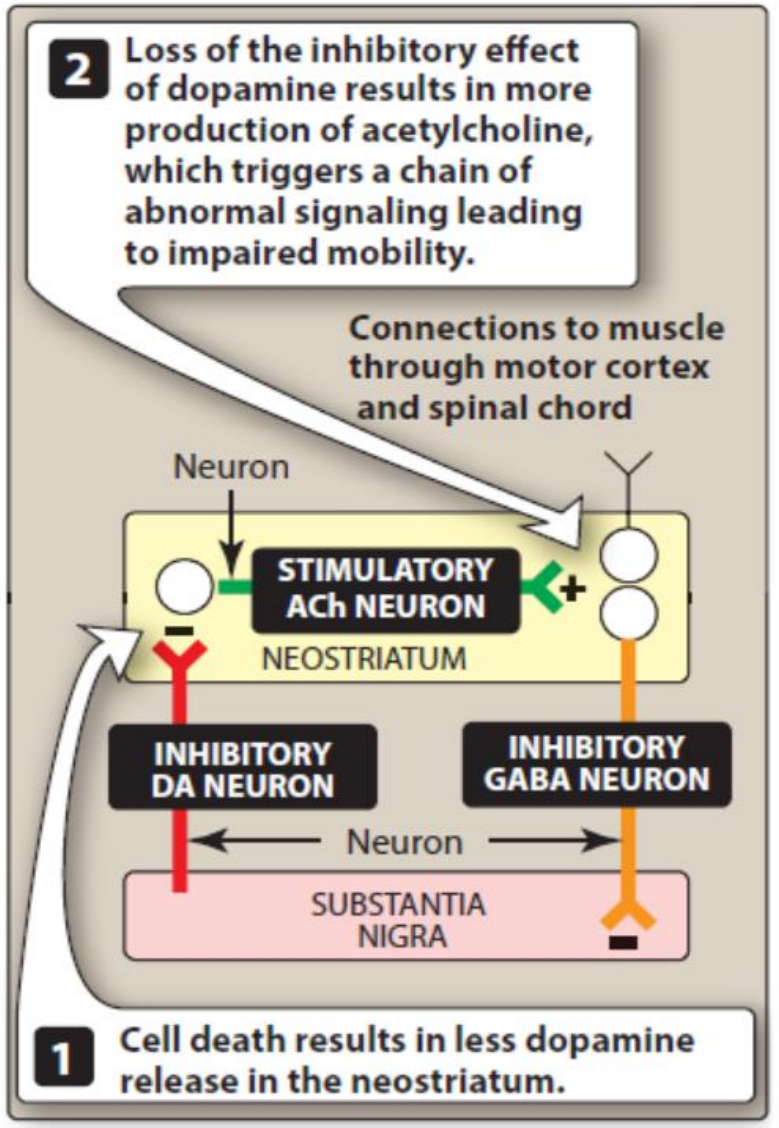
R Rigidity: stiffness of the limbs, neck, or trunk

A Akinesia: loss or impairment in power of voluntary movement

P Posture and balance

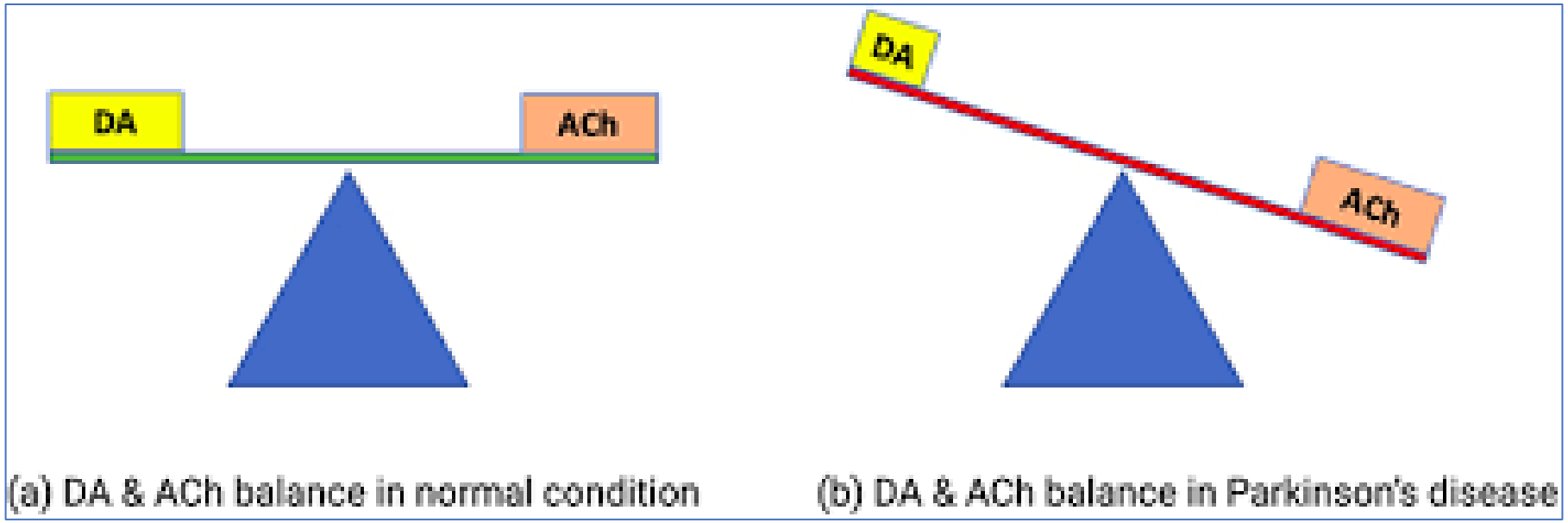
PARKINSON'S DISEASE ETIOLOGY

- The cause of Parkinson's disease is **unknown** for most patients.
- It is correlated with the **destruction of dopaminergic neurons** in the **substantia nigra** with a consequent reduction of dopamine **actions** in the **corpus striatum**.
- **Drugs** such as <u>phenothiazines</u> and <u>haloperidol</u> may produce parkinsonian symptoms (also called **pseudoparkinsonism**).
- These drugs should be used with **caution** in patients with Parkinson's disease.



STRATEGY OF TREATMENT

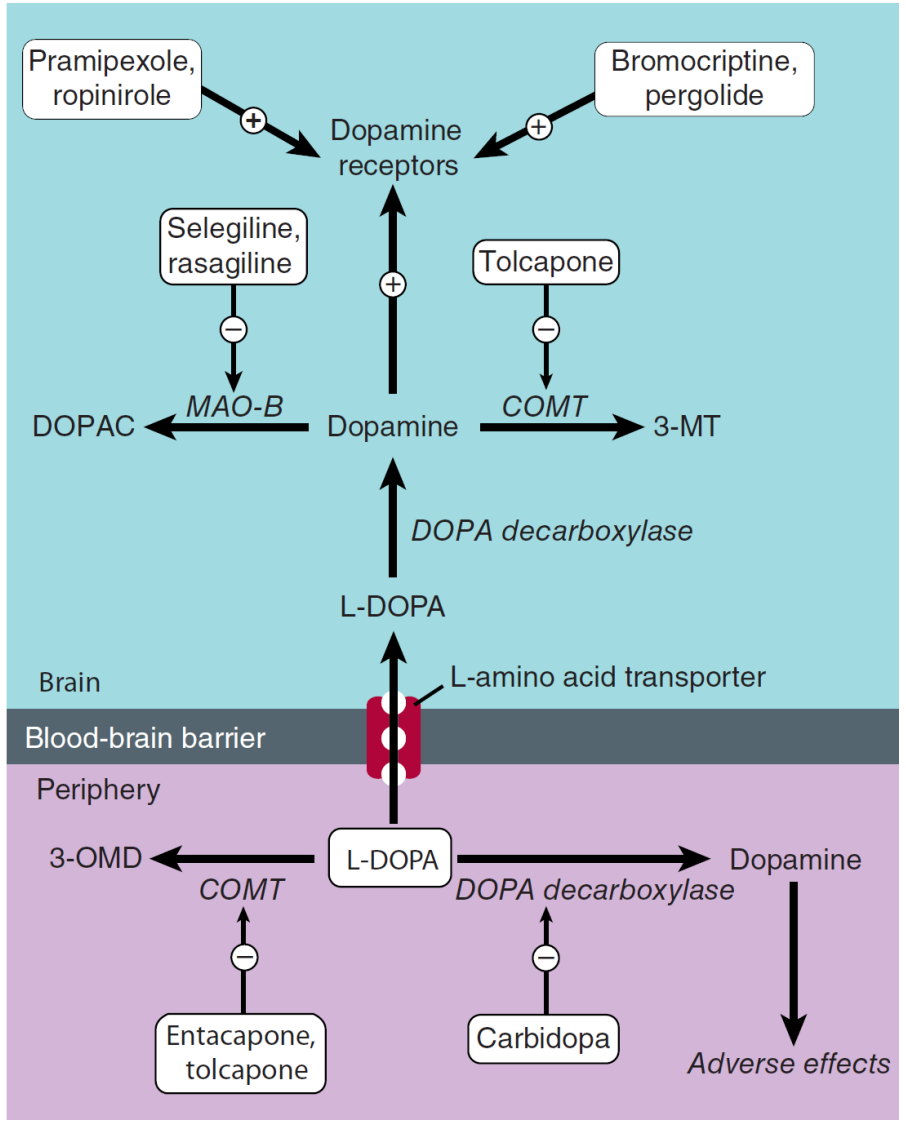
- Many of the symptoms of parkinsonism reflect an **imbalance** between the **excitatory cholinergic** neurons and the greatly **diminished** number of **inhibitory dopaminergic** neurons.
- Therapy is **aimed** at **restoring dopamine** in the basal ganglia and **antagonizing the excitatory** effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine **balance**.



(a) DA & ACh balance in normal condition (b) DA & ACh balance in Parkinson's disease

DRUGS USED IN PARKINSON'S DISEASE

1. Levodopa and carbidopa
2. Selegiline and rasagiline
3. Catechol-O-methyltransferase inhibitors (Entacapone and Tolcapone)
4. Dopamine receptor agonists (bromocriptine, ropinirole, Pramipexole, Rotigotine, and the newer agent, apomorphine)
5. Amantadine
6. Antimuscarinic agents (benztropine, trihexyphenidyl, procyclidine, and biperiden)

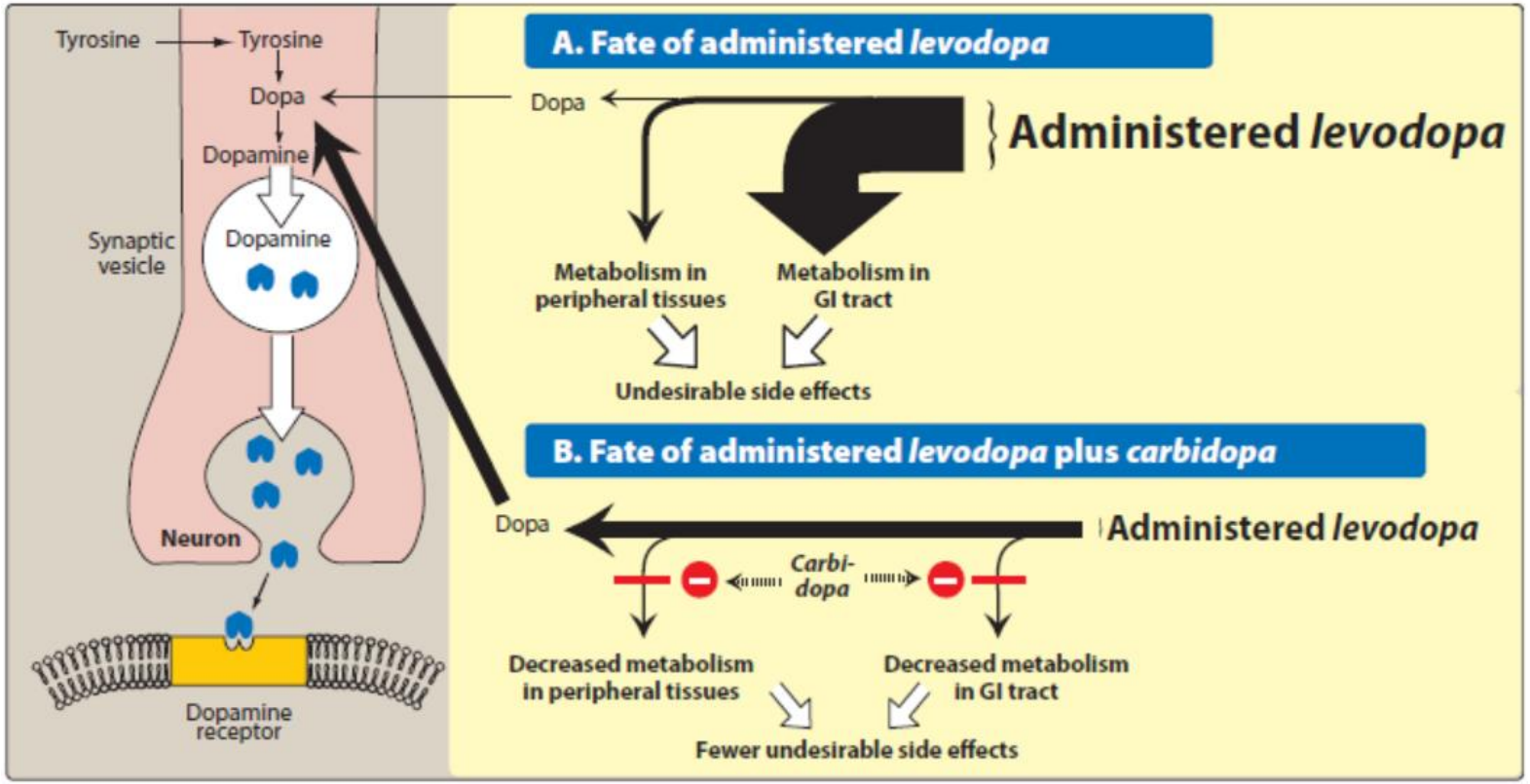


LEVODOPA & CARBIDOPA

- Levodopa is a metabolic **precursor** of dopamine.
- It **restores** dopaminergic neurotransmission in the **neostriatum** by enhancing the **synthesis** of dopamine in the surviving neurons of the **substantia nigra**.
- In **early disease**, the number of **residual** dopaminergic neurons in the substantia nigra (typically about **20%** of normal) is **adequate** for the conversion of levodopa to dopamine.
- Unfortunately, **with time**, the number of neurons **decreases**, and fewer cells are capable of **converting** exogenously administered levodopa to dopamine. Consequently, motor control **fluctuation** develops.

LEVODOPA & CARBIDOPA

- The **effects** of **levodopa** on the CNS can be greatly **enhanced** by co-administering **carbidopa**, a **dopamine decarboxylase** inhibitor that does not cross the blood-brain barrier.



MECHANISM OF ACTION

Levodopa:

- **Dopamine** does **not** cross the **BBB**, but its immediate precursor, **levodopa**, is actively **transported** into the CNS and converted to **dopamine**.
- Levodopa must be administered **with carbidopa**. Without carbidopa, much of the drug is decarboxylated to dopamine in the periphery, resulting in nausea, vomiting, cardiac arrhythmias, and hypotension.

Carbidopa:

- Carbidopa, a **dopamine decarboxylase inhibitor**, diminishes the metabolism of levodopa in the **periphery**, thereby increasing the **availability** of levodopa to the **CNS**.
- The addition of carbidopa **lowers the dose** of levodopa needed by **4-5 fold,** and consequently, **decreases** the severity of the peripheral **side effects.**

THERAPEUTIC USES

- Levodopa in combination with carbidopa is an efficacious drug regimen for the treatment of **Parkinson's disease**.
- It **decreases** rigidity, tremors, and other symptoms of parkinsonism.
- In approximately **two-thirds** of patients with Parkinson's disease, **levodopa–carbidopa** substantially **reduces** the severity of symptoms for the **first few years** of treatment.
- Patients typically **experience a decline** in response during the **3rd to 5th** year of therapy.
- **Withdrawal** from the drug must be **gradual**.

ABSORPTION AND METABOLISM

- The drug is **absorbed** rapidly from the small intestine (when **empty** of food).
- Levodopa has an extremely **short half-life** (1-2 hours), which causes fluctuations in plasma concentration.
- **\Motor fluctuations** may cause the patient to **suddenly lose normal mobility** and experience **tremors**, **cramps**, and **immobility**.
- Ingestion of **meals**, particularly if high in protein, **interferes** with the transport of levodopa into the CNS.
- Thus, levodopa should be taken on an empty stomach, typically **30 minutes before a meal**.

ADVERSE EFFECTS

Peripheral effects:

- Anorexia, nausea, and vomiting occur because of stimulation of the **CTZ**.
- Tachycardia and ventricular extrasystoles result from dopaminergic action on the **heart**.
- **Hypotension** may also develop.
- Saliva and urine are a **brownish colour** because of the **melanin pigment** produced from **catecholamine oxidation**.

CNS effects:

- Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur.
- Levodopa can also cause mood changes, depression, psychosis, and anxiety.

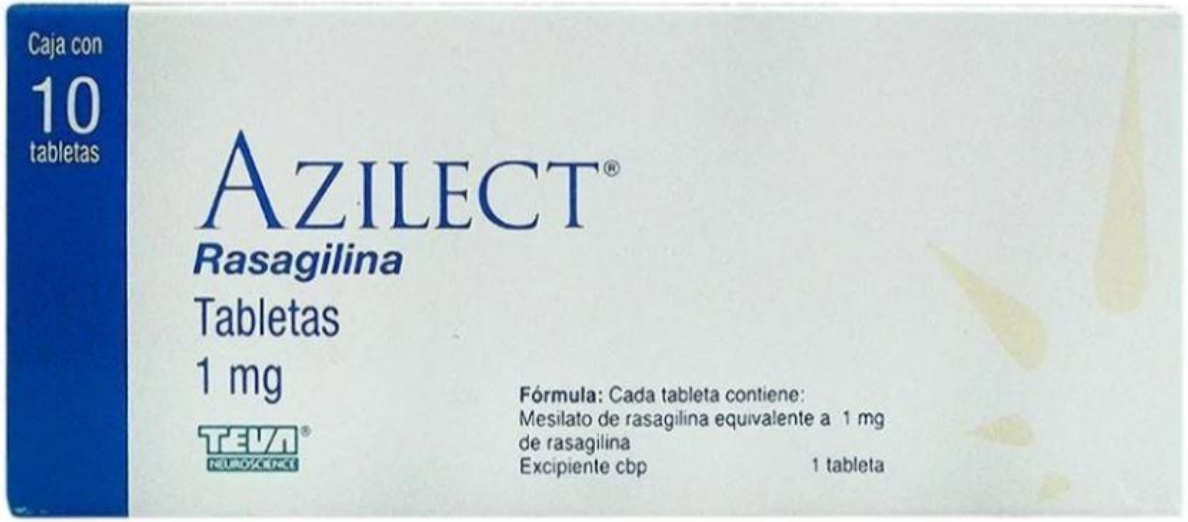
NOTE: Pyridoxine increases the peripheral breakdown of levodopa and diminishes its effectiveness.

SELEGILINE AND RASAGILINE

- **Selegiline** selectively **inhibits MAO-B** at low to moderate doses, then selegiline increases dopamine levels in the brain.
- When selegiline is administered **with levodopa**, it **enhances** the actions of levodopa and substantially **reduces** the required dose.
- Selegiline is **metabolized** to methamphetamine and amphetamine, whose stimulating properties may produce **insomnia.**

SELEGILINE AND RASAGILINE

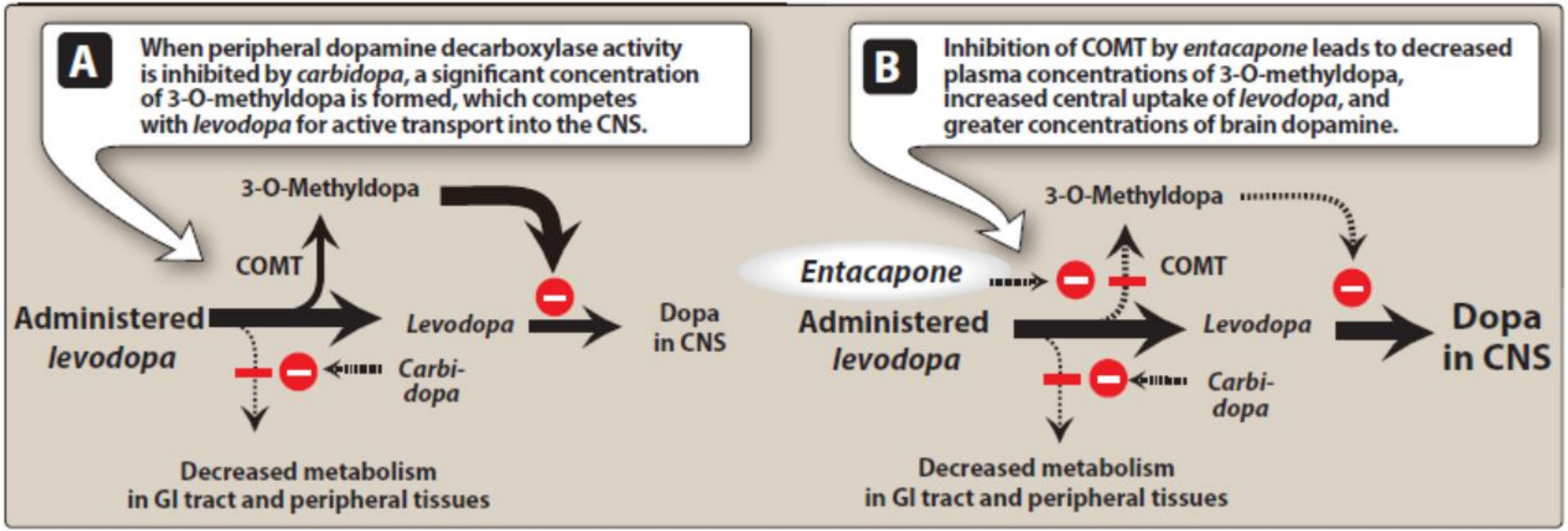
- **Rasagiline** is an irreversible and selective inhibitor of brain **MAO-B.**
- **It has five times** the potency of **selegiline**.
- **Unlike** selegiline, rasagiline is **not** metabolized to an **amphetamine-like substance**.



CATECHOL-O-METHYLTRANSFERASE INHIBITORS

- Normally, the **methylation** of levodopa by **COMT** to 3-O-methyldopa is a **minor** pathway for levodopa metabolism.
- However, when **peripheral dopamine decarboxylase** activity is **inhibited** by carbidopa, a significant concentration of **3-O-methyldopa** is formed that competes with levodopa for active transport into the CNS.
- **Entacapone** and **Tolcapone** selectively and reversibly inhibit COMT.
- Inhibition of COMT by these agents leads to **decreased** plasma concentrations of **3-O-methyldopa**, increased **central uptake** of levodopa.
- Both of these agents **reduce the symptoms of "wearing-off" phenomena** seen in patients on levodopa–carbidopa.

CATECHOL-O-METHYLTRANSFERASE INHIBITORS



Effect of entacapone on dopa concentration in the central nervous system (CNS).

CATECHOL-O-METHYLTRANSFERASE INHIBITORS

Pharmacokinetics:

- **Oral** absorption of **both** drugs occurs **readily** and is **not** influenced by **food**.
- **Tolcapone** has a relatively **long duration of action** (probably due to its **affinity** for the enzyme) compared to **entacapone**.
- **Both** drugs are extensively **metabolized** and eliminated in feces and urine.
- The **dosage** may need to be **adjusted** in patients with moderate or severe cirrhosis.

Adverse effects:

- **Both** drugs exhibit adverse effects that including diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, and sleep disorders.
- Most seriously, fulminating **hepatic necrosis** is associated with **tolcapone** use.
- **Entacapone** does **not** exhibit this toxicity and has largely **replaced tolcapone**.

DOPAMINE RECEPTOR AGONISTS

- These include **bromocriptine**, an ergot derivative, the non-ergot drugs, **ropinirole, pramipexole, rotigotine**, and the newer agent, **apomorphine**.
- These agents have a **longer duration of action** than that of **levodopa** and are effective in patients exhibiting **fluctuations** in response to levodopa.
- **Initial therapy** with these drugs is associated with **less risk** of developing **dyskinesias and motor fluctuations** as compared to patients started on **levodopa**.
- However, these drugs are **ineffective** in patients who have **not** responded to **levodopa**.
- **Apomorphine** is an **injectable** dopamine agonist that is used in **severe and advanced** stages of the disease to supplement oral medications.

AMANTADINE

- It was **accidentally** discovered that the **antiviral** drug amantadine, used to treat influenza, has an **antiparkinsonian** action.
- Amantadine has **several effects** on a number of neurotransmitters implicated in parkinsonism, including:

1. Increasing the release of **dopamine**
2. Blocking **cholinergic** receptors
3. Inhibiting the **NMDA** glutamate receptors.

- The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic **psychosis**.
- Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur.
- Amantadine is **less efficacious** than levodopa, and **tolerance** develops more readily.

ANTIMUSCARINIC AGENTS

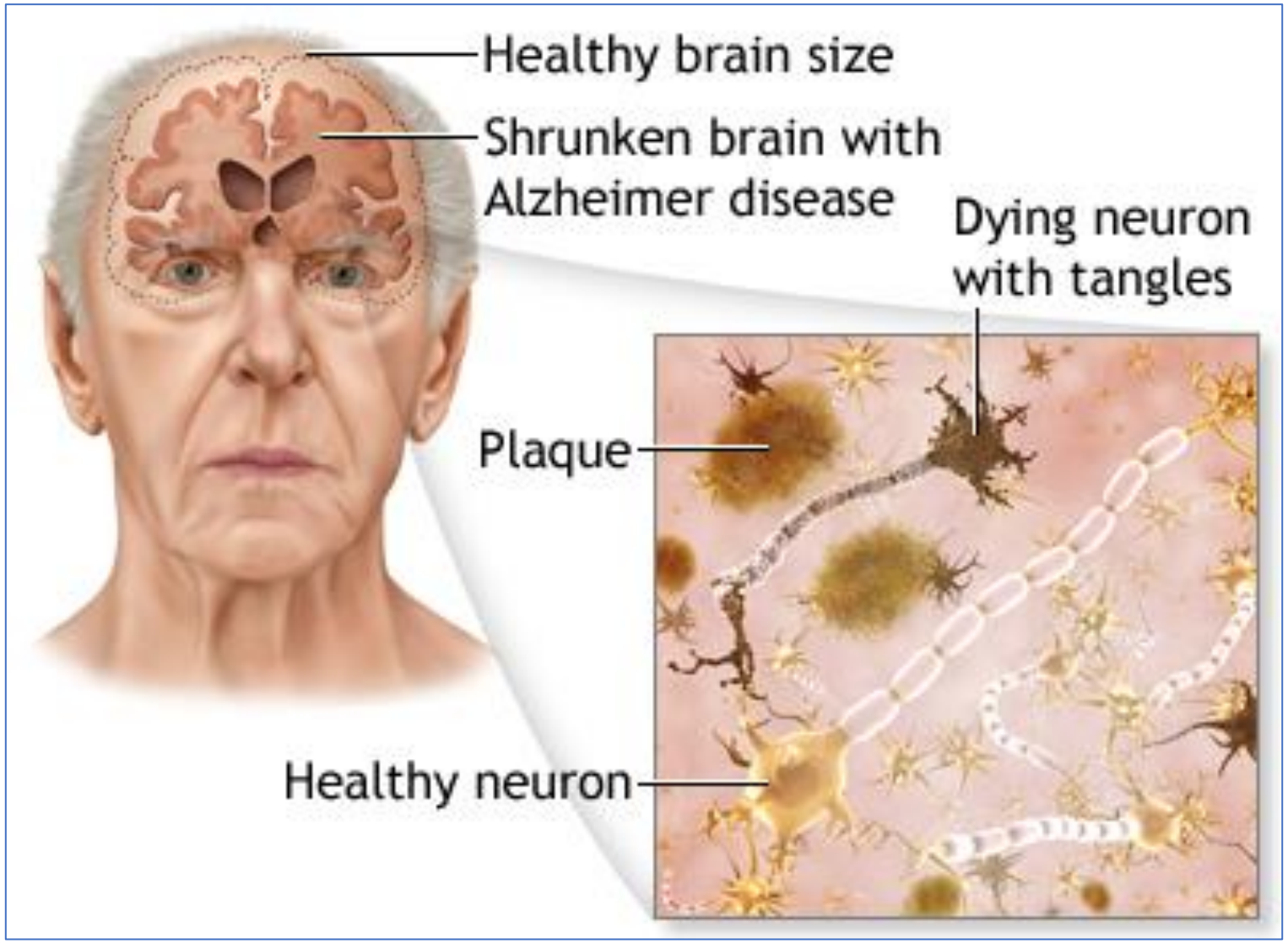
- The **antimuscarinic** agents are much **less efficacious** than levodopa and play only an **adjuvant** role in antiparkinsonism therapy.
- The **actions** of benztropine, trihexyphenidyl, procyclidine, and biperiden are **similar**.
- **Blockage** of cholinergic transmission produces effects **similar** to **augmentation** of dopaminergic transmission.
- These agents can induce mood changes and produce xerostomia, constipation, and visual problems typical of **muscarinic blockers**.
- They are **contraindicated** in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis.

DRUGS USED IN ALZHEIMER'S DISEASE

- **Alzheimer's** disease is a **progressive neurologic** disorder that causes the **brain to shrink** (atrophy) and brain **cells to die**.
- Alzheimer's disease is the most common cause of **dementia.**
- The **early signs** of the disease include **forgetting recent** events or conversations.
- As the disease **progresses**, a person with Alzheimer's disease will **develop severe** memory impairment and **lose the ability** to carry out everyday tasks.
- Dementia of the Alzheimer's type has three distinguishing features:

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

DRUGS USED IN ALZHEIMER'S DISEASE



DRUGS USED IN ALZHEIMER'S DISEASE

- Current therapies **aim to**:

1. Either **improves cholinergic** transmission within the CNS
2. Or **prevent excitotoxic** actions resulting from overstimulation of **NMDA glutamate receptors** in selected areas of the brain.

- Pharmacologic intervention for Alzheimer's disease is **only palliative** and provides **modest short-term** benefits.
- **None** of the available therapeutic agents **alter** the **underlying** neurodegenerative **process**.

ACETYLCHOLINESTERASE INHIBITORS

- The **inhibition** of AChE within the CNS will **improve cholinergic transmission**, at least at those neurons that are still functioning.
- The **reversible** AChE inhibitors **approved** for the treatment of mild to moderate Alzheimer's disease include donepezil, galantamine, and rivastigmine.
- At best, these compounds provide a **modest reduction** in the rate of loss of cognitive functioning in Alzheimer patients.
- **Rivastigmine** is **the only agent** approved for the management of dementia associated with Parkinson's disease and also the only AChE inhibitor available as a transdermal formulation.
- Common **adverse effects** include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps.

NMDA receptor antagonist

- **Stimulation** of **glutamate receptors** in the CNS appears to be critical for the **formation of certain memories**.
- However, **overstimulation** of glutamate receptors, particularly of the NMDA type, may result in **excitotoxic effects** on neurons and is suggested as a mechanism for **neurodegenerative** or **apoptotic** processes.
- **Memantine** is an NMDA receptor antagonist indicated for moderate to severe Alzheimer's disease.
- It acts by **blocking** the NMDA receptor and **limiting Ca^{2+} influx** into the neuron, such that **toxic intracellular levels** are **not** achieved.
- Memantine is **well tolerated**, with **few** dose-dependent **adverse events** such as confusion, agitation, and restlessness.

THANK YOU FOR YOUR ATTENTION