DRUGS THAT ACT IN THE CNS

Drugs for Neurodegenerative Diseases 2

Dr Karamallah S. Mahmood

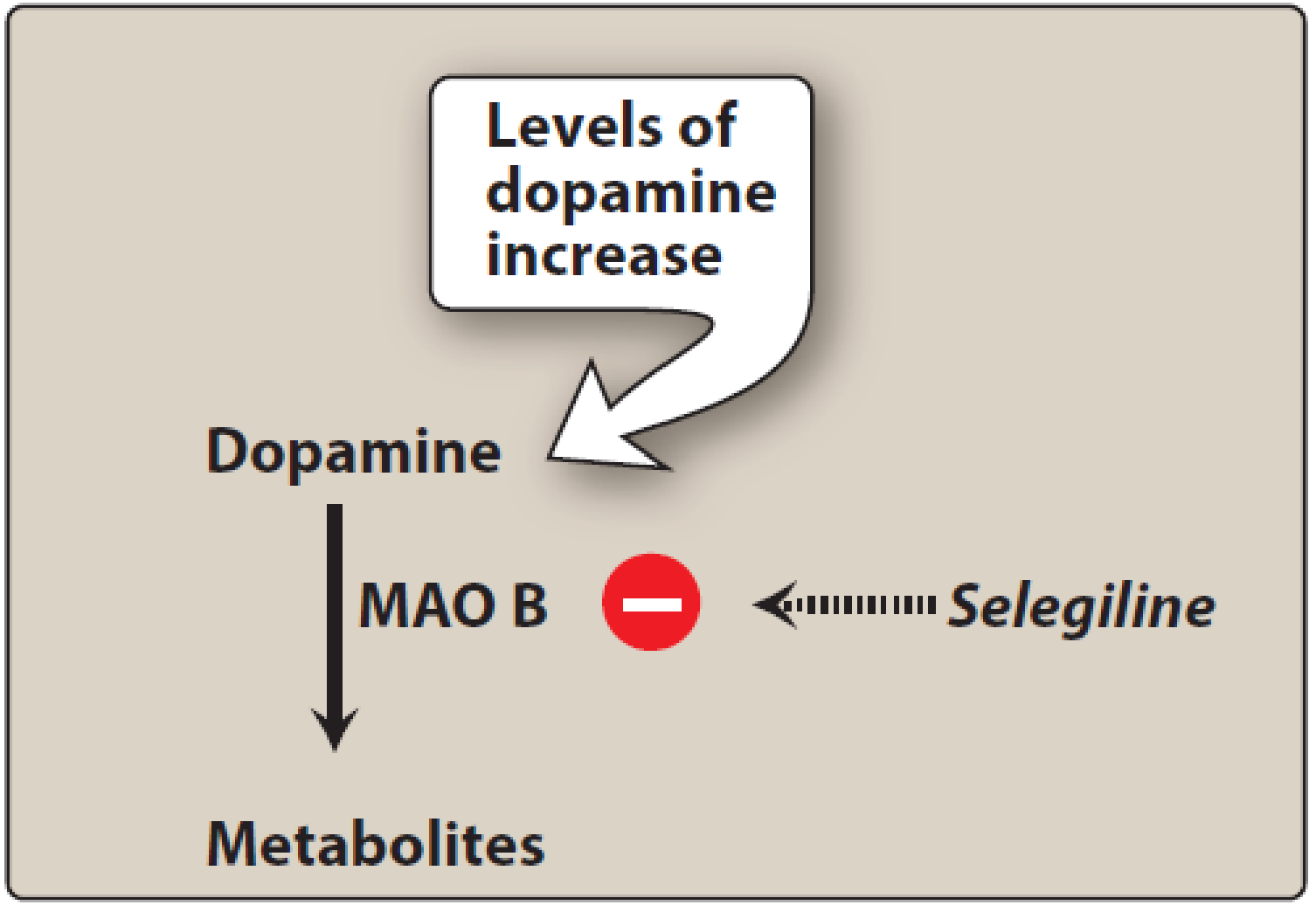
PhD Clinical Pharmacology

DRUGS USED IN PARKINSON'S DISEASE/ B. Selegiline and rasagiline

Selegiline , also called **deprenyl** , selectively inhibits monoamine oxidase **(MAO) type B** (metabolizes dopamine) at low to moderate doses.

It does not inhibit **MAO type A** (metabolizes norepinephrine and serotonin) unless given above recommended doses, where it loses its selectivity.

By decreasing the metabolism of dopamine, selegiline increases dopamine levels in the brain .



DRUGS USED IN PARKINSON'S DISEASE/ B. Selegiline and rasagiline

Unlike nonselective MAOIs, selegiline at recommended doses has little potential for causing **hypertensive crises**.

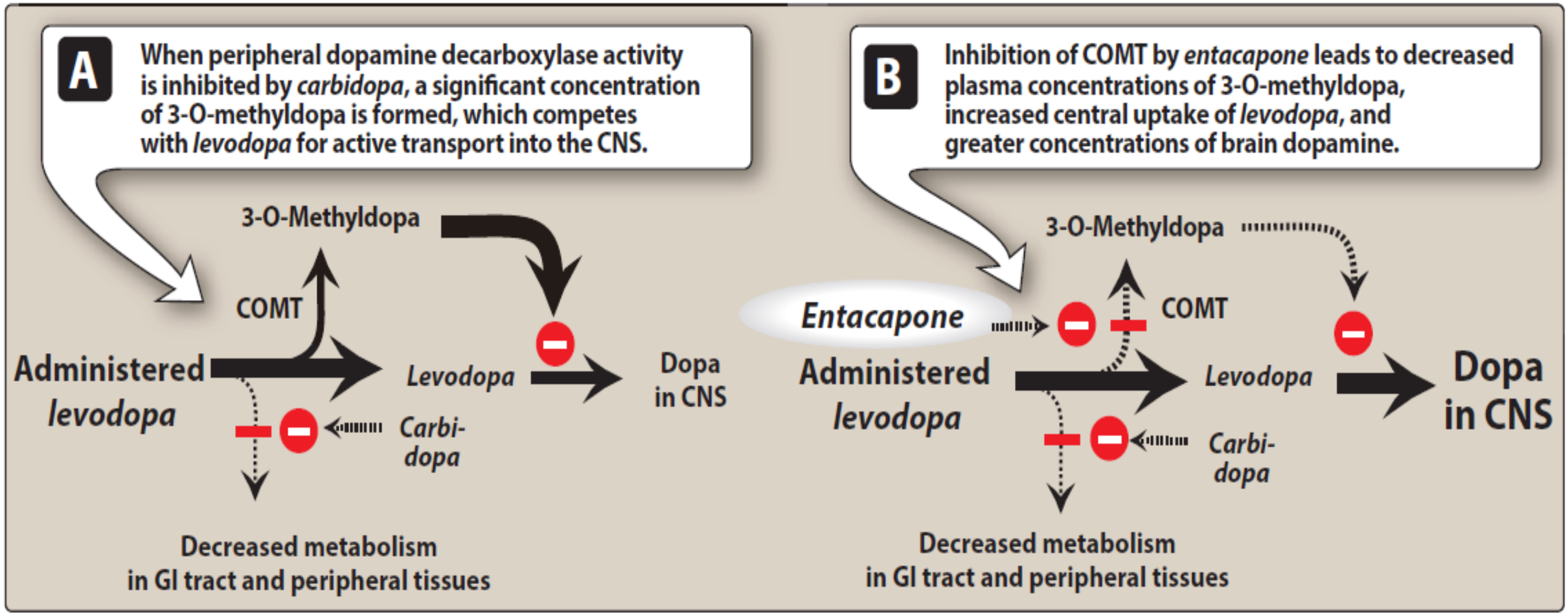
However, the drug loses selectivity at **high doses**, and there is a risk for severe hypertension.

Selegiline is metabolized to **methamphetamine and amphetamine**, whose stimulating properties may produce **insomnia** if the drug is administered later than mid-afternoon.

Rasagiline , an irreversible and selective inhibitor of brain MAO type B, has five times the **potency** of selegiline.

Unlike selegiline, rasagiline is not metabolized to an amphetamine-like substance.

DRUGS USED IN PARKINSON'S DISEASE/ C. COMT inhibitors



DRUGS USED IN PARKINSON'S DISEASE/ C. COMT inhibitors

Normally, the methylation of levodopa by catechol-O-methyltransferase (**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, and greater concentrations of brain dopamine.

DRUGS USED IN PARKINSON'S DISEASE/ C. COMT inhibitors/Pharmacokinetics:

Oral absorption of both drugs occurs readily and is not influenced by food.

They are extensively bound to plasma albumin, with a limited volume of distribution.

Tolcapone has a relatively **long duration** of action (probably due to its **affinity** for the enzyme) compared to entacapone, which requires more frequent dosing. 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.

DRUGS USED IN PARKINSON'S DISEASE/ C. COMT inhibitors/Adverse effects:

Both drugs exhibit adverse effects that are observed in patients taking levodopa–carbidopa, including diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, and sleep disorders.

Most seriously, hepatic necrosis is associated with tolcapone use.

Entacapone does not exhibit this toxicity and has largely replaced tolcapone.

DRUGS USED IN PARKINSON'S DISEASE/ D. Dopamine receptor agonists

This group of antiparkinsonian compounds includes **bromocriptine**, an **ergot** derivative, the **nonergot 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.

Apomorphine is an injectable dopamine agonist that is used in severe and advanced stages of the disease to supplement oral medications. Side effects severely limit the utility of the dopamine agonists

DRUGS USED IN PARKINSON'S DISEASE/ D. Dopamine receptor agonists/ 1. Bromocriptine:

Sedation

Confusion

Hypotension

Hallucinations

Nausea

DRUGS USED IN PARKINSON'S DISEASE/ D. Dopamine receptor agonists/ 1. Bromocriptine:

The actions of the ergot derivative bromocriptine are similar to those of levodopa, except that **hallucinations, confusion, delirium, nausea, and orthostatic hypotension** are more common, whereas **dyskinesia** is less prominent.

It should be used with caution in patients with a history **of myocardial infarction or peripheral vascular disease.**

Because bromocriptine is **an ergot derivative**, it has the potential to cause **pulmonary fibrosis.**

DRUGS USED IN PARKINSON'S DISEASE/ D. Dopamine receptor agonists/ 2. nonergot drugs:

Apomorphine, pramipexole, ropinirole, and rotigotine are **nonergot** dopamine agonists that are approved for the treatment of Parkinson's disease.

These agents alleviate the motor deficits in patients who have **never taken levodopa** and also in patients with **advanced Parkinson's** disease who are treated with levodopa.

Dopamine agonists may delay the need to use levodopa in early Parkinson's disease and may decrease the dose of levodopa in advanced Parkinson's disease.

DRUGS USED IN PARKINSON'S DISEASE/ D. Dopamine receptor agonists/ 2. nonergot drugs:

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]

DRUGS USED IN PARKINSON'S DISEASE/ D. Dopamine receptor agonists/ 2. nonergot drugs:

Unlike the ergotamine derivatives, these agents do not exacerbate peripheral vascular disorders or cause fibrosis.

Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are among the more distressing side effects of these drugs, **but dyskinesias are less frequent** than with levodopa.

Pramipexole is mainly excreted unchanged in the urine, and dosage adjustments are needed in renal dysfunction.

Cimetidine inhibits renal tubular secretion of organic bases and may significantly increase the half-life of pramipexole.

DRUGS USED IN PARKINSON'S DISEASE/ E. Amantadine:

It was accidentally discovered that the **antiviral** drug amantadin, used to treat influenza, has an antiparkinsonian action.

Amantadine has several effects on a number of neurotransmitters implicated in parkinsonism, including increasing the release of **dopamine**, blocking **cholinergic** receptors, and inhibiting the N-methyld-aspartate (**NMDA**) type of glutamate receptors.

Current evidence supports action at NMDA receptors as the primary action at therapeutic concentrations.

DRUGS USED IN PARKINSON'S DISEASE/ E. Amantadine:

Note: If dopamine release is already at a maximum, amantadine has **no effect**.

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.

However, amantadine has **fewer side effects**.

DRUGS USED IN PARKINSON'S DISEASE/ F. Antimuscarinic agents:

The antimuscarinic agents are much **less efficacious** than levodopa and play only an adjuvant role in antiparkinsonism therapy.

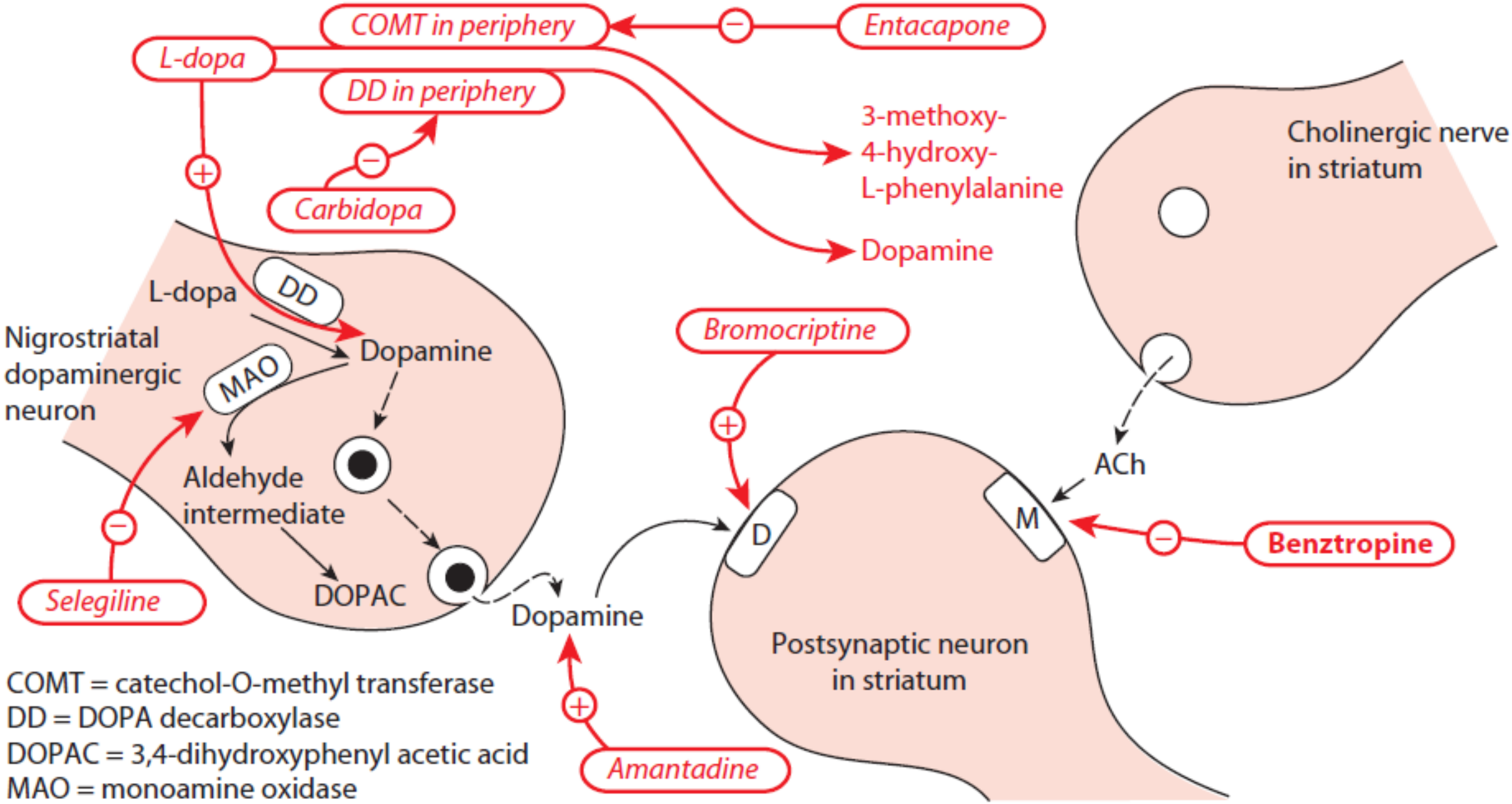
The actions of **benztropine, trihexyphenidyl, procyclidine, and biperiden** are similar, although individual patients may respond more favorably to one drug.

Blockage of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission, since it helps to correct the imbalance in the dopamine/acetylcholine ratio.

These agents can induce **mood changes** and produce xerostomia (dryness of the mouth), constipation, and visual problems typical of muscarinic blockers.

They interfere with gastrointestinal peristalsis and are **contraindicated** in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis.

Transmitter systems in the striatum providing targets for antiparkinsonian drugs



COMT = catechol-O-methyl transferase
DD = DOPA decarboxylase
DOPAC = 3,4-dihydroxyphenyl acetic acid
MAO = monoamine oxidase

DRUGS USED IN ALZHEIMER'S DISEASE

The most common early symptom is **short-term memory loss**. As the disease advances, symptoms can include problems **with language, disorientation** (including easily getting lost), **loss of motivation, not managing self care, and behavioural issues**.

AD distinguishing feature is the loss of cortical neurons, particularly **cholinergic neurons**.

Current therapies aim to either **improve cholinergic** transmission within the CNS 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 benefit.

None of the available therapeutic agents alter the **underlying neurodegenerative** process.

DRUGS USED IN ALZHEIMER'S DISEASE/ A. AChE inhibitors

Numerous studies have linked the progressive **loss of cholinergic neurons** and, presumably, cholinergic transmission within the cortex to the **memory loss** that is a hallmark symptom of Alzheimer's disease.

It is postulated that inhibition of acetylcholinesterase (**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**.

All of them have some **selectivity** for AChE in the CNS, as compared to the periphery.

DRUGS USED IN ALZHEIMER'S DISEASE/ A. AChE inhibitors

Galantamine may also augment the action of acetylcholine at **nicotinic receptors** in the CNS.

At best, these compounds provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer patients.

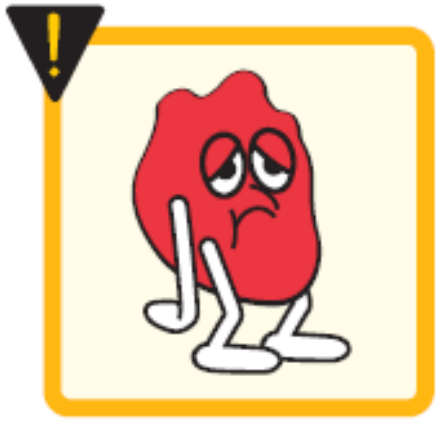
Rivastigmine is the only agent **approved** for the management of dementia associated with Parkinson's disease.

DRUGS USED IN ALZHEIMER'S DISEASE/ AChE inhibitors

Tremors

Nausea

Anorexia

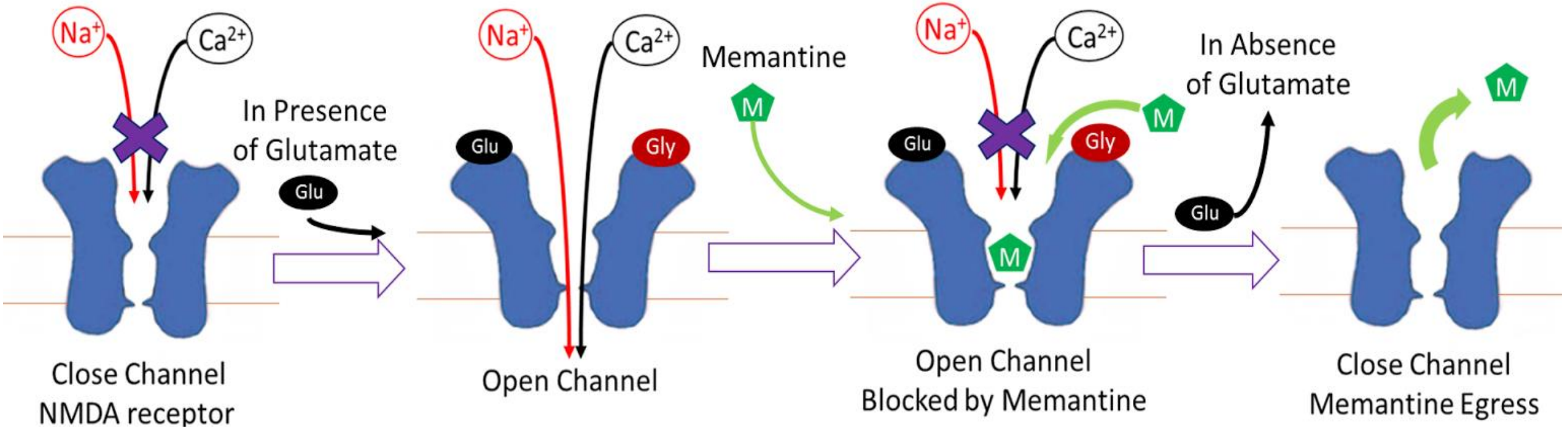


Bradycardia

Diarrhea

Myalgia

DRUGS USED IN ALZHEIMER'S DISEASE/ B. NMDA receptor antagonist



Memantine is an **NMDA receptor antagonist** indicated for Alzheimer's disease

DRUGS USED IN ALZHEIMER'S DISEASE/ B. 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** (programmed cell death) processes.

Binding of glutamate to the NMDA receptor assists in the opening of an ion channel that allows Ca2+ to enter the neuron. **Excess intracellular Ca2+** can activate a number of processes that ultimately damage neurons and lead to **apoptosis**.

Memantine is an **NMDA receptor antagonist** indicated for moderate to severe Alzheimer's disease.

DRUGS USED IN ALZHEIMER'S DISEASE/ B. NMDA receptor antagonist

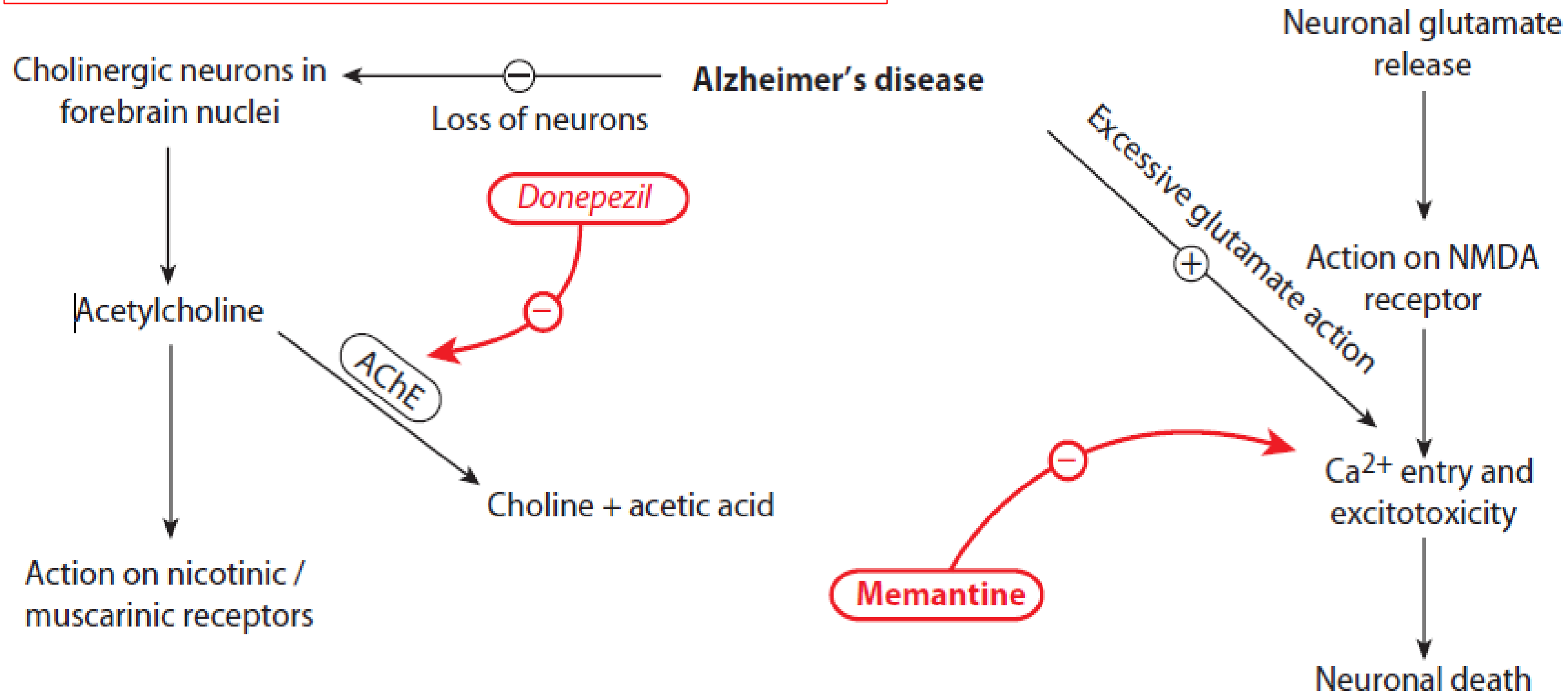
It acts by **blocking the NMDA receptor** and limiting Ca2+ influx into the neuron, such that toxic intracellular levels are not achieved.

Memantine is well tolerated, with few dose-dependent adverse events.

Expected **side effects**, such as confusion, agitation, and restlessness, are indistinguishable from the symptoms of Alzheimer's disease.

Given its different mechanism of action and possible neuroprotective effects, memantine is often given in **combination with an AChE inhibitor**.

DRUGS USED IN ALZHEIMER'S DISEASE



DRUGS USED IN MULTIPLE SCLEROSIS

Multiple sclerosis is an **autoimmune inflammatory demyelinating** disease of the CNS.

The course of MS is variable. **For some**, MS may consist of one or two acute neurologic episodes.

In others, it is a chronic, relapsing, or progressive disease that may span 10 to 20 years.

Historically, **corticosteroids** (for example, dexamethasone and prednisone) have been used to treat acute exacerbations of the disease.

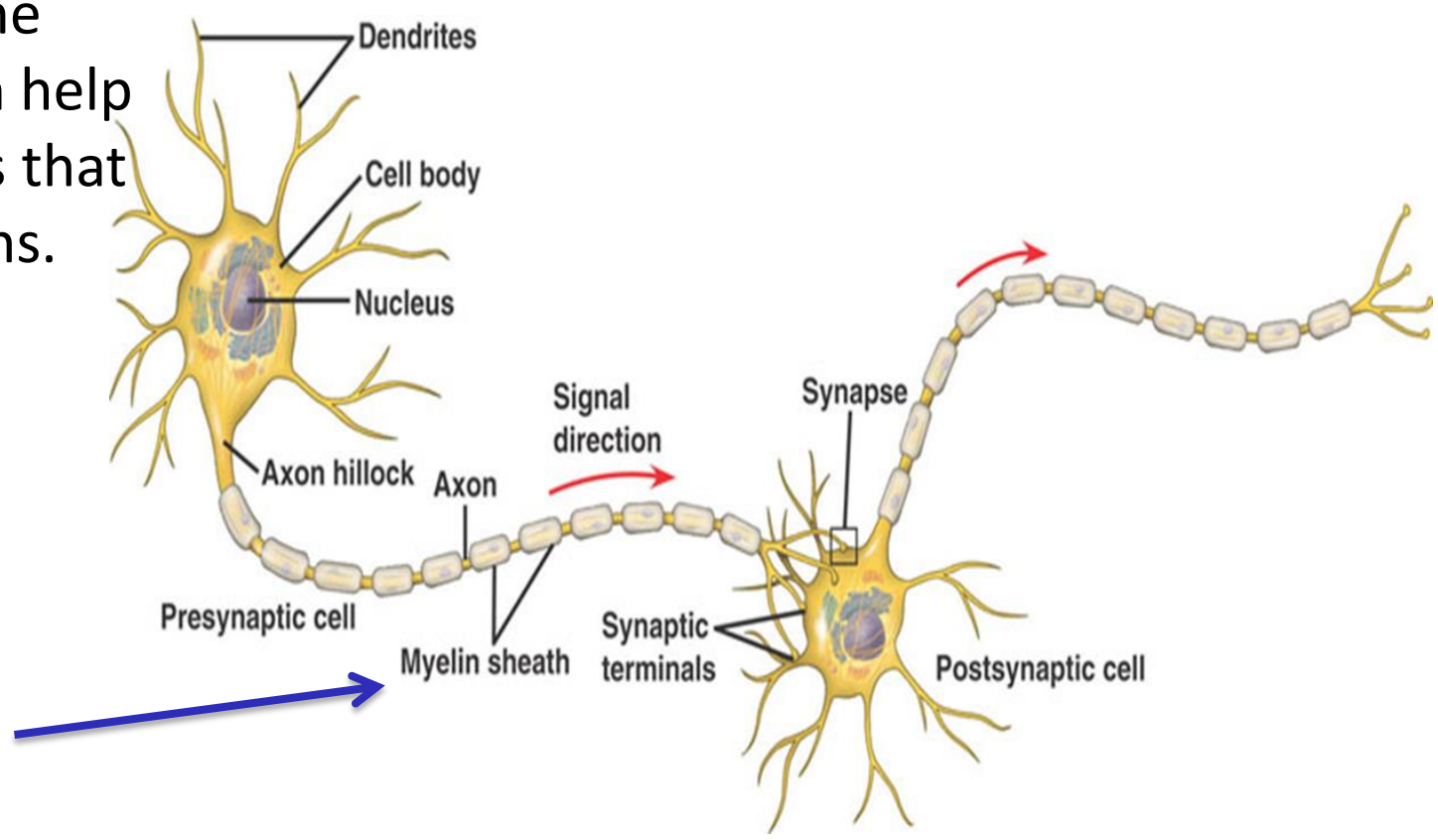
Chemotherapeutic agents, such as cyclophosphamide and azathioprine, have also been used.

DRUGS USED IN MULTIPLE SCLEROSIS/ A. Disease-modifying therapies

The major target of medications is to **modify the immune response** through inhibition of **white blood cell–mediated** inflammatory processes that eventually lead to **myelin sheath** damage and decreased or inappropriate axonal communication between cells.

1. Interferon β1a and interferon β1b: The immunomodulatory effects of interferon help to **diminish** the inflammatory responses that lead to demyelination of the axon sheaths.

Adverse effects of these medications may include depression, local injection site reactions, hepatic enzyme increases, and flu-like symptoms.



DRUGS USED IN MULTIPLE SCLEROSIS/ A. Disease-modifying therapies

2. Glatiramer: Glatiramer is a synthetic polypeptide that **resembles myelin protein** and may act as a decoy to T-cell attack.

Some patients experience a **post-injection reaction** that includes flushing, chest pain, anxiety, and itching. It is usually self-limiting.

3. Fingolimod: Fingolimod is an oral drug that **alters lymphocyte migration**, resulting in fewer lymphocytes in the CNS.

Fingolimod may cause first-dose bradycardia and is associated with an increased risk of infection and macular edema.

DRUGS USED IN MULTIPLE SCLEROSIS/ A. Disease-modifying therapies

4. Teriflunomide: Teriflunomide is an oral **pyrimidine synthesis inhibitor** that leads to a lower concentration of active lymphocytes in the CNS.

Teriflunomide may cause elevated liver enzymes. It should be avoided in pregnancy.

5. Dimethyl fumarate: Dimethyl fumarate is an oral agent that may alter the cellular response to **oxidative stress to reduce disease progression**. Flushing and abdominal pain are the most common adverse events.

6. Natalizumab: Natalizumab is a **monoclonal antibody** indicated for MS in patients who have failed first-line therapies.

7. Mitoxantrone: Mitoxantrone is a **cytotoxic** anthracycline analog that kills T cells and may also be used for MS.

DRUGS USED IN MULTIPLE SCLEROSIS/ B. Symptomatic treatment

Many different classes of drugs are used to manage **symptoms of MS** such as spasticity, constipation, bladder dysfunction, and depression.

Dalfampridine, an oral **potassium channel blocker**, improves walking speeds in patients with MS. It is the first drug approved for this use.

DRUGS USED IN AMYOTROPHIC LATERAL SCLEROSIS

ALS is characterized by progressive **degeneration** of **motor neurons**, resulting in the inability to initiate or control muscle movement.

Riluzole, an **NMDA receptor antagonist**, is currently the only drug indicated for the management of ALS. It is believed to act by inhibiting **glutamate release and blocking sodium channels**.

Riluzole may improve survival time and delay the need for ventilator support in patients suffering from ALS.