Neurodegenerative Diseases

Prepared by

HEBA AHMED HASSAN

Pharmacology Department, Mutah University

Faculty of Medicine

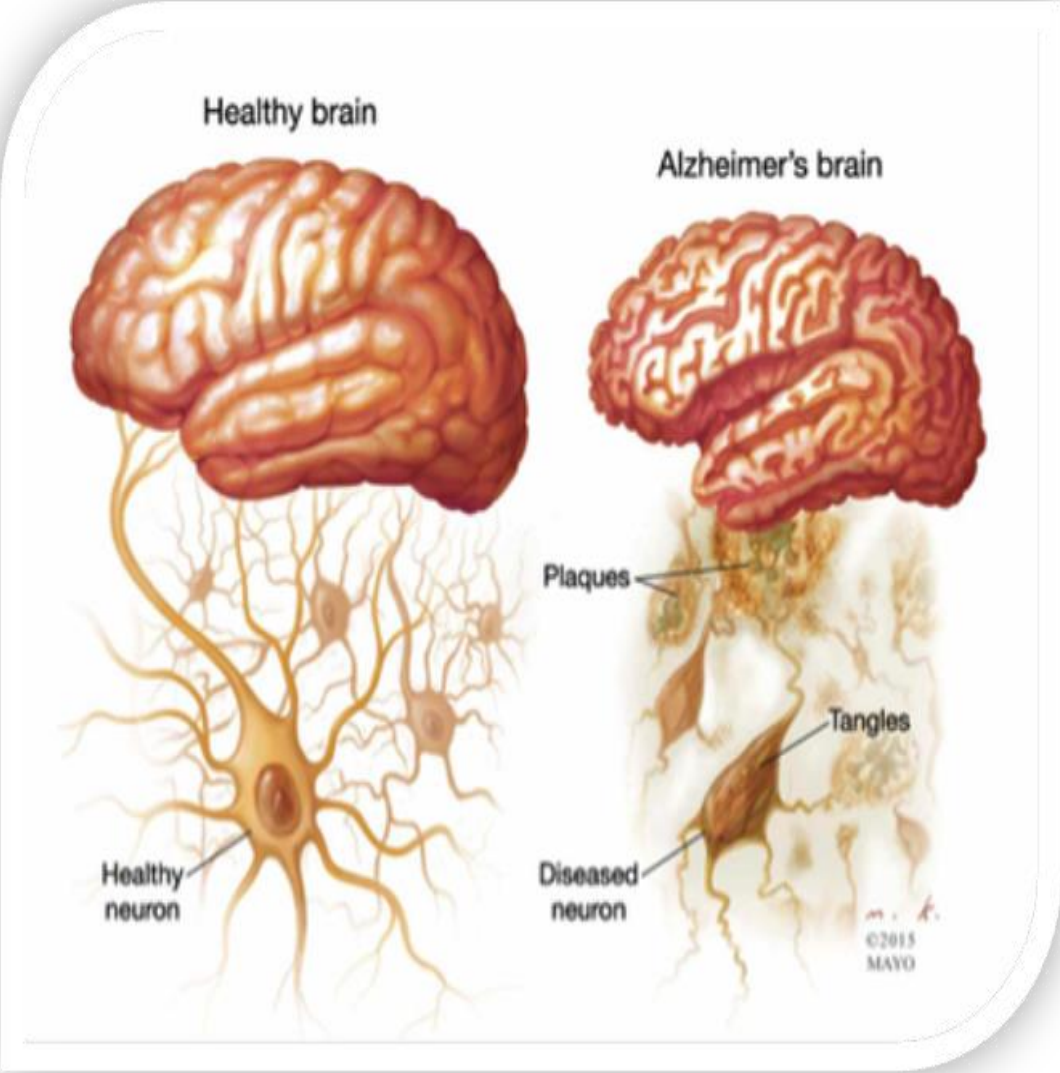
- ***Parkinson's disease***
- ***Alzheimer's disease***
- ***Huntington's disease***
- **Amyotrophic Lateral Sclerosis (ALS)**
- **Multiple Sclerosis (MS) (immune-mediated)**

Specific treatment for each disease , with many non-pharmacological management, and Symptomatic Treatment (Behavioral & Psychological Symptoms) were needed

They are characterized by the progressive loss of selected neurons in the discrete brain areas resulting in characteristic disorders of movement, cognition, or both.

Alzheimer's Disease

- It is characterized by loss of short-term memory and cognitive dysfunction.
- It occurs due to **loss of cholinergic neurons** in the basal forebrain nuclei.
- Current therapies are aimed at either *improve cholinergic transmission* **in the CNS** or *preventing the excitotoxicity actions of NMDA glutamate receptors*.
- **Treatment aims to improve symptoms (not cure) and slow progression.**



(1) Acetylcholinesterase Inhibitors

- **Members:** donepezil, galantamine, rivastigmine & tacrine.

  -They are ***reversible cholinesterase inhibitors*** approved for mild to moderate cases.

- **Mechanism of action:**
  - All are ***uncompetitive inhibitors of cholinesterase***, except galantamine, which is ***a competitive inhibitor***.
  - They appear to be more selective for cholinesterase in CNS than the periphery.

	MOA	USES	SIDE EFFECTS
A. Donepezil	Reversible acetylcholinesterase inhibitor→ ↑ ACh at synapses.	Mild, moderate, and severe AD.	GI upset (nausea, vomiting, diarrhea) Muscle cramps Insomnia Bradycardia, syncope Notes: Once-daily dosing, well tolerated.
B. Rivastigmine	Inhibits acetyl- & butyryl-cholinesterase	Mild–moderate AD; Parkinson's dementia	More GI effects than donepezil Notes: Available as a transdermal patch → fewer GI effects
C. Galantamine	Acetylcholinesterase inhibitor Allosteric agonist at nicotinic receptors → ↑ ACh release	Mild–moderate AD.	GI upset
D. Tacrine	inhibits acetylcholinesterase (AChE) → ↑ acetylcholine in CNS Similar to donepezil but less selective and more toxic	Mild to moderate Alzheimer's disease Rarely used today due to significant hepatotoxicity and better alternatives (donepezil, rivastigmine, galantamine).	Hepatotoxicity fulminant hepatic failure GI upset: nausea, vomiting, diarrhea Bradycardia Insomnia Muscarinic effects (sweating, salivation)

(2) NMDA Receptor Antagonists (Memantine)

- Overstimulation of NMDA receptors shows an **excitotoxicity effect** on neurons and is suggested as a mechanism for the neurodegenerative process.

- **Mechanism of action:**

  It is an *uncompetitive* inhibitor of NMDA receptors, slowing the rate of memory loss.

- **Use:**

Moderate–severe AD

Often combined with donepezil (Combination Therapy)

Used in moderate–severe AD to improve cognition and daily functioning.

- **Side effects:**

1. Confusion.
2. Agitation.
3. Restlessness.

3. Newer Disease-Modifying Agents (Anti-Amyloid Monoclonal Antibodies)

- **Aducanumab**

  MOA: Monoclonal antibody → removes amyloid-β plaques by binding to them and signals the brain's immune cell (microglia) to **eat and remove the plaques**.

  ROUT: Intravenous infusion (monthly).
  Use: Early AD.
  Side effects: ARIA (Amyloid-related imaging abnormalities): brain edema, microhemorrhages, and Headache

- **Lecanemab**

  MOA: Anti-amyloid antibody (Binds to protofibrils → promotes immune-mediated clearance via microglia → reduces amyloid aggregation.
  ROUT: Intravenous infusion (every 2 weeks)

- **Use**: Mild cognitive impairment & early AD.
  Side effects: ARIA, infusion reactions.

- **Donanemab ROUT:** Intravenous infusion (monthly).
  MOA: Antibody targeting modified amyloid to promote clearance.
  Use: Early AD
  Side effects: ARIA.

Note: These drugs slow disease progression, not cure it. MRI monitoring required.

1. Soluble protofibrils (toxic early aggregates) → e.g., Lecanemab
2. Existing mature plaques → e.g., Donanemab
3. Mixed forms (oligomers and plaques) → e.g., Aducanumab

Huntington's Disease

- Inherited disorder characterized by **progressive chorea and dementia.**
- **Aetiology:**
  - Degeneration of GABAergic neurons in the striatum leads to ↑ dopamine activity → chorea & psychiatric symptoms
  - There is no cure, but drugs treat symptoms.
- **Treatment:**

1. Drugs for Chorea (Involuntary Movements)

VMAT2 Inhibitors (First-line)These reduce dopamine storage and release in presynaptic terminals → ↓ chorea.

Tetrabenazine

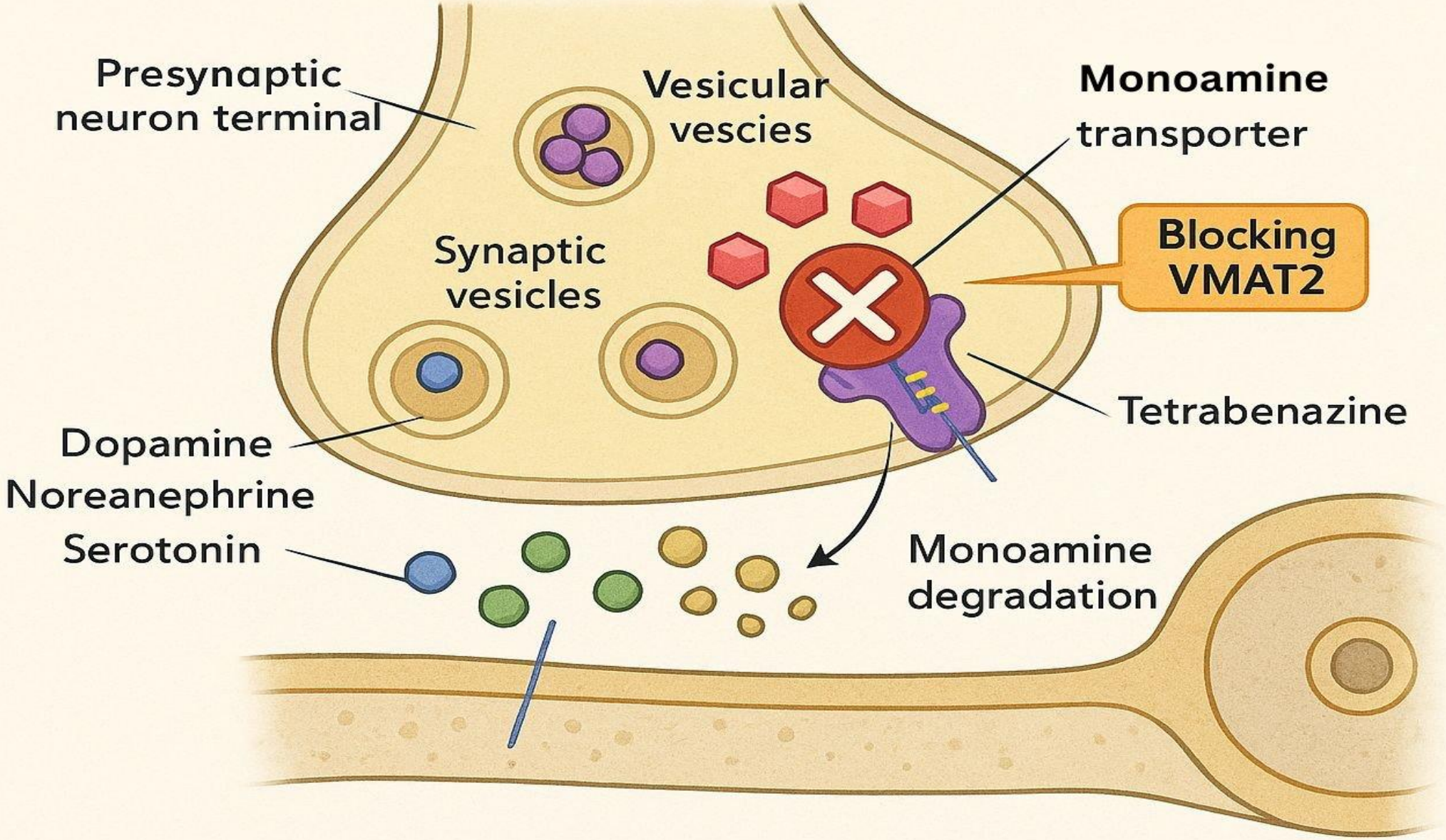
Mechanism: Reversible VMAT2 inhibitor → ↓ dopamine

Use: Moderate–severe chorea

Side effects: Depression, **suicidality**, Parkinsonism, Sedation, Hypotension and QT prolongation

Deutetrabenazine: Similar to tetrabenazine but with a longer half-life and fewer side effects. Better tolerated

MECHANISM OF ACTION OF TETRABENAZINE



PHARMACY FREAK

B. Antipsychotics (Dopamine blockers)

Used when chorea is accompanied by psychosis, aggression, or severe behavioral issues.

Typical antipsychotics: Haloperidol, fluphenazine

Mechanism: D2 blockade → ↓ dopaminergic activity

Use: Severe chorea, agitation, psychiatric symptoms

Side effects: Extrapyramidal symptoms, tardive dyskinesia

Atypical antipsychotics: Olanzapine, risperidone, quetiapine

Better tolerated with fewer EPS. Good for irritability, agitation, psychosis

2. Drugs for Psychiatric Symptoms

Depression: SSRIs (sertraline, fluoxetine, citalopram) – first-line SNRIs for resistant cases

Anxiety: SSRIs/SNRIs, Buspirone (non-sedating)

Irritability / Aggression: Atypical antipsychotics (olanzapine, risperidone)Mood stabilizers: valproate, carbamazepine

Obsessive–compulsive symptoms: SSRIs, clomipramine

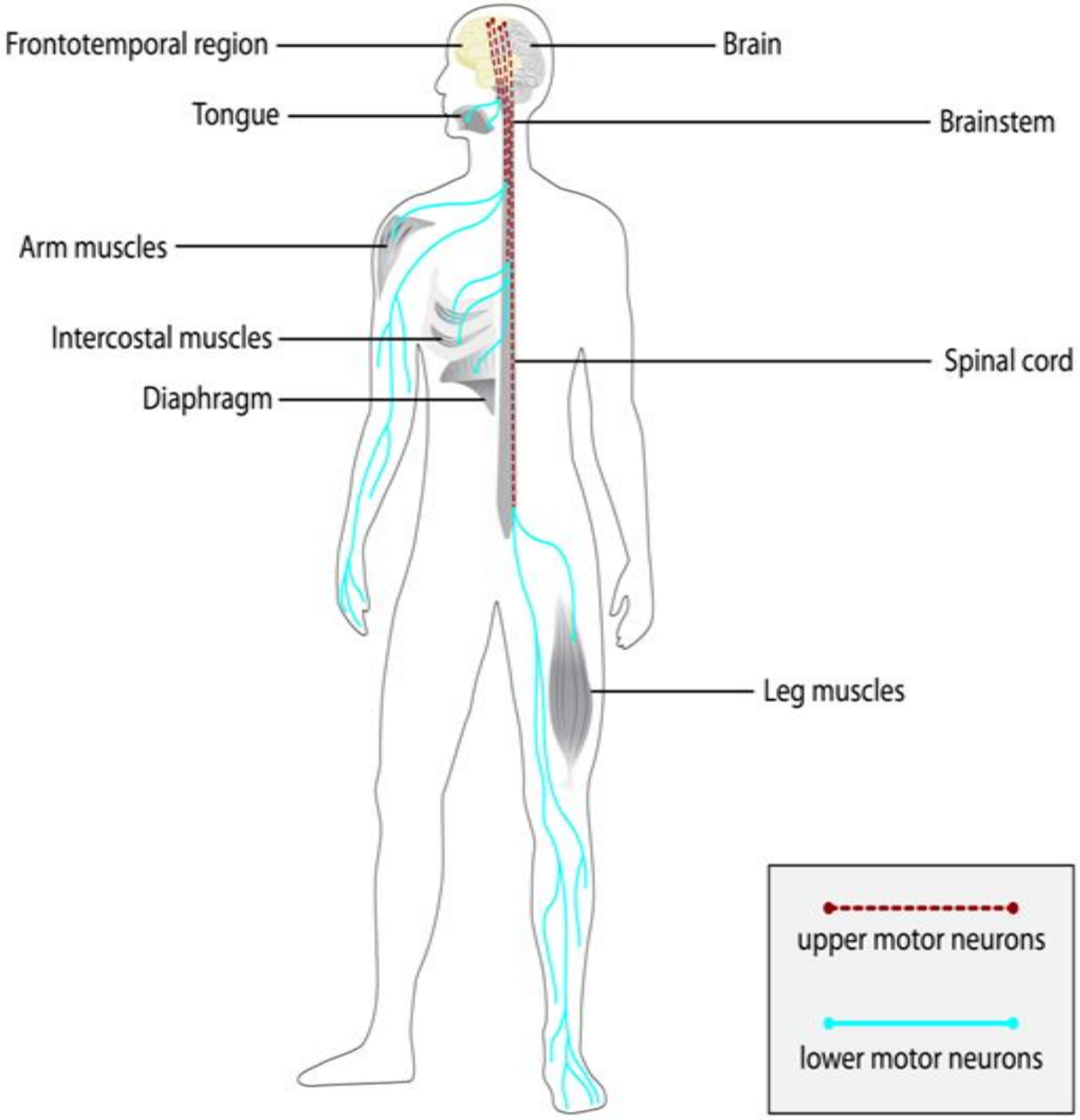
Sleep Disturbance: Melatonin Low-dose, sedating agents (mirtazapine)

3. Drugs for Other Symptoms Rigidity / Parkinsonism: (late-stage HD)

Caused by striatal degeneration → ↓dopamine, Levodopa, or dopamine agonists may help in the rigid–akinetic variant.

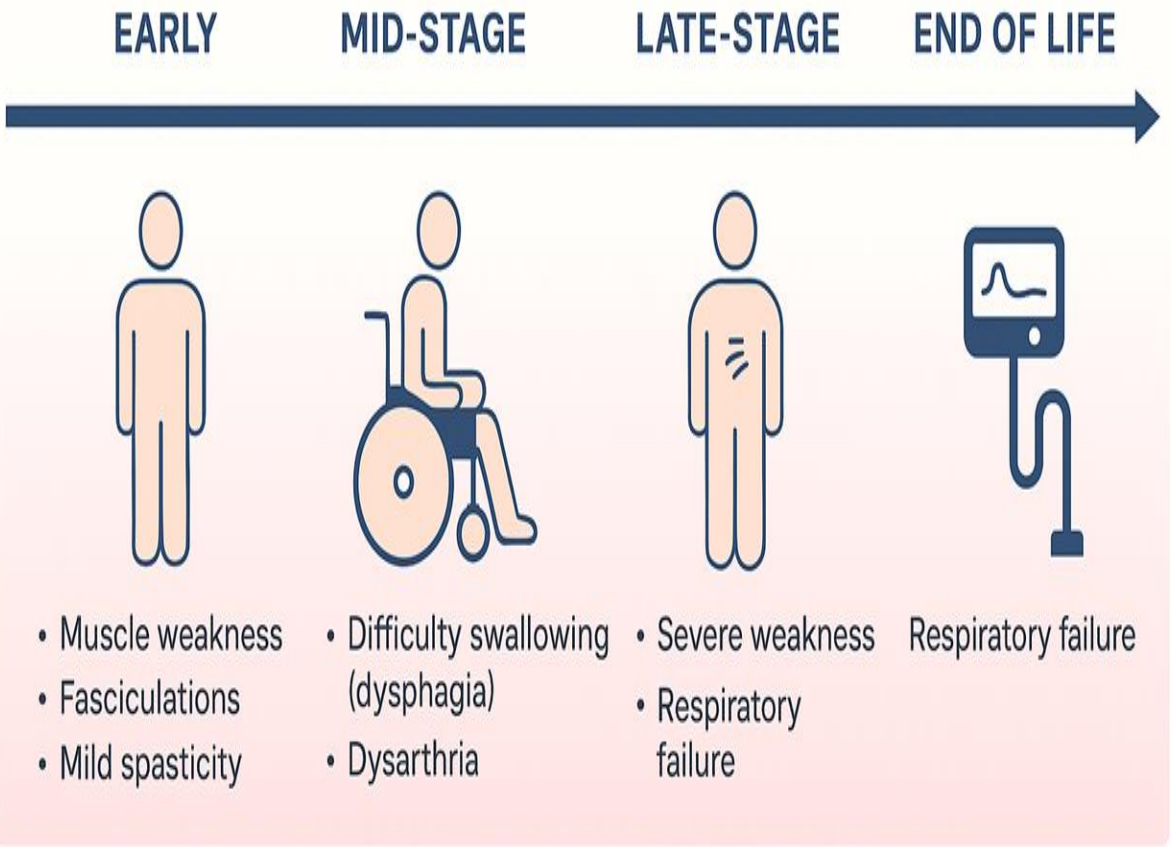
AMYOTROPHIC LATERAL SCLEROSIS (ALS)

- ALS is a progressive degeneration of upper + lower motor neurons, leading to muscle weakness, wasting, fasciculations, and respiratory failure.
- There is no cure, but two approved drugs slow disease progression
- ALS doesn't affect intelligence, thinking, seeing, or hearing.
- Survival from diagnosis 3-5 years



PROGNOSIS OF ALS

Progressive, fatal neurodegenerative disease



Disease-Modifying Drugs (Slow Progression)

A. Riluzole (FIRST-LINE)

Mechanism: Inhibits glutamate release, Blocks NMDA/AMPA receptors, inhibits voltage-gated Na^+ channels→ Reduces excitotoxicity, prolongs survival.

Benefits: Prolongs survival by 2–3 months. Delays the need for tracheostomy

Side Effects: Hepatotoxicity → Monitor LFTs, Nausea, Weakness, Neutropenia (rare)

B. Edaravone (SECOND-LINE / Add-on)

Mechanism: Free radical scavenger (antioxidant), reduces oxidative stress in motor neurons.

Benefits: Slows decline in motor function, more effective in early-stage ALS

Side Effects: Gait disturbance, Allergic reactions, Infusion-related reactions, and Confusion

MULTIPLE SCLEROSIS (MS)

- **DEF:** MS is an autoimmune demyelinating disease (white matter then grey matter) of the CNS with relapsing–remitting episodes (most common). More common in young adults (20–40 years), women > men.
- **Pathology:**

autoreactive T cells. As **CD4+ T helper cells (Th1, Th17)** cross the blood–brain barrier, **B cells** produce antibodies against myelin, and **Microglia and macrophages** mediate tissue injury leading to **Focal inflammation** → demyelination → axonal injury.

- **Pattern of Symptom Presentation:**

1- Relapsing-remitting MS (RRMS): Episodes of neurological deficits separated by periods of partial or complete recovery.

2- Progressive MS (Primary or Secondary): Gradual accumulation of symptoms without distinct relapses.

3- Symptoms often worsen with heat (Uhthoff phenomenon) or infection (pseudo-relapse).

- **Treatment goals:**

- **Manage acute relapses**
- **Modify disease course (DMTs)**
- **Control symptoms**

1. Acute Relapse Treatment:

A. High-dose IV Corticosteroids

First-line IV methylprednisolone 1 g/day for 3–5 days.

Mechanism: Anti-inflammatory, decreases edema around demyelinating plaques

Side effects: Hyperglycemia, Mood changes, GI upset, Hypertension

B. Plasma Exchange :

Used when steroids fail or for severe relapses to remove pathogenic antibodies

C. IV Immunoglobulin (IVIG): Occasionally used if steroids are contraindicated

2. Disease-Modifying Therapies (DMTs):

These reduce the relapse rate, lesion formation, and disability progression

Feature	First-Line (Moderate-Efficacy)	High-Efficacy
Drugs	Interferon-β, Glatiramer acetate, Dimethyl fumarate, Teriflunomide	Natalizumab, Fingolimod, Ocrelizumab, Ofatumumab, Alemtuzumab
Route	SC, IM, or oral	IV infusion or oral/SC (depending on drug)
Mechanism	Immune modulation, reduce inflammation	Strong immunomodulation or immune cell depletion; prevent CNS infiltration
Efficacy (relapse reduction)	Moderate (~30–50%)	High (~50–70% or more)
Monitoring required	Minimal (CBC, LFTs for some)	Intensive (CBC, LFTs, ECG, ophthalmology, infection screening)
Major Risks	Flu-like symptoms, injection-site reactions, mild GI upset	Infection risk, PML (Natalizumab), bradycardia (Fingolimod), autoimmune disorders (Alemtuzumab), infusion reactions, malignancy
Indication	Mild to moderate RRMS	Highly active MS or failure of first-line therapy
Pregnancy Safety	Generally safer (Glatiramer acetate relatively safe)	Limited data, usually avoided unless benefit outweighs risk

First line of treatment with moderate efficacy

A- Interferon-β (1a, 1b) Injectable

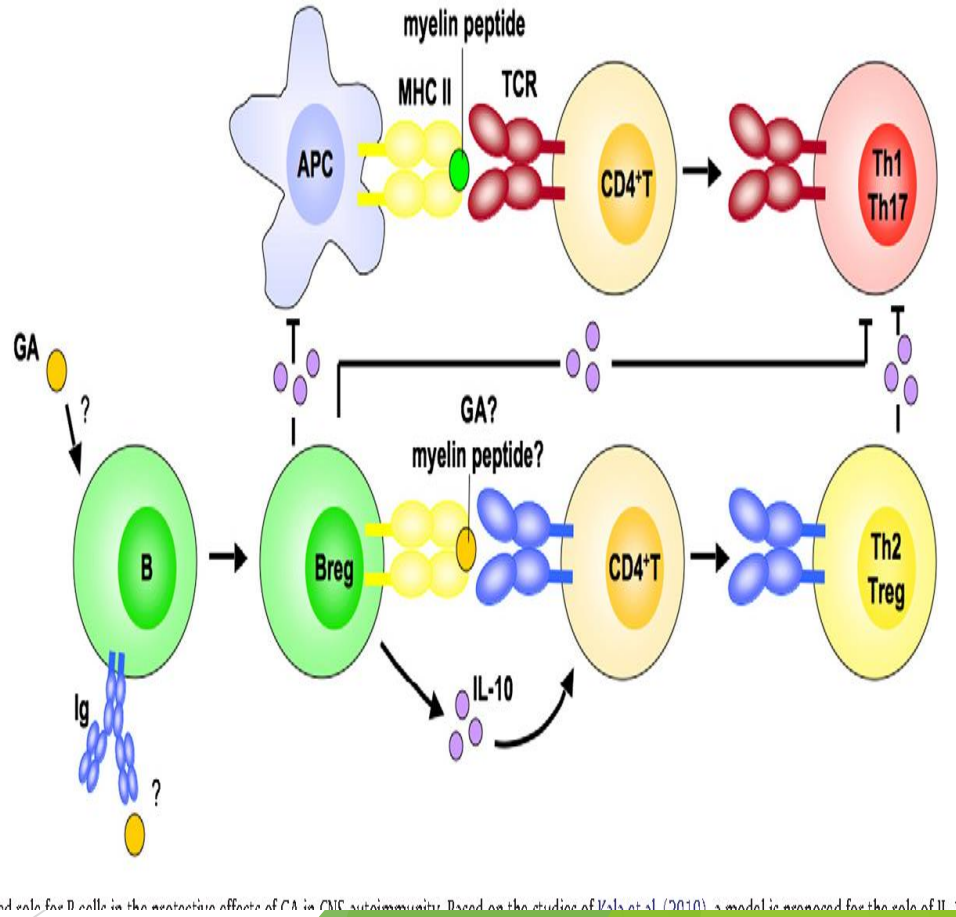
Mechanism:↓ T-cell activation↓ cytokines↓ disease activity

Side Effects: Flu-like symptoms, Depression, Injection site reactions, ↑ LFTs

B- Glatiramer Acetate: Injectable

Mechanism: mimics myelin basic protein → shifts immune response to Th2 anti-inflammatory.

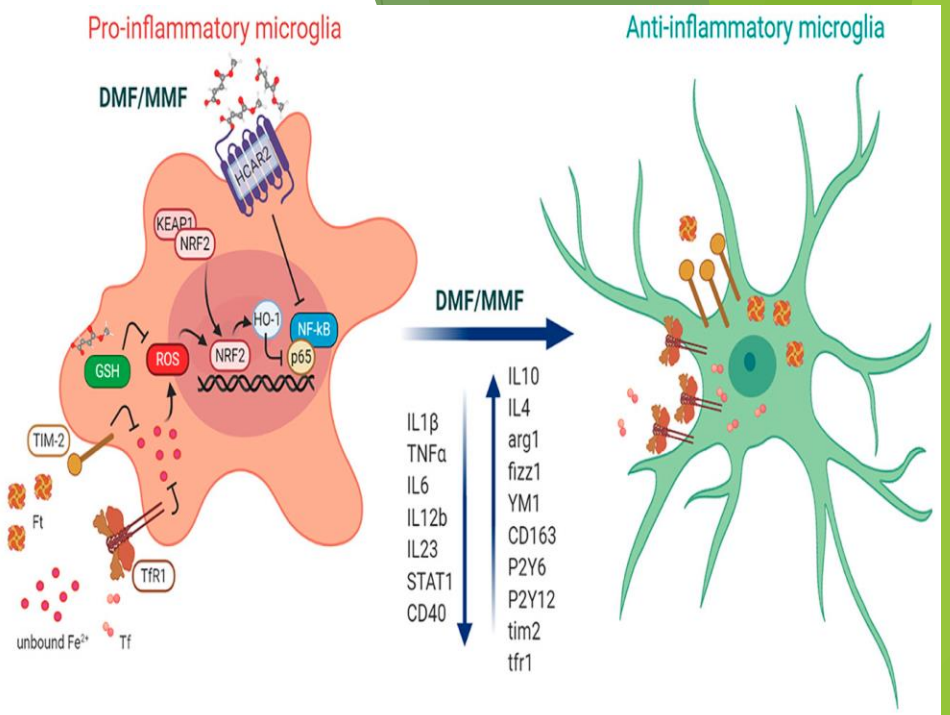
Side Effects: Injection pain, Transient chest tightness (non-cardiac)



C- Dimethyl Fumarate Oral

- Activates Nrf2 pathway → an antioxidant with reducing Th1 and Th17 activity → less pro-inflammatory signaling in the CNS.
- Enhances Th2 activity → more anti-inflammatory cytokines, which dampen autoimmune attacks

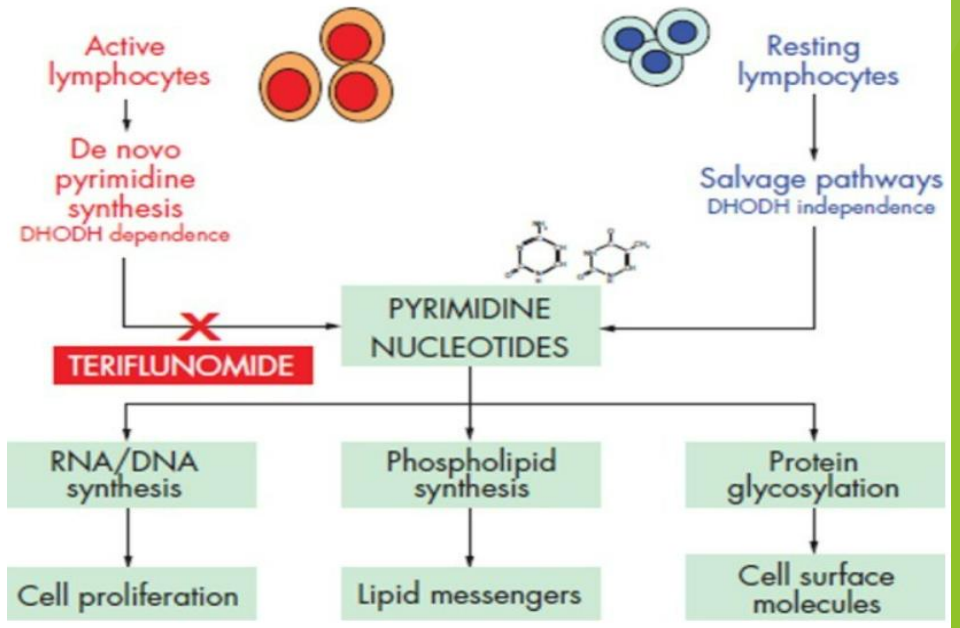
Side effects: flushing, GI upset, lymphopenia



D.Teriflunomide Oral

Inhibits pyrimidine synthesis → blocks rapidly dividing T cells

Side effects: hepatotoxicity, teratogenicity



High-Efficacy Therapies

- **Fingolimod Oral**

S1P (Sphingosine-1-phosphate) receptor modulator → traps lymphocytes in lymph nodes

Side effects: bradycardia, macular edema, infections

- **Natali**zumab: α4-integrin inhibitor-----Prevents immune cells from entering the CNS.
- **creli**zumab / Ofatumumab: Anti-CD20 monoclonal antibodies-----Deplete B cells.

Effective in relapsing and primary progressive MS.

Side effects: infusion reactions, infections

- **Alemtu**zumab: Anti-CD52 monoclonal antibody------Very potent immune suppression.

Side effects: autoimmune thyroid disease, infusion reactions, infections

- **Cladribine:** Purine analog → lymphocyte depletion------Used in highly active MS

Side effects: infections, bone marrow suppression

Thank you