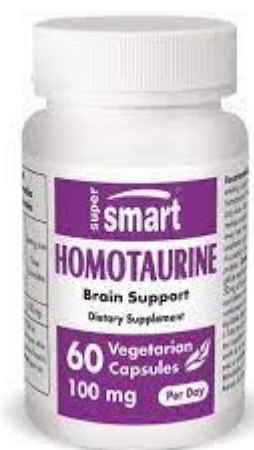
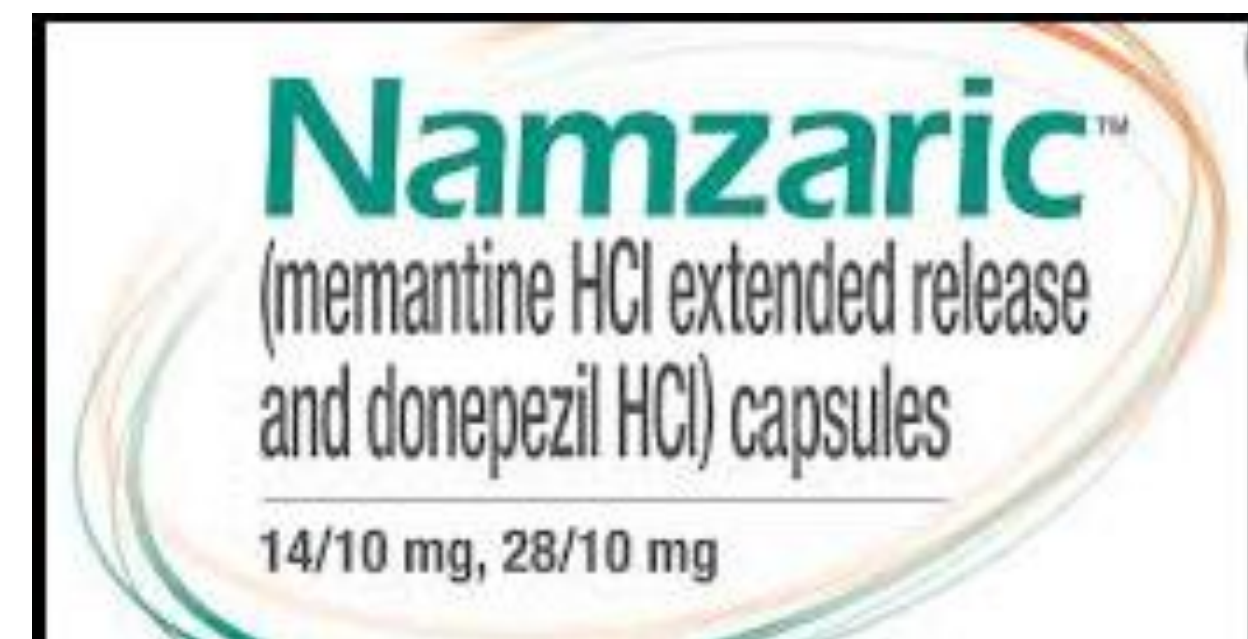
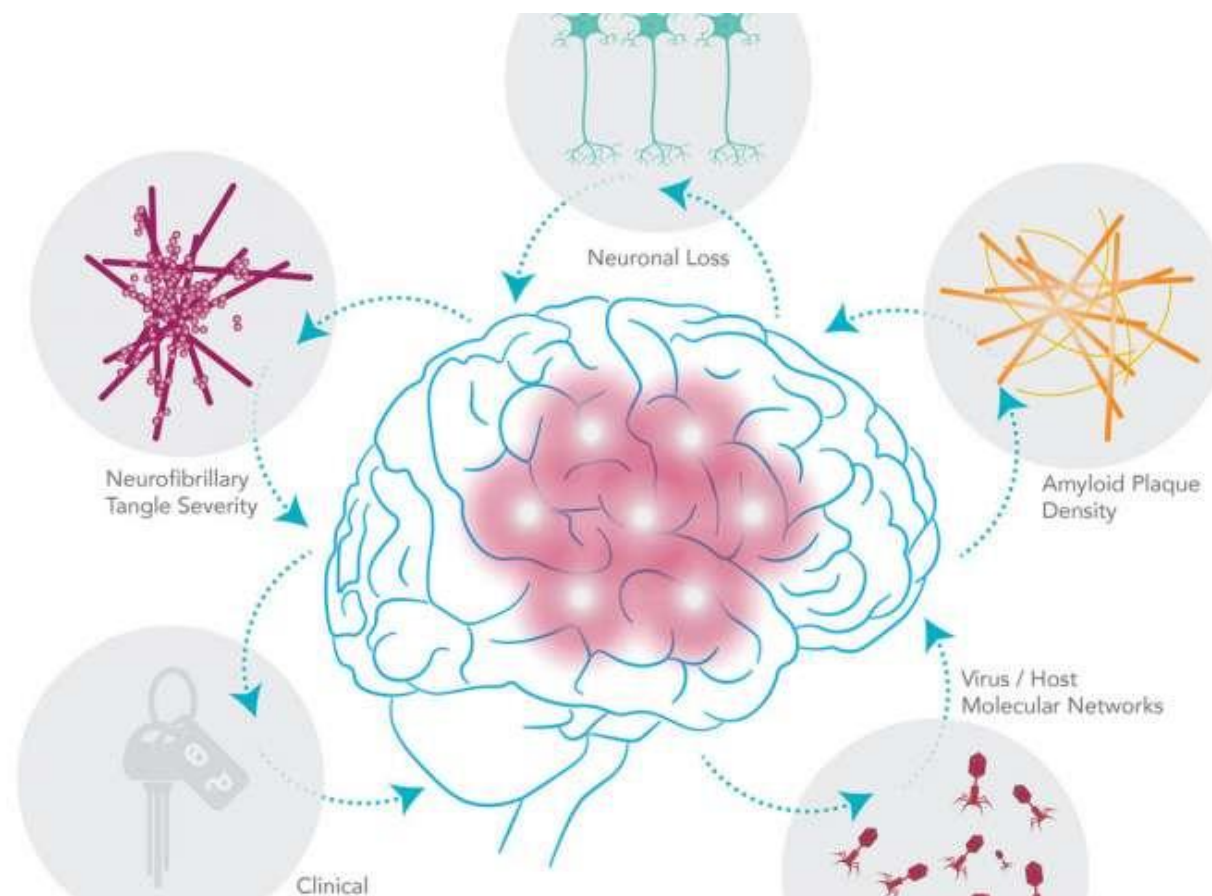


Alzheimer disease



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M.Pharm (Clinical)

Alzheimer Disease

LEARNING OBJECTIVES

● **Upon completion of the chapter, the reader will be able to:**

1. Describe the epidemiology of Alzheimer disease (AD) and its effects on society.
2. Describe the pathophysiology, including genetic and environmental factors that may be associated with AD.
3. Detail the clinical presentation of the typical patient with AD.
4. Describe the clinical course of the disease and typical patient outcomes.
5. Explain how nonpharmacologic therapy is combined with pharmacologic therapy for patients with AD.
6. Recognize and recommend treatment options for disease-specific symptoms as well as behavioral/noncognitive symptoms associated with AD.
7. Educate patients and/or caregivers about the expected outcomes for patients with AD, and provide contact information for support/advocacy agencies.

Definition

- Alzheimer's disease (AD) is a irreversible, progressive neurodegenerative disorder (dementia) characterized by:
 - ❑ gradual deterioration in cognition,
 - ❑ Deterioration of functional status.
 - ❑ behavioral disturbances.

Alzheimer's disease
Vascular dementia
Lewy body dementia
Mixed dementia
Other (Parkinson's disease, Frontotemporal dementia, Huntington's disease, Creutzfeldt–Jakob disease)
Potentially reversible causes of dementia (e.g., normal-pressure hydrocephalus, thyroid dysfunction, vitamin B₁₂ deficiency, depression, Wernicke–Korsakoff syndrome)

EPIDEMIOLOGY AND ETIOLOGY

- AD is the most common type of dementia, affecting an estimated 6 million Americans live with AD.
- It is the sixth leading cause of death across all age groups in the United States and the fifth leading cause of death for individuals 65 years of age and older

Etiology

- The exact etiology of AD is unknown maybe :
 - ❑ ***Genetic***: Genetic alteration in chromosome 1,14 or 21. Leading to errors in protein synthesis resulting in the formation of abnormal proteins
 - ❑ ***Enviromental Factor***

Pathophysiology

The **pathologic hallmarks** of the disease in the brain include:

- ❑ *Neurofibrillary tangles (NFT),*

- ❑ *Amyloid plaques:*

made up of various proteins, which result in a shortage of the neurotransmitter acetylcholine (Ach).

Mechanism of AD

***β -amyloid
aggregation
(plaque)***

***Hyperphosphoralation of
tau protein (Tangle)***

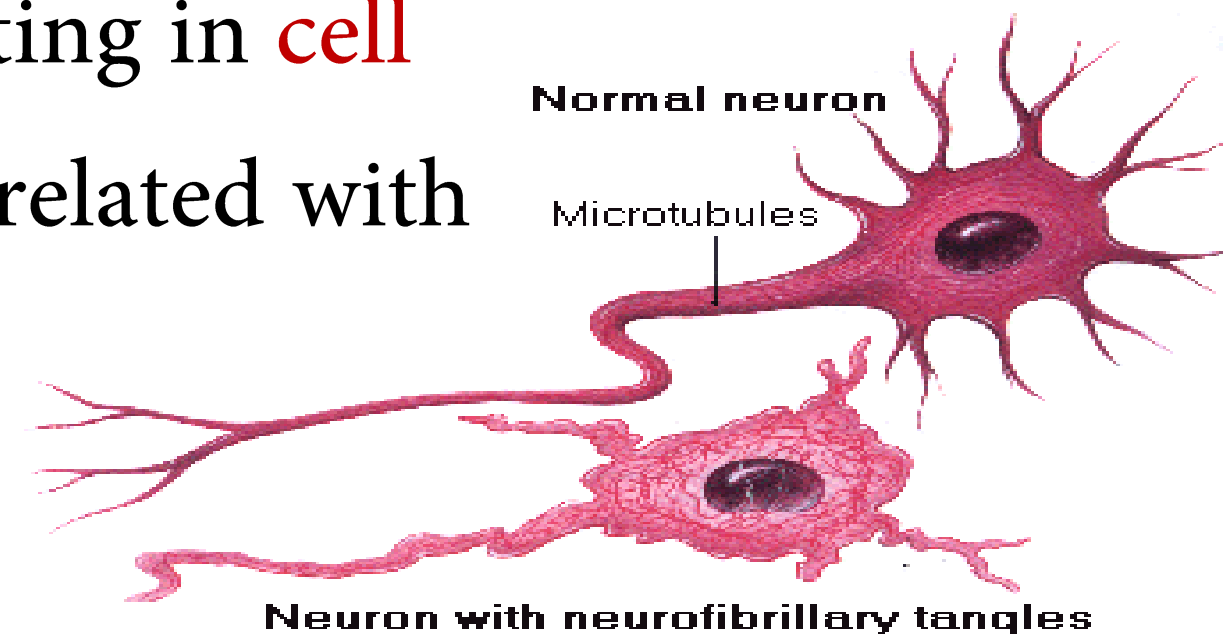
***Depletion of
neurotrophin and
NTs***

***Oxidative
stress***

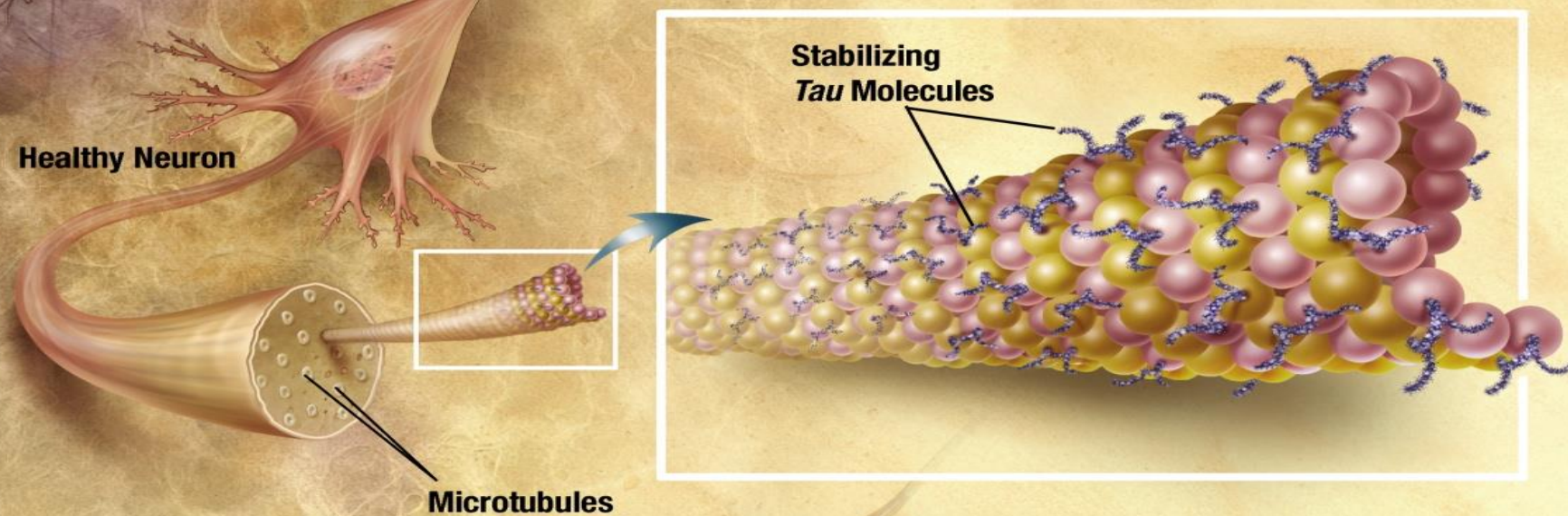
***Mitochondrial
dysfunction***

I. Neurofibrillary tangles (NFT)

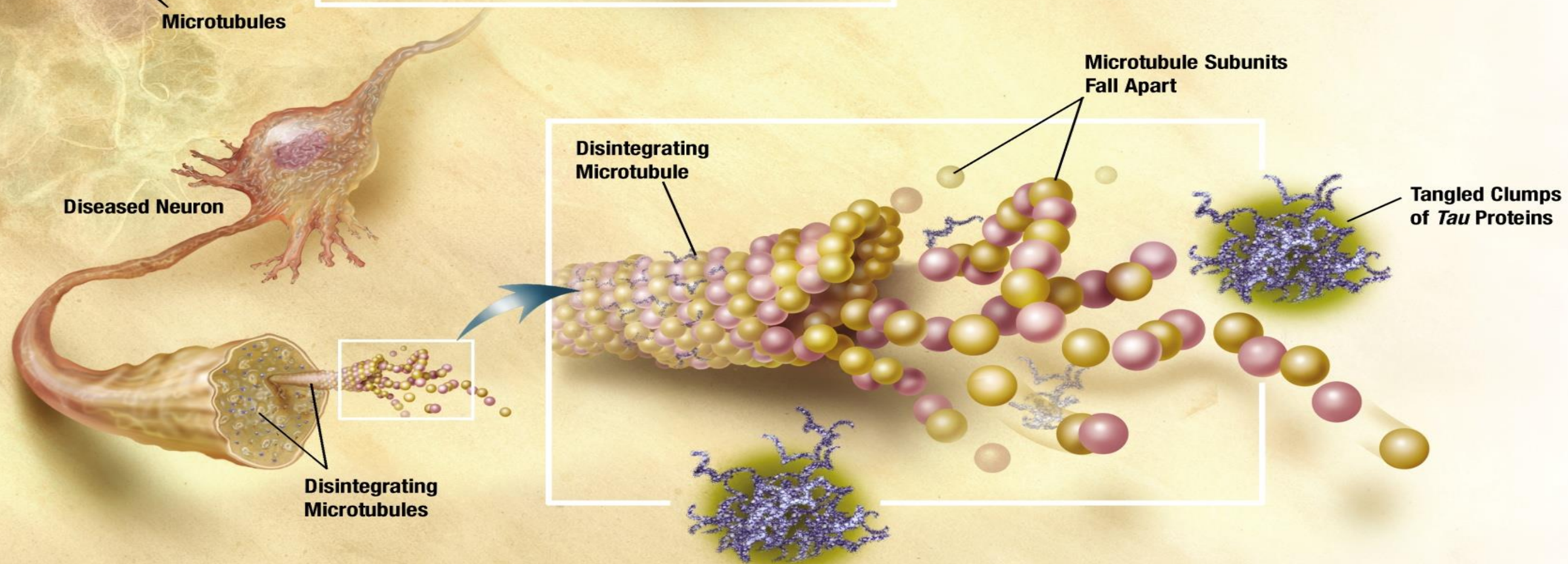
- NFT are intracellular protein and consist of abnormally hyperphosphorylation of (tau) protein, which is involved in **microtubule assembly**.
- Tangles interfere with **neuronal function**, resulting in **cell damage**, and their presence(NFT) has been correlated with the severity of dementia.



Healthy Neuron



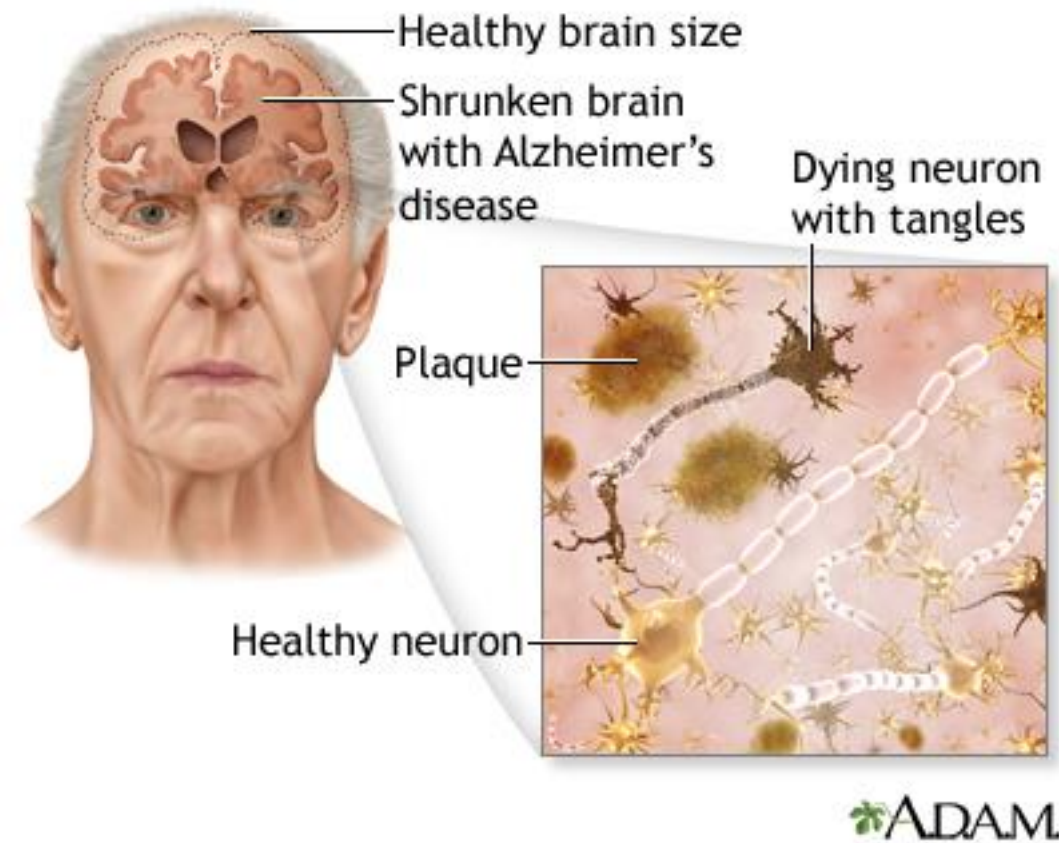
Diseased Neuron



II. plaques

- Plaques are *extracellular* protein deposits of β -amyloid protein.
- The β -amyloid protein is present in a nontoxic, soluble form in human brains. In AD, conformational changes occur that render it insoluble and deposit into plaque.
- Over time, these deposits become compacted into plaques and the β -amyloid protein becomes fibrillar and neurotoxic.
- Inflammation occurs secondary to clusters of astrocytes and microglia surrounding these plaques.

Hallmarks of AD



III. Acetylcholine

- Ach is responsible for *transmitting messages* between certain nerve cells in the brain.
- In AD, the *plaques* and *tangles* damage these pathways, leading to a *shortage of Ach*, resulting in *learning* and *memory impairment*.
- The loss of Ach activity correlates with the severity of AD.
- The basis of pharmacologic treatment of AD has been to *improve cholinergic neurotransmission in the brain*.
- *Acetylcholinesterase* is the enzyme that degrades Ach in the synaptic cleft. Blocking this enzyme leads to an increased level of Ach with a goal of stabilizing neurotransmission.

IV. glutamate

- Primary **excitatory neurotransmitter** in the CNS involved in **memory, learning**.
- It acts by **providing information** from one brain area to another and **affects cognition** through facilitation of connections with cholinergic neurons in the **cerebral cortex** and **basal forebrain**
- In AD, one type of glutamate receptor, N-methyl-D-aspartate (**NMDA**), is **less prevalent than normal**. There also appears to be **overactivation** of unregulated glutamate signaling **Leading to increased production of amyloid precursor protein (APP)**. which associated with **higher rates of plaque** development and **hyperphosphorylation of (tau) protein**.

Cholesterol:

- Increased cholesterol concentrations have been associated with AD.
- The cholesterol increases β -amyloid protein synthesis, which can lead to plaque formation.

- *Estrogen:*

Women's Health Initiative Memory Study reported that hormone replacement therapy with either estrogen alone or estrogen plus medroxyprogesterone resulted in negative effects on memory.

Clinical presentation of AD

Signs and Symptoms

- ***Cognitive:***

- ☐ memory loss,
- ☐ problems with language,
- ☐ disorientation to time and place,
- ☐ poor or decreased judgment,
- ☐ problems with learning

- ***Noncognitive:***

changes in **mood or behavior**, changes in **personality**

- ***Functional:***

difficulty performing familiar tasks

TABLE 52–1**Stages of Alzheimer's Disease**

Mild (MMSE
score 26–18)

Patient has difficulty remembering recent events. Ability to manage finances, prepare food, and carry out other household activities declines. May get lost while driving. Begins to withdraw from difficult tasks and to give up hobbies. May deny memory problems

Moderate
(MMSE score
17–10)

Patient requires assistance with activities of daily living. Frequently disoriented with regard to time (date, year, and season). Recall for recent events is severely impaired. May forget some details of past life and names of family and friends. Functioning may fluctuate from day to day. Patient generally denies problems. May become suspicious or tearful. Loses ability to drive safely. Agitation, paranoia, and delusions are common

Severe (MMSE
score 9–0)

Patient loses ability to speak, walk, and feed self. Incontinent of urine and feces. Requires care 24 hours a day, 7 days a week

MMSE, Mini-Mental Status Examination.

Treatment

I. Desired and Expected Outcomes:

There is no agent that can *cure* or *reverse the disease*.

- The primary desired outcome is to *delaying disease progression* **and** *preserve the patient's functioning* as long as possible.
- Secondary goals include:
 - ☐ treating psychiatric and behavioral symptoms that may occur during the course of the disease.

General approach to treatment

The current *gold standard of treatment* for cognitive symptoms includes:

❑ Cholinesterase (ChE) inhibitor (Donepezil, rivastigmine, galantamine)

❑ NMDA antagonist(memantine)

❑ [Aducanumab](#), a monoclonal antibody against amyloid beta (June 2021)

- **Psychiatric** and **behavioral symptoms** that occur during the course of the disease should be treated as they occur.



General approach to treatment

For *mild* to *moderate* symptoms, consider cholinesterase (ChE) inhibitor and titrate to maintenance dose.

For *moderate* to *severe* symptoms, consider adding NMDA antagonist and titrate to maintenance dose.

Nonpharmacologic Therapy

Sleep disturbances, urinary incontinence, agitation, Aggression should be managed with *behavioral interventions*.

patient and family should be educated about initial diagnosis, the course of the illness, prognosis, available treatments, legal decisions, and quality-of-life issues.

Pharmacologic treatment

- I- Treatment of cognitive symptoms
- Managing *blood pressure*, *cholesterol*, and *blood sugar* may reduce the risk of developing AD and may prevent the worsening of dementia in patients with AD.
- *Successful treatment* reflects a decline of *less* than 2-4 points each year on the MMSE score.

Cholinesterase inhibitors:

1. donepezil,
 2. rivastigmine,
 3. galantamine.
- They are indicated in mild to moderate AD, while *donepezil* is also indicated in severe AD.
 - If the decline in MMSE score is more than 2-4 points after treatment for 1 year with the initial agent, it is reasonable to change to a different cholinesterase inhibitor.

- *Sides effects:*

- **gastrointestinal symptoms** (nausea, vomiting, and diarrhea Esp. Rivastigmine).

- Other cholinergic side effects are dose-related and include:

- urinary incontinence,

- dizziness,

- headache,

- syncope,

- **bradycardia**, muscle weakness, salivation, and sweating.

- Concurrent use of anticholinergic medications with cholinesterase inhibitors should be avoided.

Table 29–6

Dosing Strategies for Cognitive Agents

	Donepezil (Aricept)	Rivastigmine (Exelon)	Galantamine (Razadyne)	Memantine (Namenda) ^a
Starting dose	5 mg daily in the evening	1.5 mg twice daily or 4.6 mg/24 hour applied daily (patch)	4 mg twice daily or 8 mg daily in the morning	5 mg daily or 7 mg daily (ER formulation)
Maintenance dose	5–23 mg daily	3–6 mg twice daily or 9.5 mg/24 hour applied daily (patch)	8–12 mg twice daily or 16–24 mg daily	10 mg twice daily or 28 mg daily (ER formulation)
Time between dose adjustments	4–6 weeks between 5 and 10 mg increment; 3 months between 10 and 23 mg increment	2 weeks for oral and 4 weeks for patch	4 weeks	1 week
Dosage adjustments for renal or hepatic impairment	None	Moderate to severe renal impairment, mild to moderate hepatic impairment, or low body weight (< 50 kg): consider maximum dose of 4.6 mg/24 hour	Do not exceed 16 mg for moderately impaired hepatic or renal function; do not administer in severe renal or hepatic impairment	Severe renal impairment: target maintenance dose of 5 mg twice daily or 14 mg daily

B. NMDA antagonist

Memantine (Namenda) blocks glutamatergic neurotransmission by antagonizing *N*-methyl-D-aspartate receptors, which may prevent....

It is indicated for treatment of ***moderate*** to ***severe AD***.

It is initiated at 5 mg/day and increased weekly by 5 mg/day to the effective dose of 10 mg twice daily.

Dosing must be **adjusted** in patients with **renal impairment**.

Well tolerated, and side effects include **constipation, confusion, dizziness, hallucinations, headache, cough, and hypertension**.

III- Other Potential Treatment Approaches

- *vitamin E can be used for* prevention of AD but not treatment.(greater than 400 IU/day is not recommended)
- *Ginkgo biloba* should not be used in individuals taking anticoagulants or antiplatelet drugs, and should be use cautiously in those taking NSAIDs.
- *Caprylidene*: can be used as **energy source** for AD patients to generate ATP and **increase pools of acetylcholine**.
 - Dose 40-g powder packets. One packet can be mixed with 120–240 mL liquid and dosed once daily after a meal.
- Tramiprosate (homotaurine), or Alzhemed, **demonstrated early promise** in the treatment of AD, but **phase III trials were disappointing**.



II- Treatment of behavioral symptoms

B. Antipsychotics

- Antipsychotic medications have traditionally been used to treat **disruptive behaviors** and **psychosis** in AD patients.
- Adverse events: **somnolence**, **extrapyramidal** symptoms, **worsening cognition**, cerebrovascular events.
- A meta-analysis concluded that only 17% to 18% of dementia patients demonstrated treatment response to **atypical antipsychotics**.

B. Antidepressants

- Depression and dementia have many symptoms in common, and the diagnosis of depression can be difficult, especially later in the course of AD.
- **Treatment with a SSRI** is usually initiated in depressed patients with AD.
- *Best evidence is for **Sertraline** and **citalopram** to treat depressed patient associated with AD. However, A recent trial suggested a lack of benefit of sertraline and mirtazapine* compared with placebo and an increased risk of adverse effects.
- ***Paroxetine** causes more anticholinergic side effects than the other SSRI.*
- Although probably equally effective, the ***tricyclic antidepressants*** are usually not recommended.

TABLE 52–4		Medications Used for Noncognitive Symptoms of Dementia		
Drugs	Starting Dose (mg)	Maintenance Dose in Dementia (mg/day)	Target Symptoms	
Antipsychotics				
Aripiprazole	10–15	30 (maximum)	Psychosis: hallucinations, delusions, suspiciousness Disruptive behaviors: agitation, aggression	
Olanzapine	2.5	5–10		
Quetiapine	25	100–400		
Risperidone	0.25	0.5–2		
Antidepressants				
Citalopram	10	10–20	Depression: poor appetite, insomnia, hopelessness, anhedonia, withdrawal, suicidal thoughts, agitation, anxiety	
Escitalopram	5	10 (maximum)		
Fluoxetine	10	10–20		
Paroxetine	10	10–40		
Sertraline	12.5	150 (maximum)		
Mirtazapine	15	15–30		
Trazodone	25	75–150		
Anticonvulsants				
Carbamazepine	100	300–600	Agitation or aggression	
Valproic acid	125	500–1,500		

Evaluation of therapeutic outcomes

- Baseline assessment should define therapeutic goals and document **cognitive status, physical status, functional performance, mood, thought processes, and behavior**. Both the patient and caregiver should be interviewed.
- Objective assessments, such as the *MMSE for cognition and the Functional Activities Questionnaire for activities of daily living*, should be used to quantify changes in symptoms and functioning.

- The patient should be observed carefully for *potential side effects* of drug therapy. The specific side effects to be monitored and the method and frequency of monitoring should be documented.
- Assessments for drug effectiveness, side effects, compliance, need for dosage adjustment, or change in treatment should occur at least monthly.
- A treatment period of *6 months to 1 year* may be required to determine whether therapy is beneficial effect.

Table 29-7

Adverse Effects for Currently Approved Medications for Alzheimer Disease^a

Adverse Event	Donepezil 5–10 mg/day (%) (n = 747)	Donepezil 23 mg/day (%) (n = 963)	Rivastigmine 6–12 mg/day (%) (n = 1189)	Galantamine IR 16–24 mg/day (%) (n = 1040)	Memantine IR 5–20 mg/day (%) (n = 940)	Memantine XR 28 mg/day (%) (n = 341)
Nausea	11	12	47	24	NR	NR
Vomiting	5	9	31	13	3	2
Diarrhea	10	8	19	9	NR	5
Headache	10	4	17	8	6	6
Dizziness	8	5	21	9	7	5
Muscle cramps	6	NR	NR	NR	NR	NR
Insomnia	9	3	9	5	NR	NR
Fatigue	5	2	9	5	2	3
Anorexia	4	5	17	9	NR	NR
Depression	3	NR	6	7	NR	3
Abnormal dreams	3	NR	NR	NR	NR	NR
Weight decrease	3	5	3	7	NR	NR
Abdominal pain	NR	NR	13	5	NR	2
Rhinitis	NR	NR	4	4	NR	NR

NR, not reported.