Alzheimer Disease

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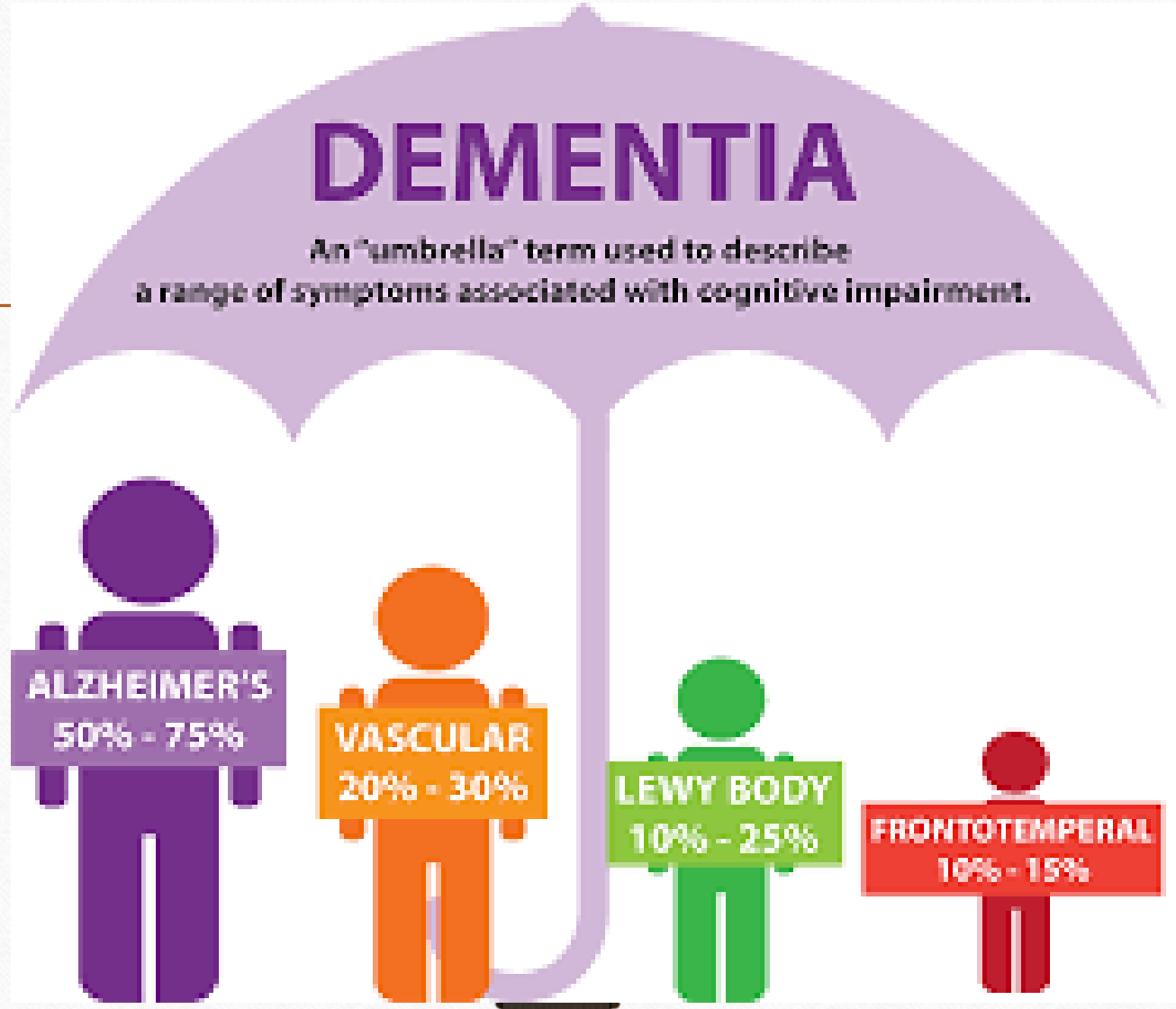
Introduction

- Alzheimer disease (AD), first characterized by Alois Alzheimer in 1907, is a gradually progressive dementia affecting cognition, behavior, and functional status.
- The exact pathophysiologic mechanisms underlying AD are not entirely known, and no cure exists.
- Although drugs may reduce AD symptoms for a time, the disease is eventually fatal.
- Alzheimer disease profoundly affects the family as well as the patient. The need for supervision and assistance increases until the late stages of the disease, when AD patients become totally dependent on a caregiver for all of their basic needs


DEMENTIA
An "umbrella" term used to describe
a range of symptoms associated with cognitive impairment.
ALZHEIMER'S
50% - 75%
VASCULAR
20% - 30%
LEWY BODY
10% - 25%
FRONTOTEMPERAL
10% - 15%

Etiology

- A definitive cause for AD has yet to be determined. Several risk factors, however, have been identified.

- **Advancing age** is the primary risk factor for AD; other risks include **family history**, **head trauma, metabolic syndrome, diabetes, hypertension and cardiovascular disease**.

- **Genetics** plays a **significant role** in the development of Alzheimer's disease. The high familial occurrence of AD has been linked to autosomal-dominant traits on **chromosomes 21, 14, and 1**

Etiology

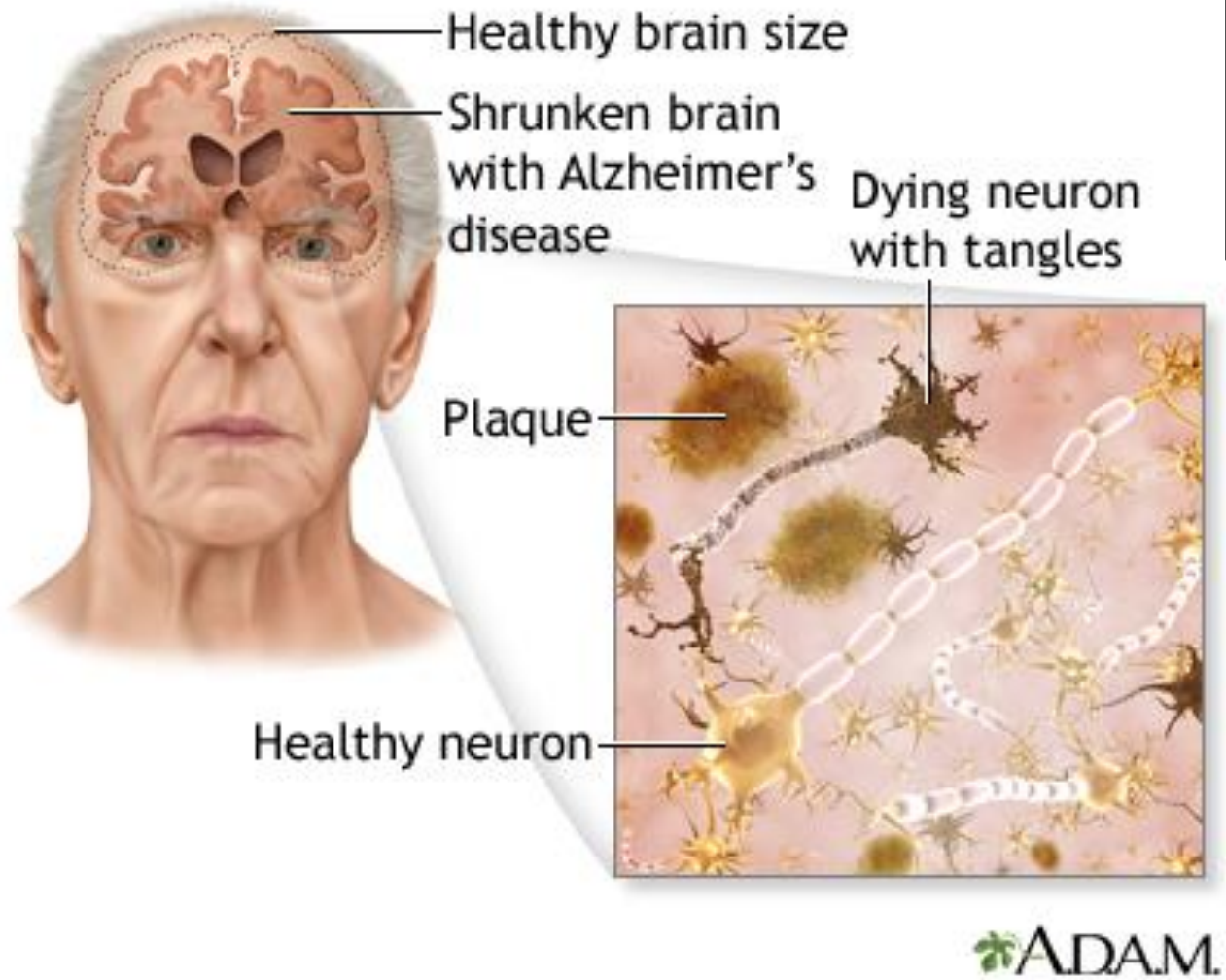
- APP (amyloid precursor protein), a normal protein found throughout the body, maps on chromosome 21 and plays a pivotal role in AD neuropathology.
- Because of overproduction or transcription errors, an abnormal subunit (i.e., β-amyloid) is produced.
- Mutations on chromosomes 14 (presenilin-1 gene) and 1 (presenilin-2 gene) and the presence of apolipoprotein E4 allele code for alterations in the processing of APP.
- The abnormal cleavage of APP produces a 42–amino acid form of β-amyloid (Aβ) that demonstrates a higher toxicity than other amyloid forms

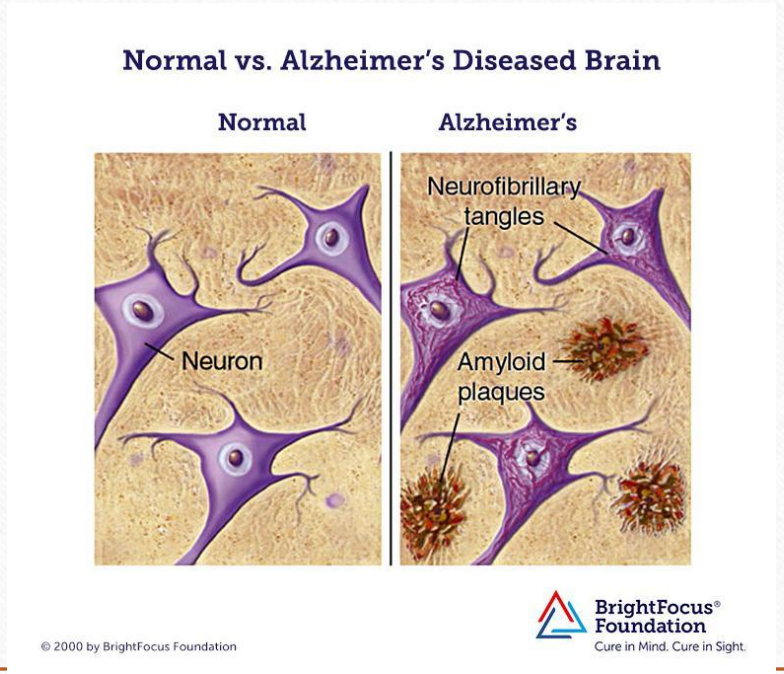
Etiology

- The presence of ApoE-4, the protein coded for by the E4 allele, appears to increase the deposition of Aβ and promote its change to a more pathological configuration.

- The presence of one or two copies of ApoE4 increases the **risk of developing AD twofold or fivefold**, respectively

brain atrophy is the most obvious finding among patients with Alzheimer type dementia, it is not diagnostic for AD or other dementias because some degree of atrophy **accompanies normal aging**. **Atrophic changes** induced by AD are found primarily in the **temporal, parietal, and frontal** areas of the brain;





Etiology

- Accompanying these changes are **decreased** concentrations of several **neurotransmitters and enzymes**. **Choline acetyltransferase** levels are reduced 60% to 90% in the **cortical and hippocampal regions.**

- **Acetylcholine and acetylcholinesterase (AChE) are also decreased.**
- The **release of glutamate** in the central nervous system that can lead to excitotoxic reactions and cell death in AD and other neurodegenerative disorders. (NMDA receptors)

- **Decreased choline acetyltransferase activity has been correlated with plaque density and disease severity**. Cortical synapse loss, especially in the **midfrontal region, is associated with disease severity.**

Clinical Presentation and Diagnosis

Symptoms Suggesting Dementia

Symptom	Evidence
Difficulty learning or retaining new information	Repeats questions; difficulty remembering recent conversations, events, etc.; loses items
Unable to handle complex tasks	Cannot complete tasks that require multiple steps (e.g., difficulty following a shopping list)
Impaired reasoning	Difficulty solving everyday problems; inappropriate social behavior
Impaired spatial orientation and abilities	Gets lost in familiar places; difficulty with driving
Language deficits	Problems finding appropriate words (e.g., difficulty with naming common objects)
Behavior changes	Changes in personality; suspiciousness

Causes of Dementia Symptoms

Central Nervous System Disorders	Systemic Illness	Medications
Adjustment disorder (e.g., inability to adjust to retirement)	Cardiovascular disease Arrhythmia Heart failure	Anticholinergic agents Anticonvulsants Antidepressants Antihistamines
Amnestic syndrome (e.g., isolated memory impairment) Delirium	Vascular occlusion Deficiency states Vitamin B_{12} Folate Iron	Anti-infectives Antineoplastic agents Antipsychotic agents Cardiovascular agents Antiarrhythmics
Depression Intracranial causes Brain abscess Normal pressure Hydrocephalus Stroke Subdural hematoma Tumor	Infections Metabolic disorders Adrenal Glucose Renal failure Thyroid	Antihypertensives Corticosteroids H_2-receptor antagonists Immunosuppressants Narcotic analgesics Nonsteroidal anti-inflammatory agents Sedative hypnotics and anxiolytics Skeletal muscle relaxants

Dementia Screening Tests

Test	Rationale for Testing
Complete blood count with sedimentation rate	Anemic anoxia, infection, neoplasms
Metabolic screen	
Serum electrolytes	Hypernatremia, hyponatremia; renal function
Blood urea nitrogen, creatinine	Renal function
Bilirubin	Hepatic dysfunction (e.g., portal systemic encephalopathy, hepatocerebral degeneration)
Thyroid function	Hypothyroidism, hyperthyroidism
Iron, vitamin B_{12}, folate, vitamin D	Deficiency states (vitamin B_{12}, folate neuropathies, vitamin D deficiency), anemias
Stool occult blood	Blood loss, anemia
HIV and RPR	Infection
Urinalysis	Infection, proteinuria
Chest roentgenogram	Neoplasms, infection, airway disease (anoxia)
Electrocardiogram	Cardiac disease (stagnant anoxia)
Brain scan	Cerebral tumors, cerebrovascular disease
Mental status testing	General cognitive screen
Depression testing	Depression, pseudodementia

NCD due to Alzheimer's Disease

Criteria for either mild or major NCD are met

Insidious onset and gradual progression of impairment

- Mild: impairment in one cognitive domain
- Major: impairment in at least two cognitive domains

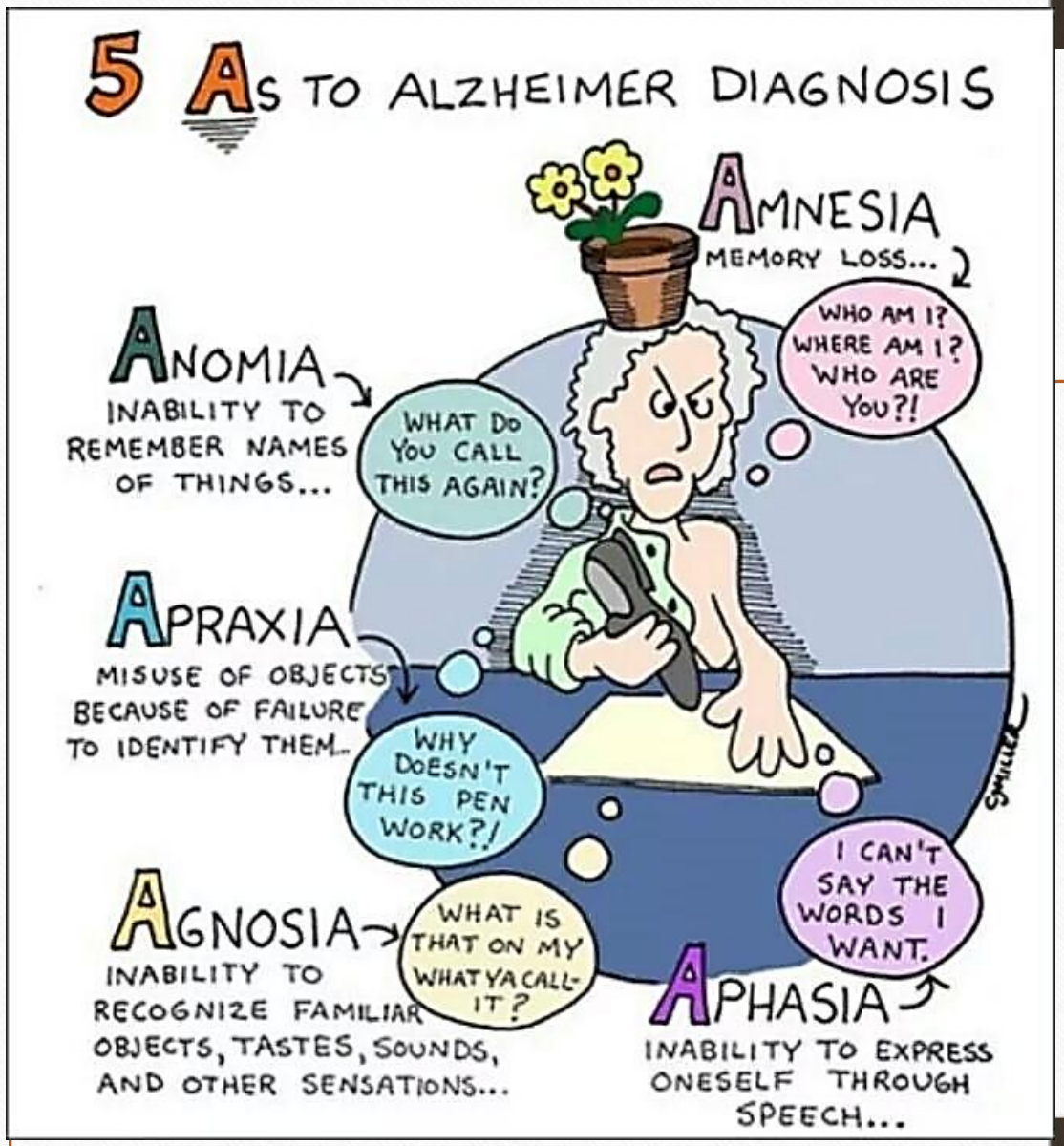
Probable Alzheimer's disease (either of the following must be present)

- Alzheimer's disease genetic mutation based on family history or genetic testing
- All of the following are present:
  - Decline in memory and learning plus one other cognitive domain
  - Steady and gradual cognitive decline
  - No evidence of another condition that is likely to cause cognitive decline

Possible Alzheimer's disease

- Lack of an Alzheimer's disease genetic mutation
- All of the following are present:
  - Decline in memory and learning
  - Steady and gradual cognitive decline
  - No evidence of another condition that is likely to cause cognitive decline

Cognitive decline is not better explained by cerebrovascular disease or another condition associated with cognitive decline or neurodegeneration


5 As to Alzheimer Diagnosis
Amnesia
memory loss...
Who am I? Where am I? Who are you?!
Anomia
inability to remember names of things...
What do you call this again?
Apraxia
misuse of objects because of failure to identify them...
Why doesn't this pen work?!
Agnosia
inability to recognize familiar objects, tastes, sounds, and other sensations...
What is that on my whatya call-it?
Aphasia
inability to express oneself through speech...
I can't say the words I want.

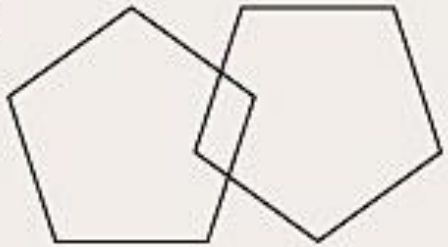

APHASIA
Do you feel pickle today?
APRAXIA
AGNOSIA
Is it a pen?
↓EXECUTIVE FUNCTIONING
Tomorrow I will go to the beach

Stages of Dementia of the Alzheimer Type

Stage of Cognitive Decline	Features
No cognitive decline	Normal cognitive state
Very mild cognitive decline	Forgetfulness, subjective complaints only; no objective decline
Mild cognitive decline	Objective decline through psychiatric testing; work and social impairment; mild anxiety and denial
Moderate cognitive decline	Concentration, complex skills decline; flat affect and withdrawal
Moderately severe cognitive decline	Early dementia; difficulty in interactions; unable to recall or recognize people or places
Severe cognitive decline	Requires assistance with bathing, toileting; behavioral symptoms present (agitation, delusions, aggressive behavior)
Very severe cognitive decline	Loss of psychomotor skills and verbal abilities; incontinence; total dependence

The Mini-Mental State Exam

Max.	Score	
		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
		Attention and calculation
5	( )	Serial 7's. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3	( )	Ask for the 3 objects repeated above.
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No ifs, ands, or buts"
3	( )	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



Give 1 point for each correct answer.
Total score _____

Stages of Alzheimer Disease

Mild (MMSE score 26–21)	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 20–10)	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

Prognosis

- AD follows a predictable course that may progress over the course of 10 years or more.

- Death in the late stage of AD is commonly associated with the development of infections such as **pneumonia, urinary tract infections, or decubitus ulcers**.

Treatment

- Maintaining independence as long as possible is an important goal in treating a patient with dementia.
- Keeping patients in familiar surroundings allows them to function without the added burden of having to attempt to adapt to a strange environment.
- **Concurrent diseases and many medications** can **reduce function and increase cognitive impairment in patients with dementia**

Pharmacotherapy

- Currently, there are two classes of medications that are used in the treatment of Alzheimer's disease, cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonist.
- They are pharmacologically distinct and can be prescribed **concurrently in** patients in the **moderate to severe stages** of the illness.

- An untreated patient has an average decline of **two to four points in MMSE** score **per year.** Successful treatment would reflect a decline of **less than two points a year**

Cholinesterase Inhibitors

- Tacrine was the first such drug to be examined in a systematic fashion. However, tacrine was fraught with significant side effects, including **hepatotoxicity**, which severely limited its usefulness.
- Tacrine is no longer available in the market, having been replaced by safer, more tolerable cholinesterase inhibitors
- The newer cholinesterase inhibitors **donepezil, rivastigmine, and galantamine** show similar modest symptomatic improvements in cognitive, global, and functional outcomes in patients with mild to moderate AD, and duration of benefit varies **from 3 to 24 months**

Cholinesterase Inhibitors

- Patients and caregivers should be cautioned **against abrupt discontinuation** of cholinesterase inhibitor therapy, as this can lead to **worsening cognition and behavior** in some patients.

- When switching from one cholinesterase inhibitor to another due to side effect intolerance, a **washout period is recommended**

DONEPEZIL

- Donepezil is a piperidine derivative that is somewhat selective for central AChE.
- It reversibly inhibits cholinesterase activity. Donepezil is highly bioavailable and exhibits **a long half-life**, allowing it to be given as a single daily dose.

- Donepezil is indicated also for the severe stage of AD.
- Dosing regimen: 5-10 mg daily in mild to moderate AD
- 10-23 mg daily in moderate to severe AD

Safety concern

- The most common adverse effects of donepezil are associated with **cholinergic activity**.
- They tend to be **mild to moderate in nature** and resolve with stabilization of the dose.
- In a 144-week extension trial of donepezil, the most frequently encountered adverse effects were **nausea, diarrhea, and headache.**

RIVASTIGMINE

- Rivastigmine is a carbamate derivative that inhibits both AChE and butyrylcholinesterase (BChE) activity.
- BChE provides an alternative pathway for acetylcholine metabolism. The drug binds to the esteratic sites of the AChE and BChE molecules and slowly dissociates.

- Rivastigmine's biological half-life is approximately **1 hour**, but because its slow dissociation extends **its activity for at least 10 hours**, it can be **dosed twice daily.**
- It undergoes a significant first-pass effect, the **resultant bioavailability is approximately 36%.**

Safety Concerns

- Adverse effects typically include **nausea, vomiting, diarrhea, and other cholinergic mediated GI effects.**
- They are most common when rivastigmine is taken **on an empty stomach or when the dose escalation is too rapid.**
- **Headache, dizziness, and fatigue** are also common adverse effects.

- Increasing the dose by 1.5 mg twice daily at 4- week intervals increases drug tolerability and reduces the frequency and severity of GI side effects.

Rivastigmine (Exelon)

- **InitiaL dosing**: 1.5 mg twice daily (capsule, oral solution) 4.6 mg/day (transdermal patch)
- **Maintenance dose**: 3-6 mg twice a day (capsule, oral solution) 9.5-13.3 mg/day (transdermal patch)

GALANTAMINE

- Like other agents used to treat AD, galantamine enhances cholinergic activity by inhibiting AChE.
- However, it also stimulates nicotinic receptors (α 7-nicotinic receptor agonist) at a site distinct from that stimulated by acetylcholine, an action that **does not rely on the presence of acetylcholine**.

- Galantamine is rapidly and completely absorbed, reaches peak serum levels **in less than 2 hours, and has a half-life of approximately 5 hours.**
- Galantamine is metabolized **primarily** by **cytochrome P-450 (CYP) isoenzymes CYP2D6 and CYP3A4, and is eliminated in the urine**

GALANTAMINE

- Galantamine to be effective for the symptomatic treatment of mild to moderate AD.

- Doses of **16 and 24 mg/day produced clinically meaningful improvement**.
- **Initial dose**: 4 mg twice daily (tablet, oral solution), 8 mg daily in the morning (extendedrelease capsule)
- **Maintenance dose**: 8-12 mg twice a day (tablet, oral solution) 16-24 mg (extendedrelease capsule)

Safety Concerns

- As with the other ChEIs, cholinergic effects in the GI tract are the most commonly encountered adverse effects. **Nausea, diarrhea, vomiting, and anorexia** were the most frequent events encountered during clinical trials.
- They were typically present during the dose escalation phases of the studies.
- **A dose titration interval of 4 weeks reduces the severity of adverse effects and increases tolerability.**

Memantine

- Memantine is a noncompetitive NMDA receptor **antagonist** with moderate affinity and voltage-dependent binding.
- It is completely absorbed after oral administration, reaches **peak** serum concentrations in **3 to 8 hours**, and is moderately protein bound.
- Overall, the benefits of memantine are **modest**.
- The **combined use of memantine and a ChEI** has been shown to be **superior** to a ChEI alone by improving daily function in individuals with moderate to severe dementiaOverall, the benefits of memantine are modest.

Safety Concerns & Dosing

- Common adverse effects include diarrhea, insomnia, dizziness, headache, and hallucinations.
- Memantine may mitigate GI adverse effects associated with cholinesterase inhibitor therapy
- It should be started 5 mg daily, with the dosage increased in **weekly** intervals by 5 mg/day, up to a dose of **10 mg twice daily.**
- As an alternative, it can be started on the **extended-releas**e formulation given in weekly escalating doses of 7, 14, 21, and 28 mg daily.

Safety Concerns & Dosing

- Can be taken with or without food.
- Can open extended-release capsule and sprinkle contents on applesauce for ease of administration.
- Severe renal impairment: (GFR≤ 30) recommended maintenance dose of 5 mg twice daily (tablet, oral solution) or 14 mg daily (extended-release capsule)
- Severe hepatic impairment: administer with caution

Vitamin E

- Vitamin E Based on pathophysiologic theories involving oxidative stress and the accumulation of free radicals in AD, significant interest has evolved regarding the use of antioxidants in the treatment of AD.

- there is insufficient evidence to recommend vitamin E supplementation for the treatment of AD. Vitamin E remains under investigation for the prevention of AD.

Omega-3

- **Omega-3 Fatty Acids** Arguments that omega-3 fatty acids found in fish oil, such as docosahexaenoic acid and eicosapentaenoic acid, could benefit AD subjects have existed for some years.
- A large prospective, placebo-controlled trial of docosahexaenoic acid in AD subjects was recently reported.
- For the most part, results were **disappointing,** and although it could not be ruled out that population subsets did benefit, the primary study end points were negative.
- There is **insufficient evidence** at this time to recommend docosahexaenoic acid for the treatment of AD

Ginkgo biloba

- Ginkgo biloba for the prevention and treatment of AD has been extensively studied.
- Proposed mechanisms for Ginkgo's use in AD include its potential to **increase blood flow, decrease blood viscosity, antagonize platelet-activating factor receptors, increase anoxia tolerance, inhibit monoamine oxidase, and serve as an antioxidant.**
- Most studies reporting benefit in patients with cognitive impairment or dementia have studied a standardized extract, EGb 761, in doses of 240 mg/day for 22 to 26 weeks

Ginkgo biloba

- Side effects reported from EGb 761 studies were typically mild, including **nausea, vomiting, diarrhea, headaches, dizziness, palpitations, restlessness, and weakness**.

- Because EGb also has a potent antiplatelet effect, it should be avoided by individuals **taking anticoagulant or antiplatelet therapies, and should be used cautiously in patients taking NSAIDs**

Thank You!