Pharmacotherapy of Alzheimer's disease

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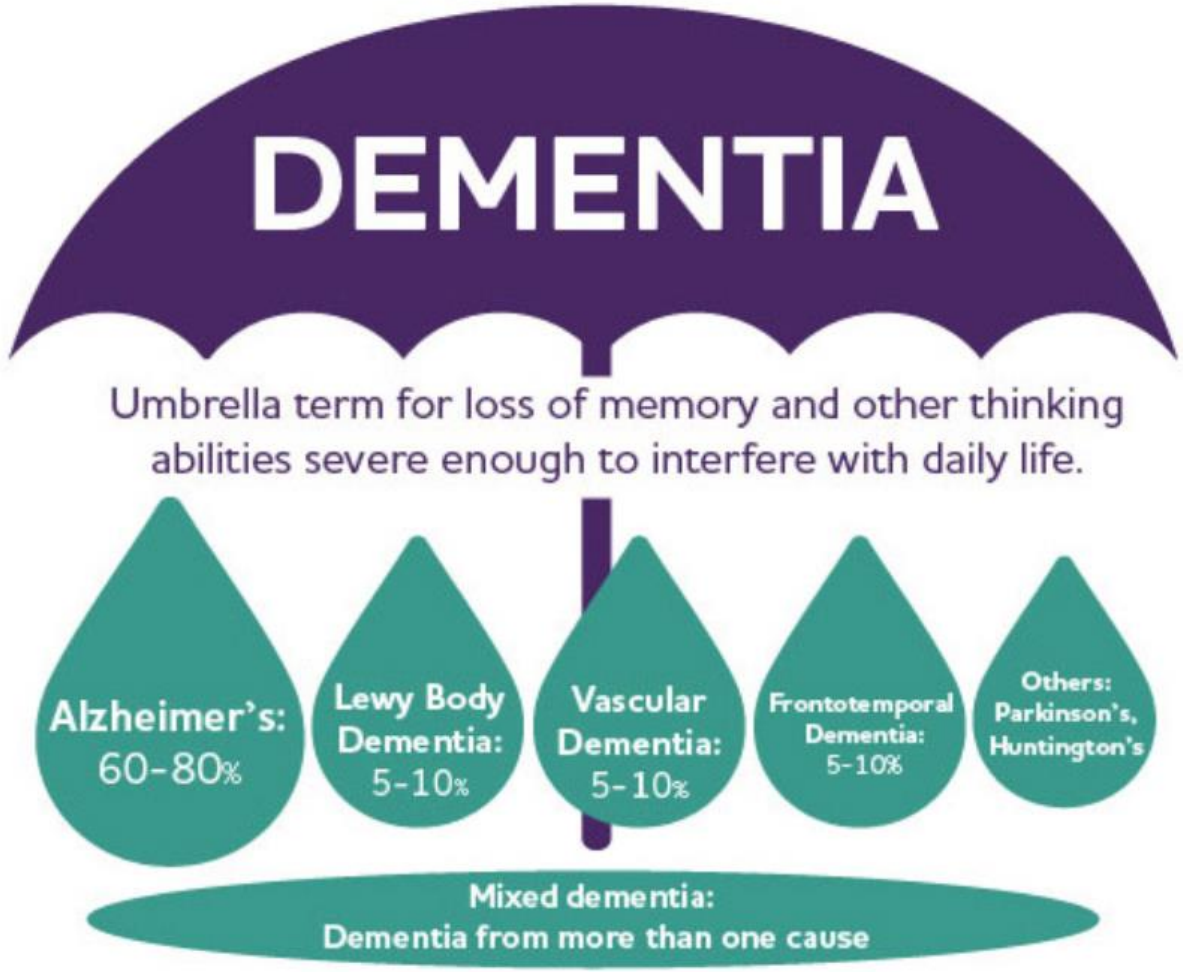
Dementia


DEMENTIA
Umbrella term for loss of memory and other thinking abilities severe enough to interfere with daily life.
Alzheimer's: 60-80%
Lewy Body Dementia: 5-10%
Vascular Dementia: 5-10%
Frontotemporal Dementia: 5-10%
Others: Parkinson's, Huntington's
Mixed dementia: Dementia from more than one cause

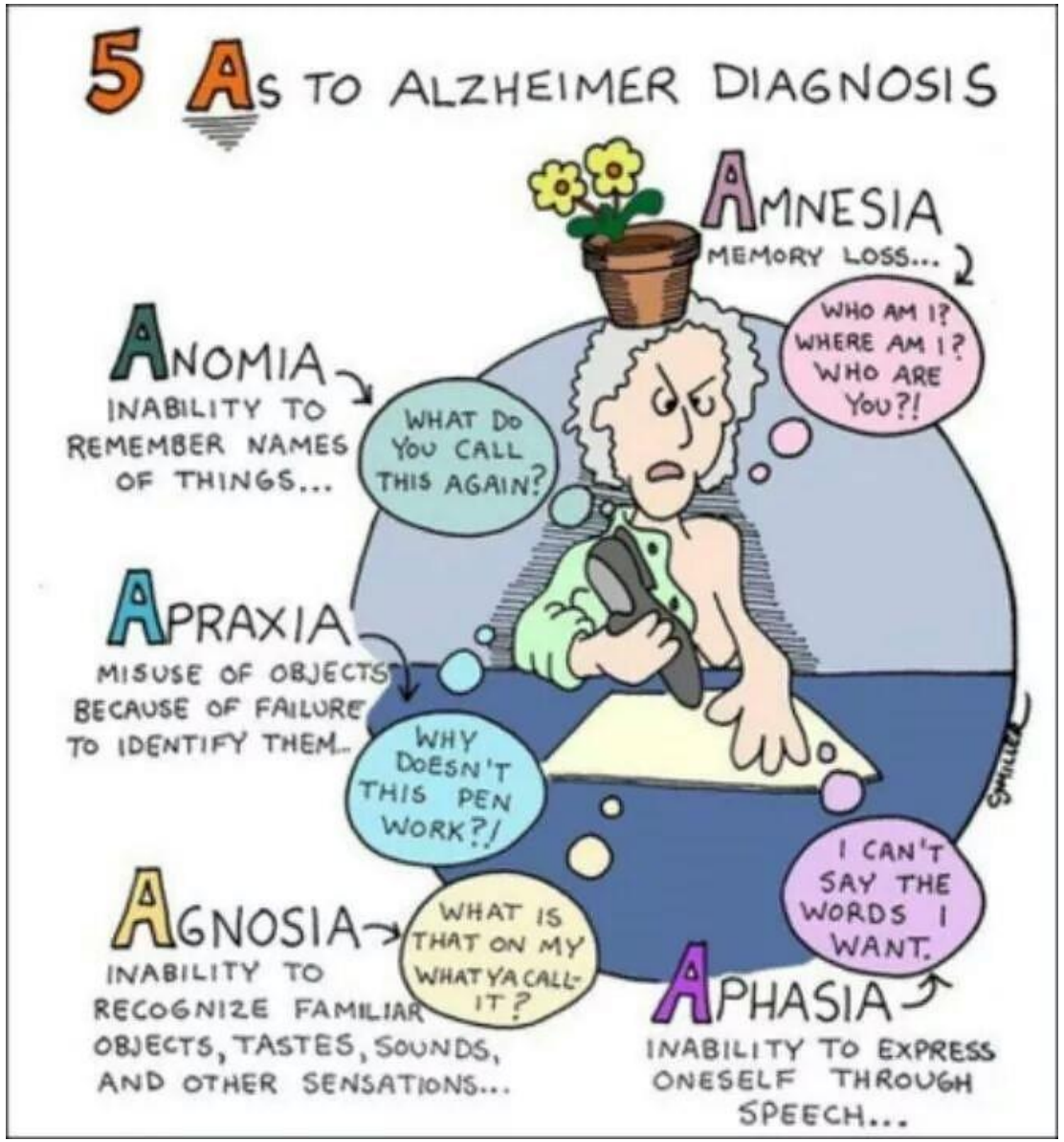
Introduction

- Alzheimer disease (AD) is a neurodegenerative disorder of uncertain cause and pathogenesis that primarily affects older adults and is the most common cause of dementia.
- The incidence increases exponentially with age over 65 years.
- Doubling in prevalence every 5 years after the age of 65 years.
- It has been estimated that the global prevalence of dementia will rise to >100 million by 2050.

Ballard C, Gauthier S, Corbett A, et al. Alzheimer's disease. Lancet 2011; 377:1019.

Cardinal symptoms

- Memory impairment
- Executive function and judgment/problem solving
- Impairments in other cognitive domains
- Behavioral and psychologic symptoms (apathy, social disengagement, and irritability)
- Other signs and symptoms….


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

Prognosis

- AD is the sixth leading cause of death.
- 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**.

Risk factors

- Advanced age
- Genetic factors
- Vascular risk factors including hypertension, obesity, and diabetes
- Brain cholesterol metabolism may be an important determinant of AD. The relationship between diet, genetics, blood lipoproteins levels, and AD is complex and inconsistent.
- Cerebrovascular disease and AD frequently coexist.
- Lifestyle risk factors – Accumulating data suggest that social, cognitive, and physical activities are inversely associated with the risk of AD

Inherited forms of AD

Early-onset (onset of symptoms in a person younger than 65) AD is unusual, and in some but not all cases is familial. Familial early-onset AD makes up less than 1 percent of cases and often follows an autosomal-dominant pattern of inheritance.

Ballard C, Gauthier S, Corbett A, et al. Alzheimer's disease. Lancet 2011; 377:1019.

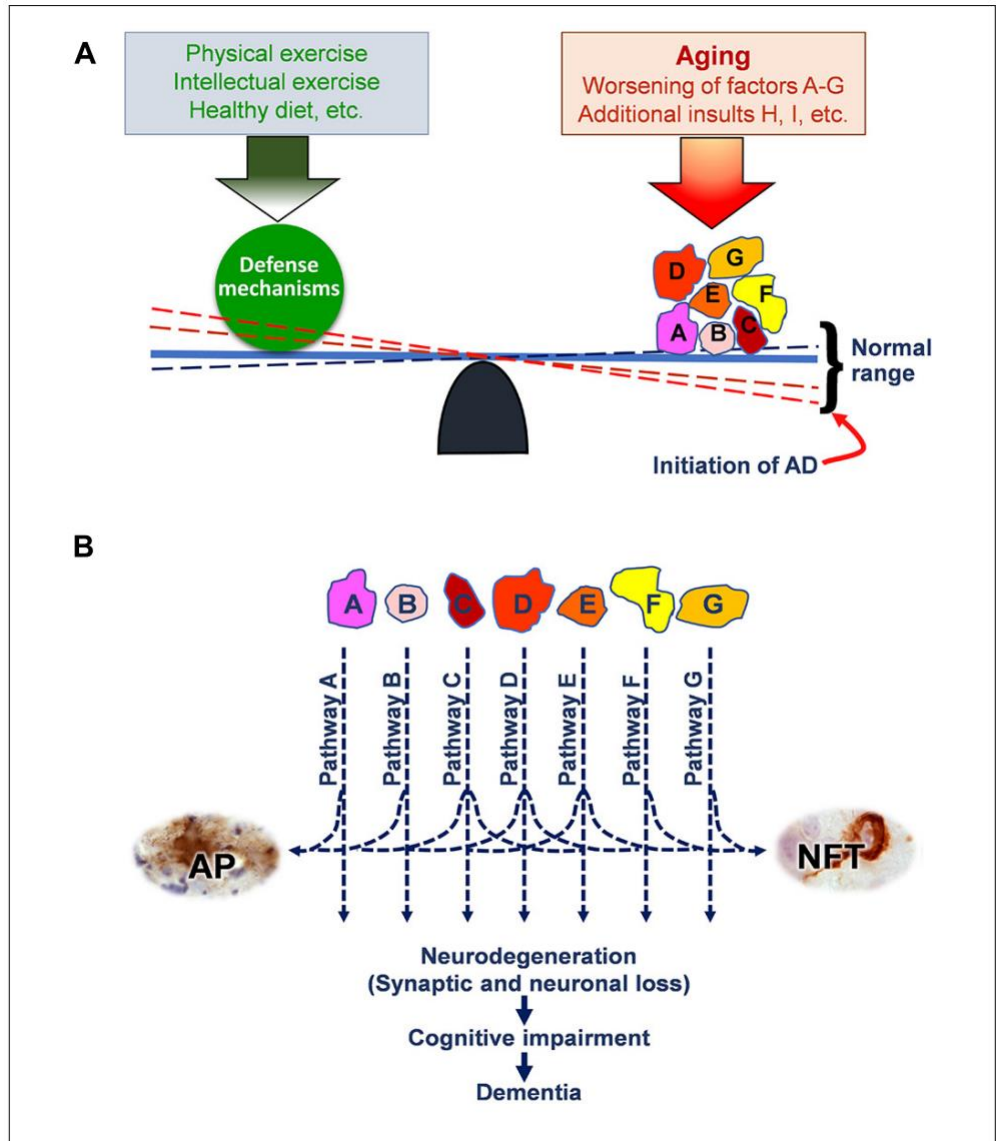
Inherited forms of AD

- APP (amyloid precursor protein), a normal protein found throughout the body, maps on chromosome 21 and plays a pivotal role in AD neuropathology.

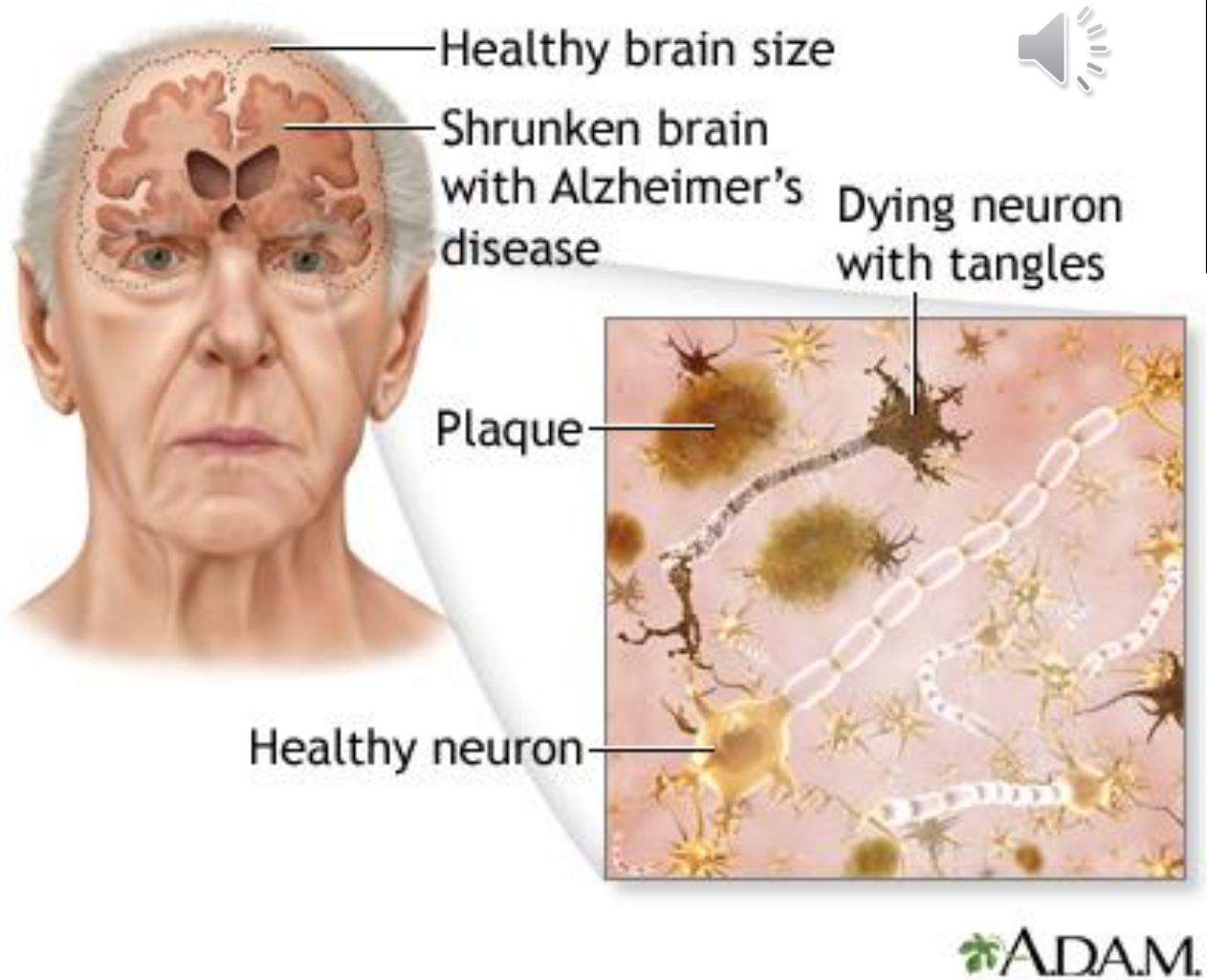
- Because of overproduction or transcription errors, an abnormal subunit (i.e., β-amyloid) is produced.

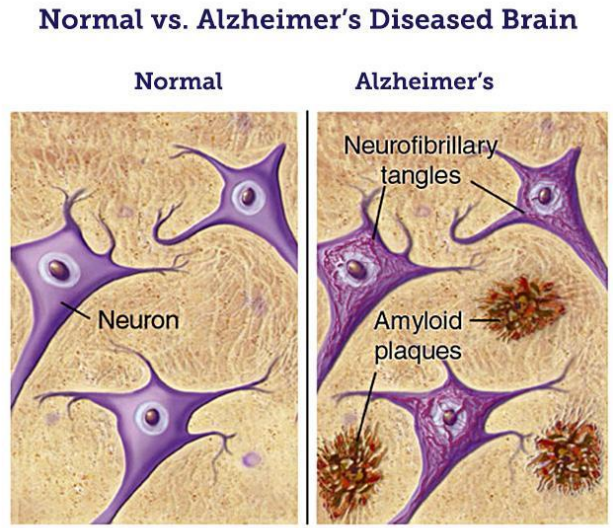
- The abnormal cleavage of APP produces a 42–amino acid form of β-amyloid (Aβ) that demonstrates a higher toxicity than other amyloid forms

- 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.


A
Physical exercise
Intellectual exercise
Healthy diet, etc.
Aging
Worsening of factors A-G
Additional insults H, I, etc.
Defense mechanisms
D
G
E
F
A
B
C
Normal range
Initiation of AD
B
A
B
C
D
E
F
G
Pathway A
Pathway B
Pathway C
Pathway D
Pathway E
Pathway F
Pathway G
AP
NFT
Neurodegeneration
(Synaptic and neuronal loss)
Cognitive impairment
Dementia

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.

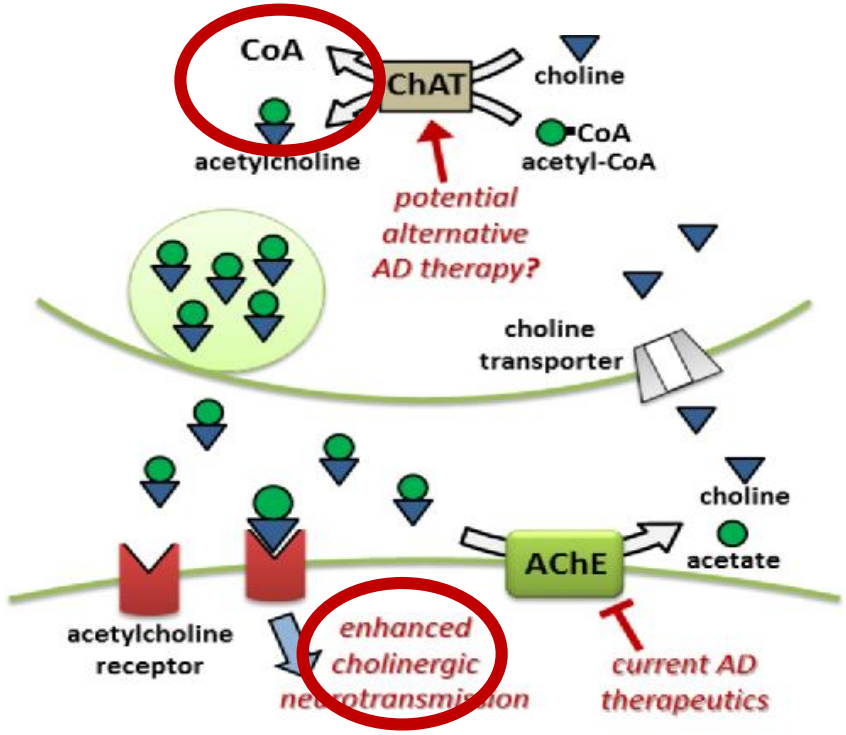


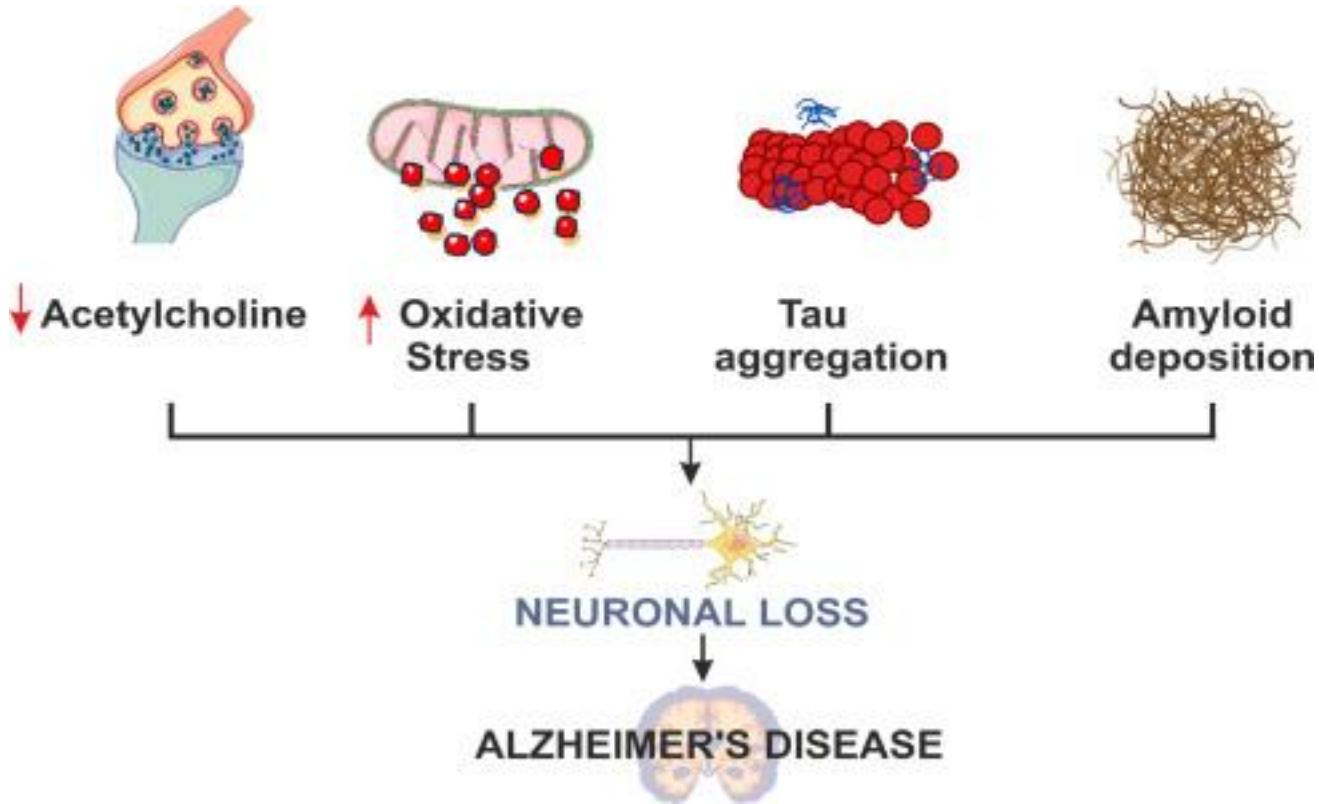


BrightFocus® Foundation
Cure in Mind. Cure in Sight.

Pathophysiology

- Amyloid-beta (Aβ) and the intracellular neurofibrillary tangles
- Marked decrease in cholinergic activity
  - ChAT levels ↓ 60% to 90%
  - ACh ↓
- The release of glutamate in the CNS (excitotoxic reactions and cell death in AD).
- Cortical synapse loss, is associated with disease severity.




Acetylcholine
Oxidative Stress
Tau aggregation
Amyloid deposition
NEURONAL LOSS
ALZHEIMER'S DISEASE

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

Diagnosis

- AD should be suspected in any older adult with **insidious onset, progressive** decline in memory, and at least one other cognitive domain leading to impaired functioning. The diagnosis of AD is made in large part by this clinical assessment.
- Neuropsychologic testing may provide confirmatory information and aid in patient management.
- A neuroimaging study should be obtained on every patient suspected of having AD.

Diagnosis

- In selected cases (eg, those with young age of onset or atypical presentations), other imaging or biomarker tests including 18-F fluorodeoxyglucose positron emission tomography (FDG-PET), cerebrospinal fluid (CSF) testing, or amyloid/tau PET may be helpful, although **access and reimbursement** for these tests may present challenges.
- If use of aducanumab is being considered, confirmation of amyloid status is necessary with either amyloid PET or CSF testing.

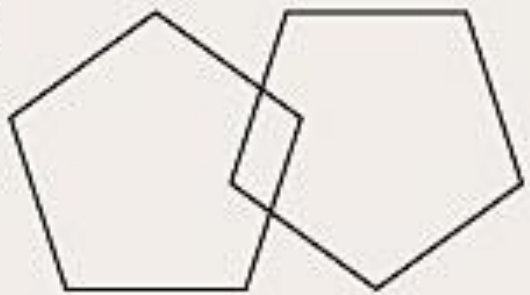
Neuropsychologic testing

- Clinical dementia rating (CDR)
- Mini-Mental score exam (MMSE)
- Montreal Cognitive Assessment (MoCA)

- Mild dementia – MMSE 19 to 26; MoCA 12 to 16; CDR 1
- Moderate dementia – MMSE 10 to 18; MoCA 4 to 11; CDR 2
- Severe dementia – MMSE <10; MoCA <4; CDR 3

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

Treatment

Goal

- Maintaining independence as long as possible is an important goal in treating a patient with dementia.

Supportive care

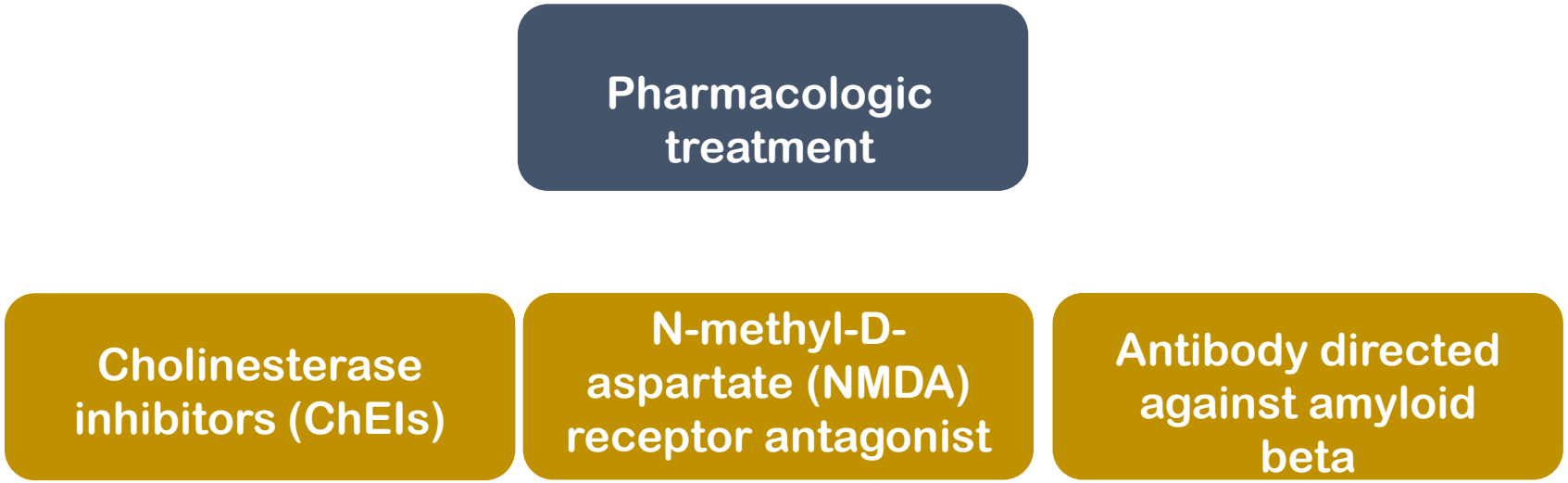
- Keeping patients in familiar surroundings allows them to function without the added burden of having to attempt to adapt to a strange environment.

✓ Concurrent diseases and many medications can reduce function and increase cognitive impairment in patients with dementia

Nonpharmacologic therapy and supportive care

- Nutrition
- Cognitive rehabilitation
- Exercise programs
- And occupational therapy

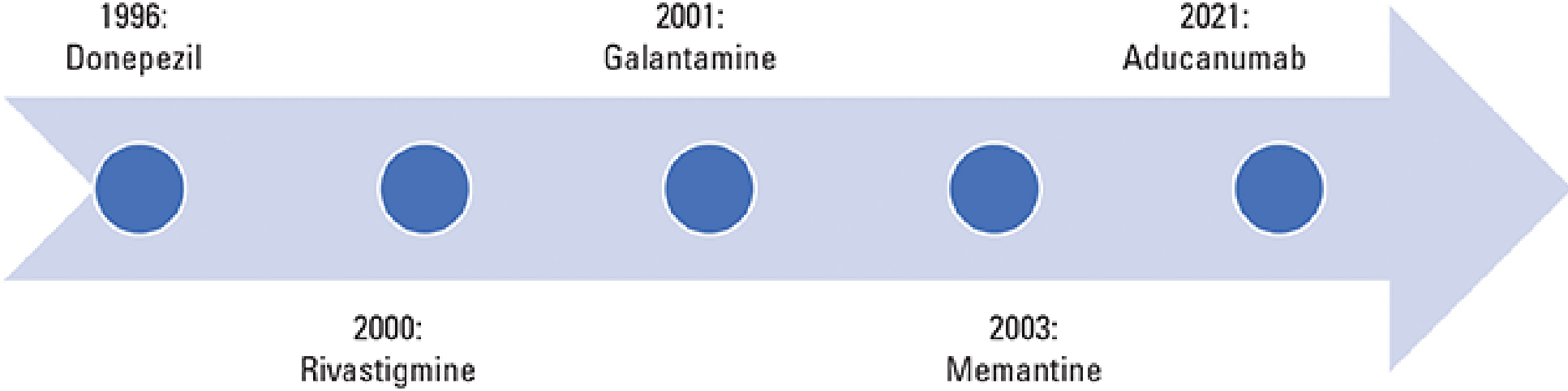
Pharmacologic treatments



They are pharmacologically distinct and can be prescribed concurrently in patients in the moderate to severe stages of the illness.

Figure 1

Timeline of FDA Approvals of Dementia Drugs



Source: References 1, 8, 15, 16, 18.

Cholinesterase Inhibitors

- Tacrine (no longer available, hepathotoxicity)
- The newer cholinesterase inhibitors:
  - Donepezil
  - Rivastigmine
  - And galantamine

✓Similar modest symptomatic improvements in cognitive, global, and functional outcomes in patients with mild to moderate AD

✓Duration of benefit varies from 3 to 24 months

- **Mild to moderate dementia – MMSE 10 to 26; MoCA 4 to 16; CDR 1&2**

Donepezil

- Highly bioavailable, long half-life, single daily dose.
- Donepezil is indicated also for the severe stage of AD.
- Dosing regimen
  - Dosage form: Tab 5 mg, 10 mg & 23 mg
  - Patch Weekly, Transdermal, as hydrochloride:Adlarity: 5 mg/day;10 mg/day
  - 5-10 mg daily in mild to moderate AD
  - 10-23 mg daily in moderate to severe AD

❑ Take at bedtime

❑ Take with or without food

Adverse effect

- 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.
- The most frequently encountered adverse effects:
  - Nausea
  - Diarrhea
  - Headache
  - Weight loss and/or anorexia (Risk factors: Higher doses (≥10 mg/day), Dose initiation or titration, Patients weighing <55 kg)
  - Conduction abnormalities & arrhythmias (QT prolongation and bradycardia), hypertension

Rivastigmine

- Rivastigmine's biological half-life is approximately 1 hour, but because its slow dissociation from AChE and BChE molecules, extends its activity for at least 10 hours, it can be dosed twice daily.

Rivastigmine Dosing

- **Dosage form: Cap 1.5 mg, 3 mg, 4.5 mg & 6 mg**
  - Transdermal patch 4.6 mg/24 hr; 9.5 mg/24 hr; 13.3 mg/24 hr
  - Oral solution (2mg/ml)
- **Initial dosing:** 1.5 mg twice daily (capsule, oral solution)
- **Maintenance dose:** 3-6 mg twice a day (capsule, oral solution)

Adverse effect

- Typically include nausea, vomiting, diarrhea, and other cholinergic mediated GI effects. Headache, dizziness, and fatigue are also common adverse effects.
- Dehydration, weight loss, decreased appetite, and/or anorexia may also occur

- Additional risk factors: Lack of retitration following prolonged (>3 days) treatment interruption, Females, and Patients weighing <50 kg
- They are most common when rivastigmine is taken on an empty stomach or when the dose escalation is too rapid. 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.*

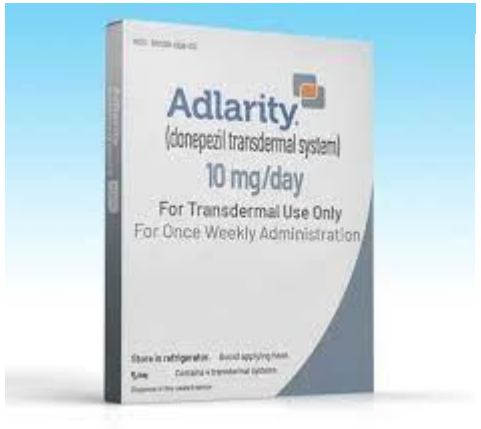
- Cardiovascular side effects: bradycardia, atrioventricular block, arrhythmias and hypertension

Warnings/Precautions

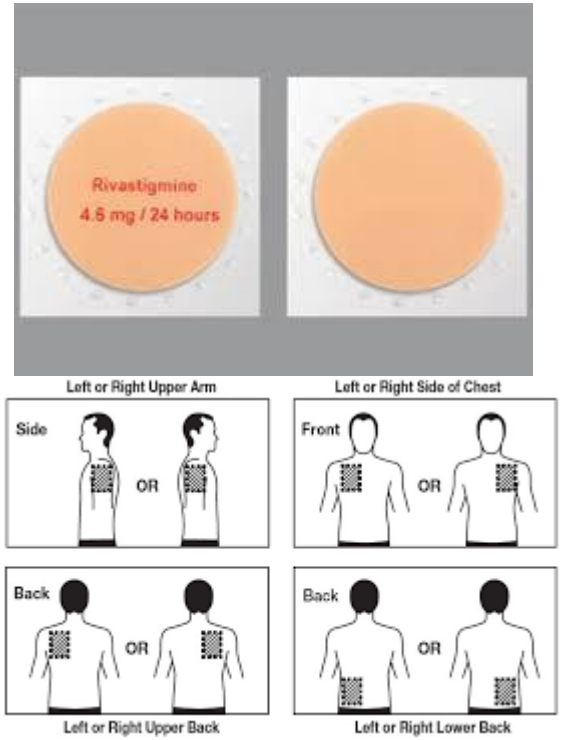
- **CNS depression:** May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks that require mental alertness (eg, operating machinery or driving).

- **Extrapyramidal effects:** May exacerbate or induce extrapyramidal symptoms; worsening of symptoms (eg, tremor) in patients with Parkinson disease has been observed.

Patch administration



I. Approved by FDA in March 2022
II. Applied weekly to the back, thigh, or buttocks
III. Use within 24 hours of removing from the refrigerator
IV. Press firmly for 30 seconds
V. Rotate patch sites weekly



Daily use
Avoid reapplication to same spot of skin for 14 days

Galantamine

- Indicated for the symptomatic treatment of mild to moderate AD.

- Galantamine is rapidly and completely absorbed, reaches peak serum levels in less than 2 hours, and has a half-life of approximately 5 hours.

- Dosage form:
  - Tab: 4mg, 8mg & 12mg ER tablet: 8mg, 16 mg & 24mg

  - Solution 4mg/ml: If using oral solution, mix dose with 3 to 4 ounces of any nonalcoholic beverage; mix well and drink immediately.

Galantamine dosing

- 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 (extended release tablet)
  - **Maintenance dose:** 8-12 mg twice a day (tablet, oral solution) 16-24 mg (extended release tablet)
  - If therapy is interrupted for ≥3 days, restart at the lowest dose and increase to current dose.

Adverse effect

- Associated with cholinergic activity and include:
  - Nausea
  - Diarrhea
  - Vomiting
  - And anorexia
- Typically present during the dose escalation phases
- A dose titration interval of 4 weeks reduces the severity of adverse effects and increases tolerability.

Memantine

- Memantine is a noncompetitive NMDA receptor antagonist
- It is completely absorbed after oral administration, reaches peak serum concentrations in 3 to 8 hours.
- 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 dementia.

Memantine dosing & administration

Dosage form: Tab:

- Tablet: 5mg, 10 mg & 20 mg **solution:** 10mg/5ml
- Extended release cap: 7mg, 14mg, 21mg & 28mg

- 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 ER formulation given in weekly escalating doses of 7, 14, 21, and 28 mg daily.

- Can be taken with or without food.

- Can open extended-release capsule and sprinkle contents on applesauce for ease of administration

Adverse effect

- Common adverse effects include
  - Diarrhea
  - Insomnia
  - Dizziness
  - Headache
  - And hallucinations.

- Memantine may mitigate GI adverse effects associated with cholinesterase inhibitor therapy

Aducanumab

- Recombinant monoclonal antibody directed against amyloid beta.
- The US FDA has approved aducanumab for the treatment of mild AD using the accelerated approval pathway, based on the positive clinical results of one of the two pivotal phase III trials (the results in the other were negative) and aducanumab's effect on a surrogate endpoint of reducing amyloid beta plaques in the brain.

Controversy

- The approval of this medication has led to significant controversy given that the FDA scientific advisory panel had previously recommended against approval of aducanumab, and since the surrogate endpoint of reducing amyloid beta plaques is not yet established as predicting clinical benefit.
- Post-approval trials are required to verify the clinical benefit. As the first new therapy for AD since 2003, there is a great deal of excitement in the community, but this must be tempered by the lack of clarity in the clinical trials, the risk of adverse effects, and the monitoring requirements.

Patient selection

- Mild cognitive impairment or mild dementia

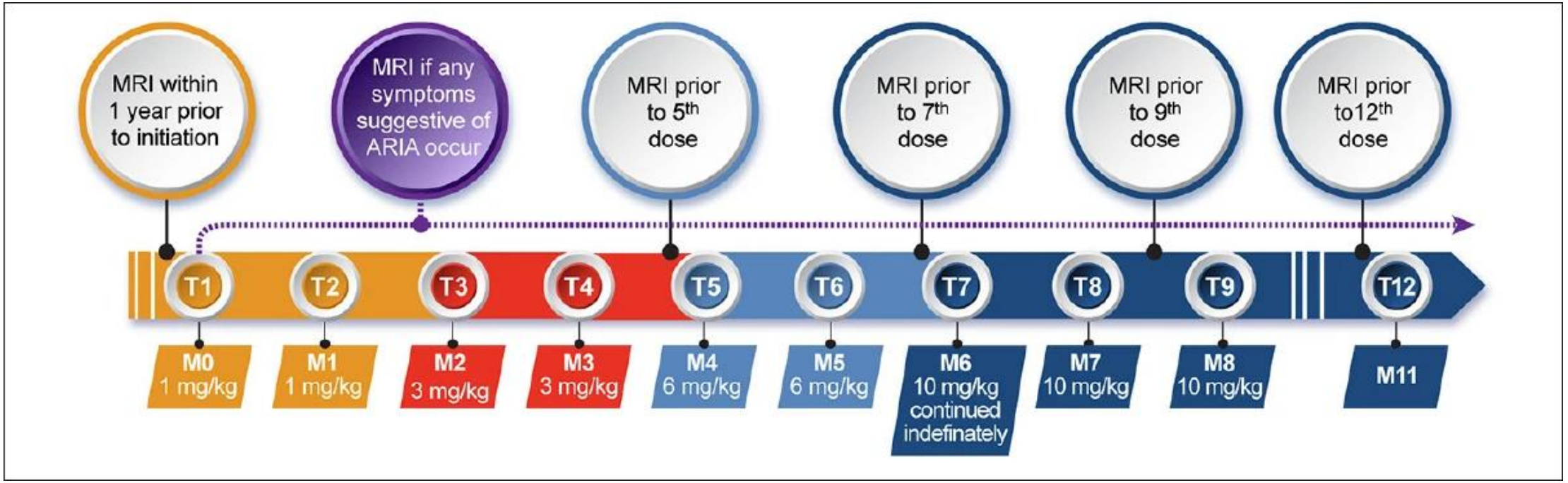
(MMSE) ≥21, Montreal Cognitive Assessment (MoCA) ≥17, or clinical dementia rating (CDR) 0.5 to 1 can be used.

- Documented amyloid pathology – Clinicians should limit use of aducanumab to those patients proven to be amyloid positive (by amyloid positron emission tomography [PET] scan or lumbar puncture), as was required in the clinical trials that evaluated the drug.
- No contraindications

Contraindication

- Cognitive decline attributed to non-AD pathologies (eg, lewy body disease, vascular dementia [VAD]) and down syndrome
- Hemorrhagic findings on brain MRI including >4 microhemorrhages, any areas of superficial siderosis, prior macrohemorrhage, and underlying brain lesion or vascular malformation. Other risk factors contraindicating treatment are anticoagulant or antiplatelet use (other than aspirin 81 mg daily), bleeding disorders, or any other condition leading to increased risk of central nervous system (CNS) hemorrhage.
- Pregnancy or breastfeeding

Dosing and administration



Aducanumab is administered by intravenous (IV) infusion every four weeks, typically in an infusion center.

Supplements

- Vitamin E — we feel that vitamin E (1000 international units twice daily) is a reasonable intervention in patients with mild to moderate AD.
- Modest benefit in delaying functional progression in patients with mild to moderate ad, with no measurable effect on cognitive performance.
- No advantage for the use of selegiline, which has more side effects and is more costly.

High-dose vitamin E supplementation has been inconsistently associated with an increase in all-cause mortality and also with heart failure in patients with cardiovascular disease. Such concerns have not been validated in the AD population, however; in the VA study described above, patients assigned to 2000 international units of vitamin E daily had a trend towards lower annual mortality compared with patients assigned to memantine, the combination, or placebo.

I. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. JAMA 2014; 311:33.

II. Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005; 142:37.

Supplements

- Omega-3 fatty acids – Observational studies have suggested a possible association between dietary intake of fish and omega-3 fatty acids and a lower risk of dementia.
- However, clinical trials have not supported a therapeutic role for omega-3 fatty acid supplementation in the treatment of AD.

Quinn JF, Raman R, Thomas RG, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA 2010; 304:1903.
Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. Arch Neurol 2006; 63:1402.

Supplements

- Vitamin B – Supplementation with B vitamins, in particular those that are involved in homocysteine metabolism, have been studied in patients with AD in hopes that they may demonstrate efficacy in preventing or slowing the progression of AD. An 18-month randomized trial of high-dose vitamin B-complex supplementation (folate, B6, B12) in 340 patients with mild to moderate AD found no beneficial effect on cognitive measures.

Aisen PS, Schneider LS, Sano M, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA 2008; 300:1774.

Therapies with unproven benefit

- Estrogen replacement
- Antiinflammatory drugs (NSAIDs)
- Ginkgo biloba

I. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003; 289:2651.
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VII. Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev 2009; :CD003120.
VIII. Angell M, Kassirer JP. Alternative medicine--the risks of untested and unregulated remedies. N Engl J Med 1998; 339:839.

Herbal medicine

- Lavandula angustifolia
- Ginkgo biloba
- Melissa officinalis
- Crocus sativus
- Ginseng
- Salvia miltiorrhiza
- and Magnolia officinalis

have been widely used for relief of symptoms of some neurological disorders.

Soheili M, Karimian M, Hamidi G, Salami M. Alzheimer's disease treatment: The share of herbal medicines. Iran J Basic Med Sci. 2021 Feb;24(2):123-135.

Take home message:

- No cure exists, although drugs may reduce AD symptoms for a time, the disease is eventually fatal.
- The benefit duration of each medication varies from 3 to 24 months
- The adverse effects typically present during the dose-escalation phases & ablated over time
- A longer dose titration interval (4 weeks) reduces the severity of adverse effects and increases tolerability.
- Memantine may mitigate GI adverse effects associated with cholinesterase inhibitor therapy

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2. Applied therapeutics : the clinical use of drugs. 2018.

3. Daniel p. Cholinesterase inhibitors in the treatment of Alzheimer disease. UpToDate 2020.