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Alzheimer's Disease

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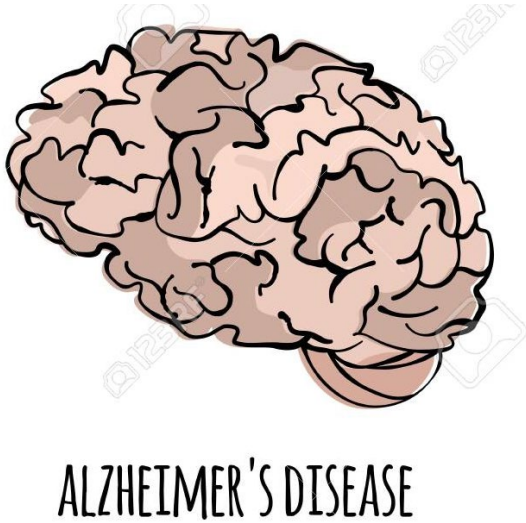
Objectives

1. Define Alzheimer's disease
2. Discuss epidemiology and pathophysiology of Alzheimer's disease
3. Describe the nation's financial cost on managing Alzheimer's disease
4. Discuss current non-pharmacological and pharmacological treatment for Alzheimer's symptoms
5. Discuss potential new therapeutic strategies for treatment of Alzheimer's disease

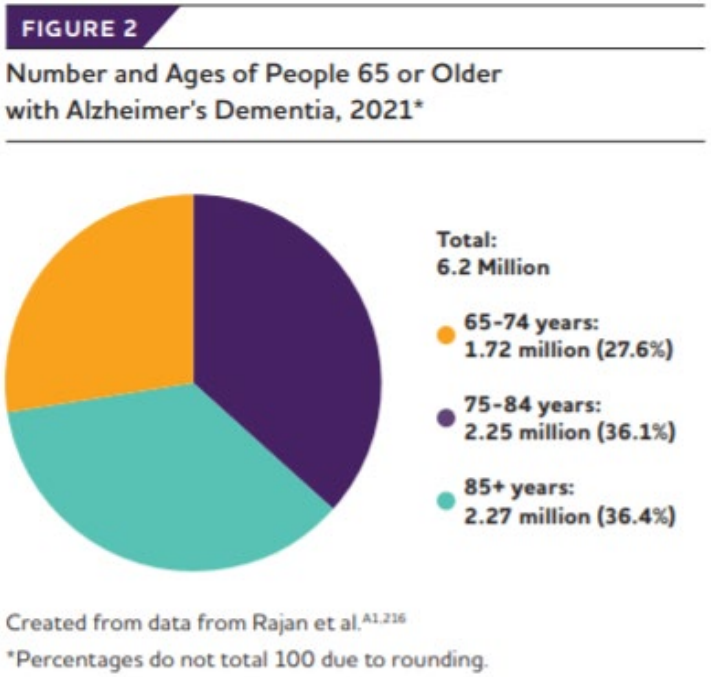
What is Alzheimer's Disease?

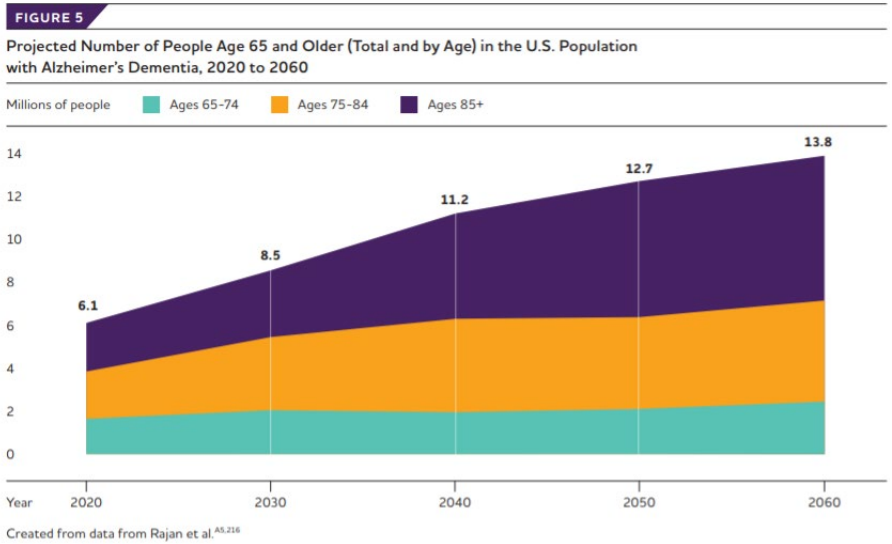


- Irreversible progressive disease that begins with mild memory loss and can progress to significant decline in intellectual, social, and functional abilities
- Most common type of dementia
- Symptoms arise as a result of damaged or destroyed neurons that are involved in cognitive function
- Alzheimer's disease is primarily a clinical diagnosis
- No cure for Alzheimer's disease – current therapies are aimed to treat symptoms of cognitive difficulties

Epidemiology

- Leading cause of disability and poor health in older adults and sixth leading cause of death in the US
- Approximately 6.2 million Americans aged 65 years and older are living with Alzheimer's disease
- Percentages of people with Alzheimer's disease increases with age
  - 65-74: 5.3%
  - 75-84: 13.8%
  - 85+: 34.6%
- About two-thirds of Americans with Alzheimer's are women



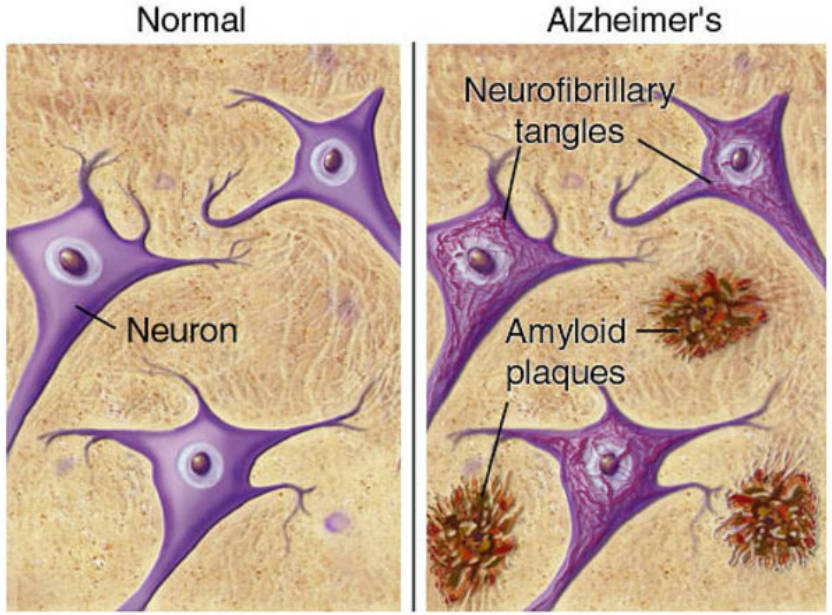


Financial Costs

- Alzheimer's and other dementia will cost the nation $355 billion
  - $239 billion in Medicare and Medicaid payments
- Expected to have more than 3-fold increase by 2050 in both government spending under Medicare, Medicaid, and out-of-pocket spending
- Patients with dementia have twice as many hospital stays per year than other older people

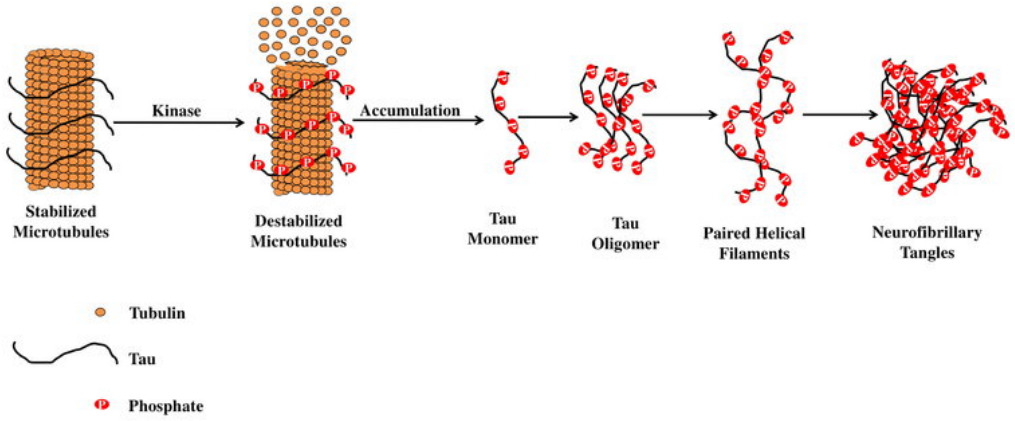
Pathophysiology: Amyloid Cascade Hypothesis

- Altered cleavage of amyloid precursor protein (APP) produces insoluble amyloid beta fibrils
- Insoluble amyloid beta fibrils aggregate into plaques
- Abnormal accumulation of amyloid beta plaques in various areas of the brain can lead to neurodegeneration
- Amyloid beta plaques interfere with neuron-to-neuron communication at synapses



Pathophysiology: Tau Hyperphosphorylation Hypothesis

- Tau is a microtubule-associated protein found in neuronal axons of the brain
- Role is to maintain microtubule structure and function, and regulate neuronal signaling
- Amyloid beta polymerization leads to activation of kinases → hyperphosphorylation of tau protein
- Causes neurofibrillary tangles which is responsible for loss of normal physiological function and achievement of neurotoxicity



Symptoms		
Cognitive	Non-Cognitive/Behavioral	Functional
• Memory loss • Disorientation • Reduced attention and ability for planning • Apraxia • Agnosia • Aphasia	• Depression • Hallucinations and delusions • Physical and verbal aggression • Uncooperativeness • Repetitive activities • Combativeness	• Inability for self-care and daily activities

Screening and Diagnosis

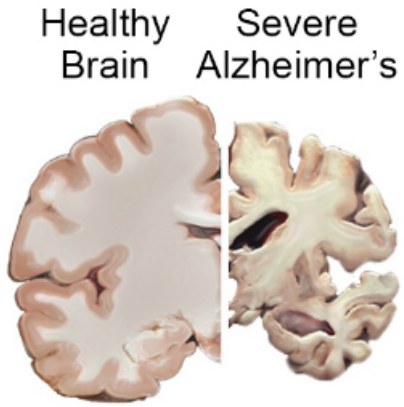
Mini-Mental State Exam (MMSE): Measures cognitive function for domains of memory, visuospatial, attention, language, and orientation – Max. score of 30 points

- Mild Dementia: 20-24
- Moderate Dementia: 13-20
- Severe Dementia: <12

- On average, MMSE score of a patient with Alzheimer's declines about 2-4 points every year

Diagnosis:

- Primarily clinical diagnosis
- Brain imaging: MRI or CT tests to rule out other conditions that may cause similar symptoms
- Future: brain imaging, CSF and other biomarkers to become more available for routine clinical use
  - Check for levels of beta-amyloid



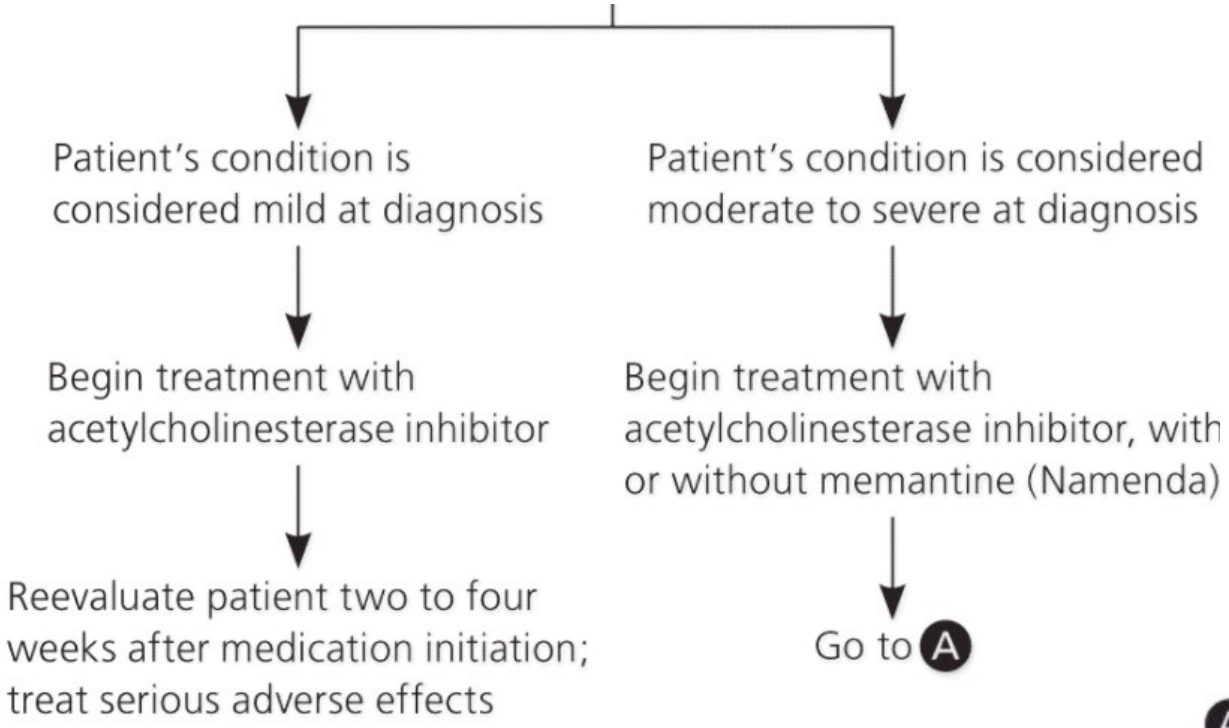
Drug-Induced Cognitive Impairment

Important to review and manage medications

Medications that can impair cognition:

- Benzodiazepines and other sedative hypnotics
- Anticholinergics
- Tricyclic antidepressants
- Diphenhydramine, antihistamines
- Opioid analgesics
- Antipsychotics
- Anticonvulsants

Treatment Algorithm

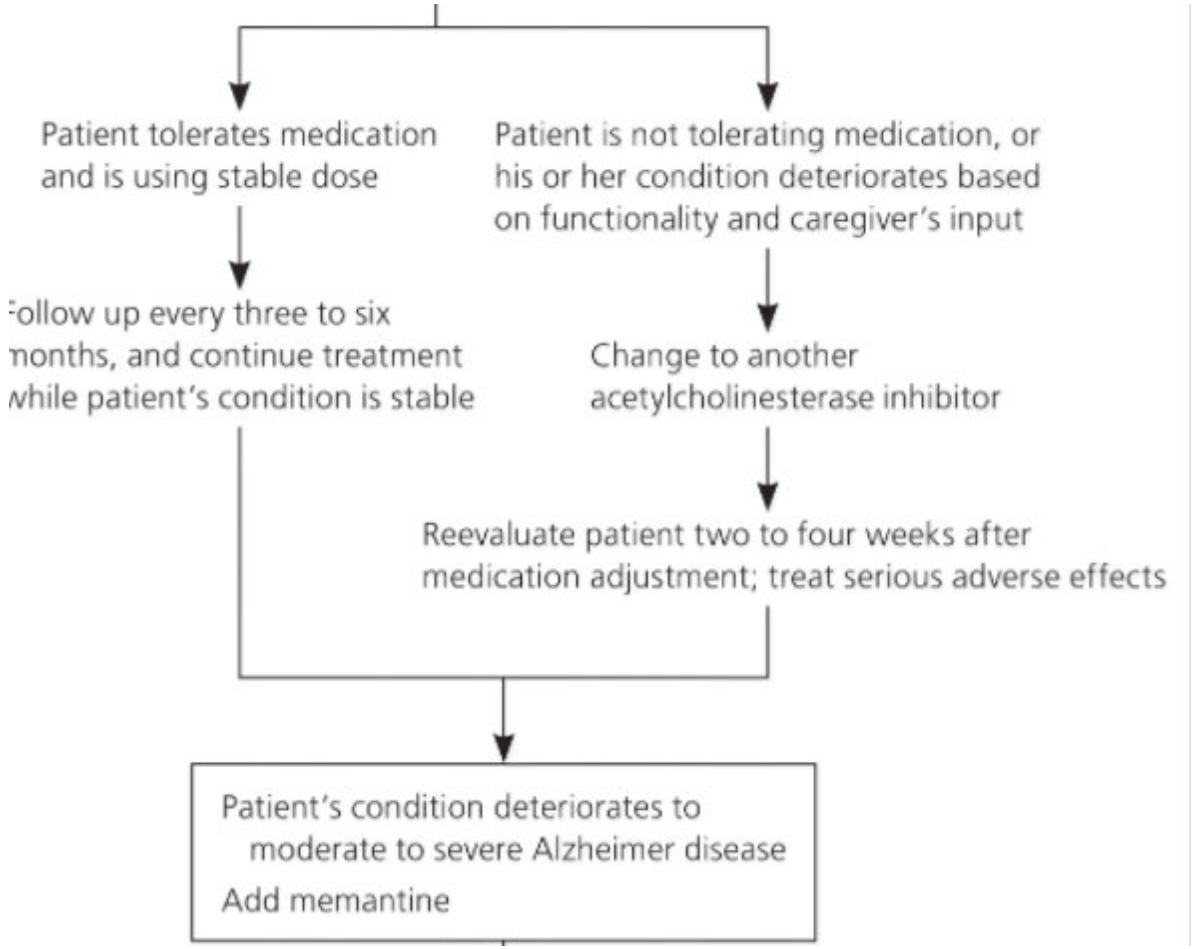


A Discontinue medications if:

- Patient does not adhere to treatment
- Deterioration continues
- Patient develops serious comorbid disease or is terminally ill
- Patient or caregiver chooses to discontinue treatment

2011 American Family Physician Treatment of Alzheimer's Disease

Treatment Algorithm for Mild Alzheimer's Disease (Continued)



2011 American Family Physician Treatment of Alzheimer's Disease

Treatment: Acetylcholinesterase Inhibitors

Mechanism of Action

- Inhibit cholinesterase enzyme from breaking down acetylcholine (ACh) → increases level of ACh
- Boosts cholinergic neurotransmission to compensate for loss of functioning brain cells

Side Effects

- Nausea, vomiting, diarrhea, muscle cramps, urinary incontinence, syncope, fatigue, bradycardia

Warnings

- Caution in patients with cardiac conduction conditions or history of falls/syncope
- Caution in patients with risk of ulcer disease: cholinesterase inhibitors may increase gastric acid secretion

Treatment: Acetylcholinesterase Inhibitors

Drug	Available Formulations	Dosing	Notes
Donepezil (Aricept)	ODT, tablet	5-10 mg daily	5 mg dose is effective N/V/D management: take with food or divide the dose to twice daily
Rivastigmine (Exelon)	Capsule, patch	**Oral:** 1.5 mg BID; Escalate to 3 mg BID after 4 weeks. May increase to 4.5 mg BID after 4 weeks and then to 6 mg BID after an additional 4 weeks **Patch:** Start 4.6 mg/24-hour patch daily. Escalate to 9.5 mg/24-hour patch daily after 1 month.	Approved for mild to moderate AD only Oral: Take with food; Less muscle cramping than other ChEIs PO → Patch: • Total daily dose >6mg: Switch to 4.6 mg/24-hour patch • Total daily dose 6-12mg: Switch to 9.5 mg/24-hour patch
Galantamine (Razadyne, Razadyne ER)	Tablet, capsule, solution	**IR:** Start 4 mg bid → After 4 weeks, 8 mg BID; may increase to 16 mg BID **ER:** Start 8 mg daily or 4 mg BID. Escalate to 16 mg daily or 8 mg BID after 4 weeks; may increase to 24 mg/day	Only approved for mild to moderate AD Initial dose is not therapeutic Renal impairment: Max dose – 16 mg/day ER: Effectiveness is not increased with 32 mg daily

Treatment: Memantine for Moderate to Severe Alzheimer's Disease

Mechanism of action	• NMDA receptor subtype antagonist of glutamate receptor → prevents over-activation of glutamate receptors
Dosing	• Initial: 5 mg daily for 1 week • Escalation: 5 mg BID x 1 week → 5 mg and 10 mg in separate doses x 1 week → 10 mg BID
Side effects	• Headache, dizziness, sedation, agitation, constipation
Monitoring	• Evaluate after 2-4 weeks of initial therapy for adverse effects • Evaluate after 3-6 months for efficacy • Evaluate every 6 months thereafter for assessment of disease symptom progression
Notes	• Prescribed as monotherapy or adjunct treatment to donepezil • Severe renal impairment (CrCl <30 ml/min): 5 mg BID is recommended

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Management of Behavioral Symptoms:

Behavioral Symptom	Non-Pharmacological Intervention
Sleep disturbances	Stimulation during the day Reduce noise and stimulation at night Sleep hygiene practices
Irritability/agitation	Breakdown and simplify tasks Redirect
Wandering	Provide safe places to wander Exercise Enroll patient in MedicAlert + Safe Return
Mood disorders	Exercise
Apathy	Stimulation and activities Simple tasks
Psychotic symptoms	Distraction rather than confrontation

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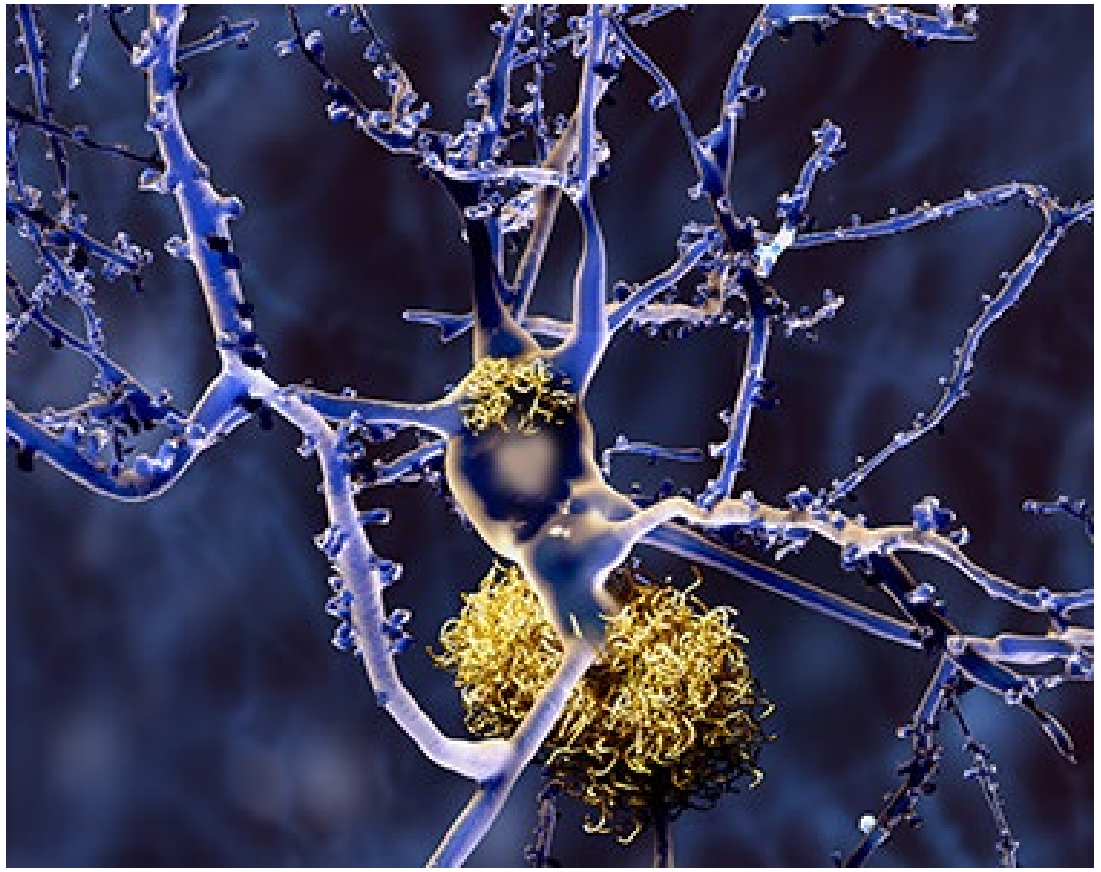
Management of Behavioral Symptoms

- No FDA approved psychotropic medications for use in patients with Alzheimer's Disease

Drug Class	Symptoms	Notes
Benzodiazepines	May be used for anxiety, insomnia, and acute agitated behaviors	Risk of falls, confusion, and worsened memory impairment Avoid if possible, but can be useful short term
Antidepressants	Depressive symptoms	SSRIs: sweating, tremors, nervousness, dizziness Tricyclics: full therapeutic trial requires at least 4-8 weeks
Atypical Antipsychotic Agents	Psychotic and aggressive behaviors	Current research supports risperidone use in low doses (1mg/day)
Mood stabilizers (Carbamazepine or Valproate)	Control delusions, hallucinations, and severe agitation/combativeness	BBW Valproate: pancreatitis, hepatotoxicity

Aducanumab (Biogen's Aduhelm)

- Amyloid beta-directed antibody
- First treatment to target underlying pathophysiology of Alzheimer's disease
- All evaluated studies showed consistent reduction in amyloid plaque levels
  - However, only one of two phase 3 clinical trials met the primary endpoint
- Currently under FDA accelerated approval pathway where company must verify clinical benefit in a post-approval trial
  - Needs to reflect surrogate endpoint: Reduction of amyloid beta plaque



Biogen's Aduhelm: Phase 3 Studies – EMERGE and ENGAGE Trials

- Enrollment: 1643 participants (EMERGE); 1653 participants (ENGAGE)
  - Mean age: 70 with MCI and early AD
- Both studies were identical, 18-month, randomized, double-blind, placebo-controlled Phase 3 studies
  - Dosing regimen: Low dose, high dose, and placebo; randomized 1:1:1
- Primary endpoint: Clinical Dementia Rating-Sum of Boxes (CDR-SB) at 18 months

Prespecified primary and secondary endpoints at Week 78

	EMERGE			ENGAGE		
	Placebo decline (n=548)	Difference vs. placebo (%)[a] p-value		Placebo decline (n=545)	Difference vs. placebo (%)[a] p-value[b]	
		Low dose (n=543)	High dose (n=547)		Low dose (n=547)	High dose (n=555)
CDR-SB	1.74	**-0.26** (-15%) 0.0901	**-0.39** (-22%) 0.0120	1.56	**-0.18** (-12%) 0.2250	**0.03** (2%) 0.8330
MMSE	-3.3	**-0.1** (3%) 0.7578	**0.6** (-18%) 0.0493	-3.5	**0.2** (-6%) 0.4795	**-0.1** (3%) 0.8106

Biogen's Aduhelm: Phase 3 Studies Summary

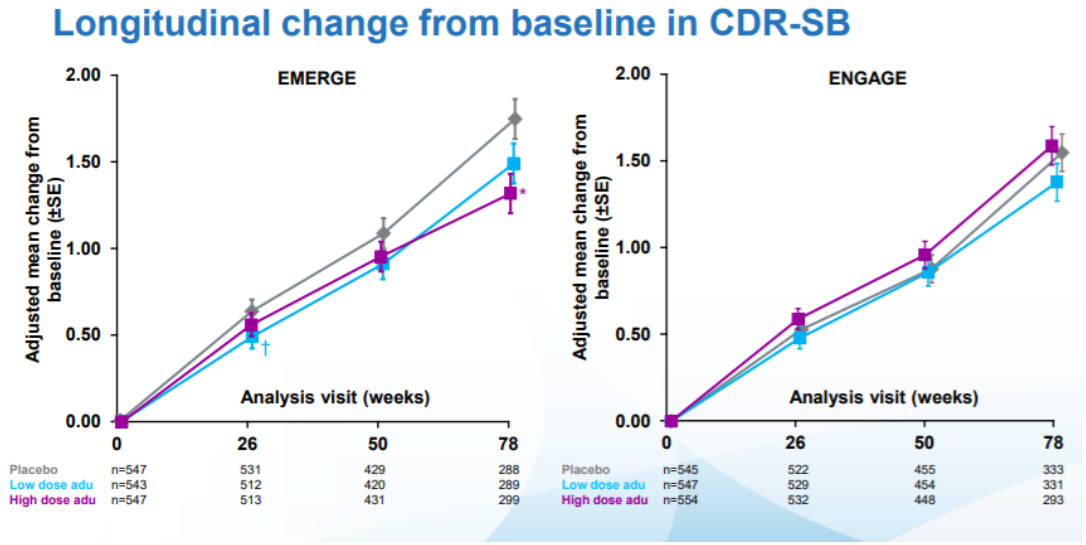
EMERGE trial: Met primary endpoint

- High dose (10mg/kg) aducanumab reduced clinical decline
- 22% improvement on the clinical dementia scale over placebo after 78 weeks

ENGAGE trial: Did not meet primary endpoint

- No reduction in clinical decline
- Possible explanation for results: More outliers (Individuals who had rapid decline)

Both trials: Most common adverse effects were headache and edema



Aducanumab (Aduhelm)

Mechanism of action

- Immunoglobulin gamma 1 (IgG1) monoclonal antibody that is directed against the accumulation of amyloid-beta plaques to reduce levels in the brain

Dosing and Administration

- Titration required for treatment initiation
- Maintenance: 10 mg/kg IV infusion over one hour every four weeks
- Dilution in 100 mL of 0.9% Sodium Chloride Injection, USP, is required prior to administration

Monitoring

- MRI prior to initiating treatment and prior to the 7th infusion (First dose of 10mg/kg)
- Monitor for hemorrhages, falls, headache, and edema

Cost of Aduhelm

- List price: $56,000 per year
- Institute for Clinical and Economic Review (ICER): Aducanumab may have a major negative effect on reducing health inequities
- Medicare generally does not cover for amyloid PET scans
- For the medication to be deemed cost-effective by ICER, the list price needs to be reduced by at least 85%
  - Health-benefit price: $3,000-$8,4000 per year

Conclusion

- There is currently no treatment for Alzheimer's disease that will slow down or prevent the progression of the disease
- Anticholinesterase inhibitors and memantine are used to treat symptoms and help retain cognitive function
- Aduhelm is the first treatment drug to target the underlying pathophysiology of Alzheimer's disease currently under FDA's accelerated approval pathway

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