What's New in Alzheimer's Disease

A presentation for HealthTrust Members
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Learning Objectives

- Pharmacist and Nurse Objectives
  - Recall current treatment modalities for Alzheimer's disease (AD)
  - Recognize findings in the current literature on emerging therapies for Alzheimer's disease management
  - Identify potential benefits and risks of new therapies for Alzheimer's disease

Learning Objectives

- Technician Objectives
  - Define dementia and Alzheimer's disease (AD)
  - Identify medications for management of Alzheimer's disease
  - Recognize preparations and storage recommendations for Alzheimer's disease

Abbreviations

- ADL: activities of daily living
- MCI: mild cognitive impairment
- AD: Alzheimer's disease
- Aß: ß-amyloid
- MMSE: Mini-mental state exam
- ADAS-cog: Alzheimer's Disease Assessment Scale–Cognitive Subscale
- iADRS: Integrated Alzheimer's Disease Rating Scale
- ADCS-iADL: Alzheimer's Disease Cooperative Study – instrumental activities of daily living
- CDR: Clinical Dementia Rating Scale
- MRI: magnetic resonance imaging
- CSF: cerebrospinal fluid
- MOA: mechanism of action
- BID: twice daily
- CI: cholinesterase inhibitors
- ODT: oral disintegrating tablet
- IR: immediate release
- ER: extended release
- ADRs: adverse drug reactions
- TD: transdermal
- FDA: US Food and Drug Administration
- IV: intravenous
- ARIA: amyloid-related imaging abnormalities
- ARIA-E: amyloid-related imaging abnormality edema/effusion
- ARIA-H: amyloid-related imaging abnormality hemorrhage/hemosiderin
- PET: positron emission tomography
- ITT: intent-to-treat
- TIA: transient ischemic attack
- HIV: human immunodeficiency virus
- MMRM: mixed model repeated measures
- WAC: wholesale acquisition cost
- CMS: Centers for Medicare & Medicaid Services

Definitions

- **Mild cognitive impairment (MCI)**
  - Early stage of memory loss, does not interfere with most ADLs
  - About 15% progress to dementia each year
- **Dementia**
  - Diagnosed when cognitive impairment has become severe enough to compromise social and/or occupational functioning
- **Alzheimer's Disease (AD)**
  - Most common type of dementia

Hugo J, Ganguli M. *Clin Geriatr Med*. 2014;30(3):421-442.

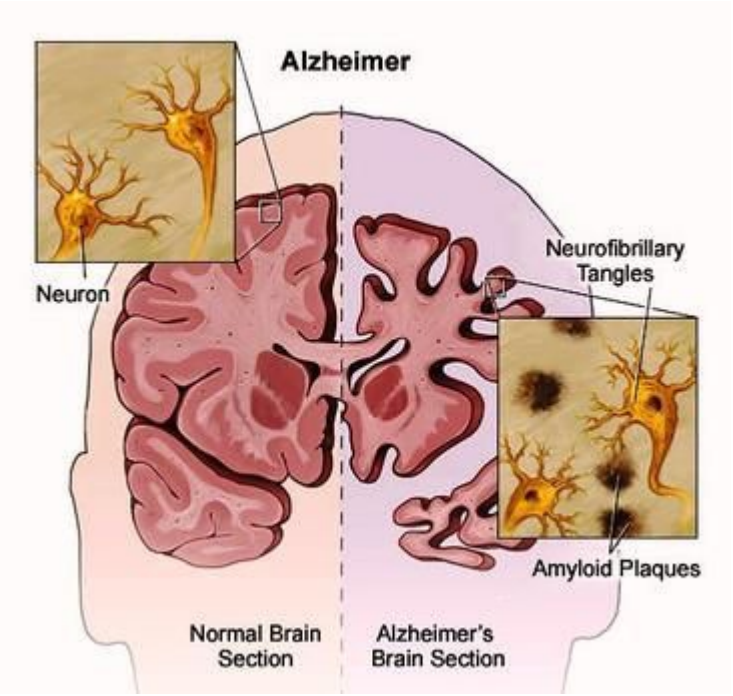
Epidemiology

- AD accounts for 60% to 80% of dementia cases
- Estimated 5.8 million Americans have AD
  - Expected to grow to 13.8 million by 2050
- 6th leading cause of death in the US
- Associated with significant healthcare cost and caregiver burden
  - In 2019, 16 million family members provided an estimated 18.6 billion hours of care
  - Total payments in 2020, estimated to be $305 billion

2020 Alzheimer's disease facts and figures. Alzheimer's Dement., 16: 391-460.

Pathological Hallmarks of AD

- **Accumulation of β-amyloid (Aβ) plaques**
  - Early event in AD - found in a widespread distribution throughout the cerebral cortex
  - Increases the likelihood of progression from MCI to dementia
  - Removal of amyloid plaques are hypothesized to slow clinical progression of AD
- **Tau-containing intracellular neurofibrillary tangles**
  - Occur initially in the medial temporal lobe
  - Potentially leads to progression of AD



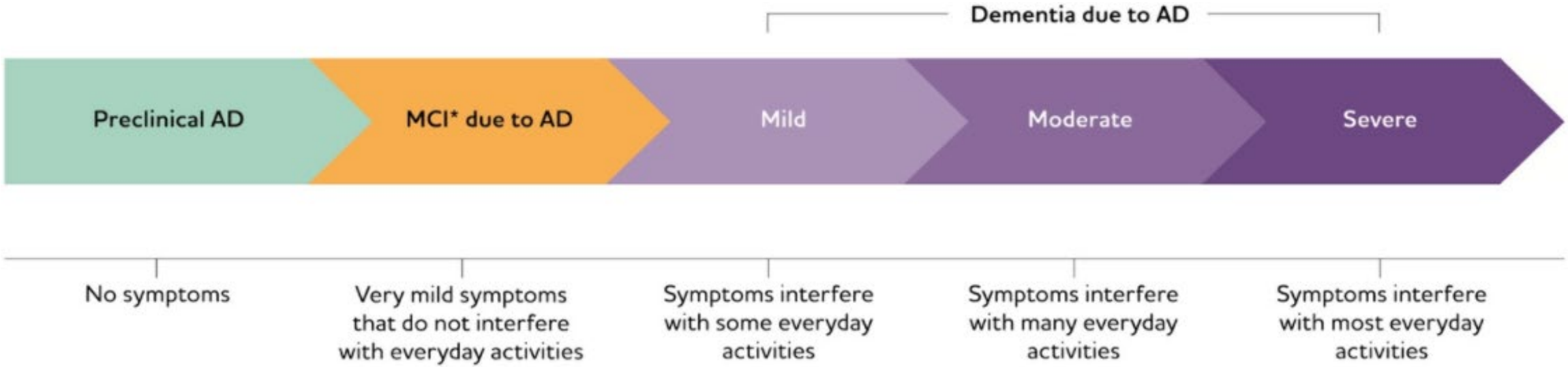
Knopman, D.S., Amieva, H., Petersen, R.C. *et al.* Alzheimer disease. *Nat Rev Dis Primers* **7,** 33 (2021).

Risk Factors

- **Age**
- **Genetic risk factors**
  - ApoE ε4 carriers
    - Increases the risk for dementia by 3–4 times in heterozygotes and by 12–15 times in homozygotes
- **Potentially modifiable risk factors**
  - Metabolic factors
  - Hearing loss
  - Traumatic brain injury
  - Alcohol abuse

2020 Alzheimer's disease facts and figures. Alzheimer's Dement., 16: 391-460.

Disease Progression



2020 Alzheimer's disease facts and figures. Alzheimer's Dement., 16: 391-460.

Screening Tools

- **Mini-Mental State Examination (MMSE)**
  - 11 questions assessing 5 domains
  - Score ranges 0 to 30
  - Categories:
    - Mild: 20-24
    - Moderate: 13-20
    - Severe: < 12
  - Limitations:
    - Education level & language can influence results
    - Copyrighted

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Hutchison LC, et al. *ASHP Publications* 2017.

Screening Tools

- **Mini-Cog**
  - 3 item recall and clock drawing test
  - Screening tool – cannot stage impairment
  - Culture, education, and language do not influence test results
- **SLUMS Examination**
  - 30-point, 11-item scale
  - Comparable to the MMSE

Mini-Cog©

Instructions for Administration & Scoring

ID: _____ Date: _____

Step 1: Three Word Registration

Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now." If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing).

The following and other word lists have been used in one or more clinical studies.[1-3] For repeated administrations, use of an alternative word list is recommended.

Version 1	Version 2	Version 3	Version 4	Version 5	Version 6
Banana	Leader	Village	River	Captain	Daughter
Sunrise	Season	Kitchen	Nation	Garden	Heaven
Chair	Table	Baby	Finger	Picture	Mountain

Step 2: Clock Drawing

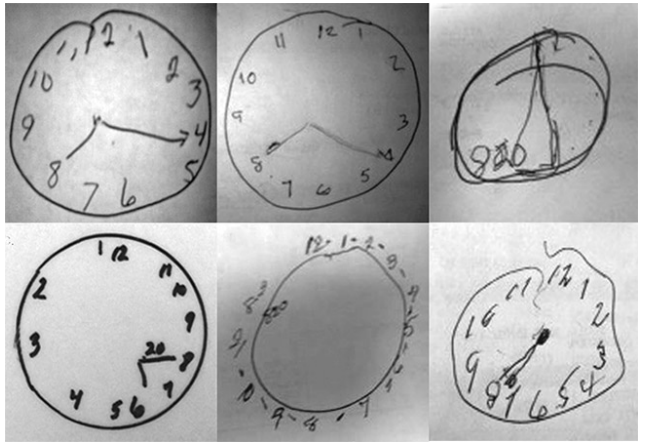
Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11."

Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to Step 3 if the clock is not complete within three minutes.

Step 3: Three Word Recall

Ask the person to recall the three words you stated in Step 1. Say: "What were the three words I asked you to remember?" Record the word list version number and the person's answers below.

Word List Version: _____ Person's Answers: _____ _____ _____



Hutchison LC, et al. *ASHP Publications* 2017.

Screening Tools in Clinical Trials

- **Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog)**
  - Gold standard of cognitive test
  - Total score range 0 to 70
    - Higher scores (≥18) indication greater cognitive impairment
    - 4 point change in 6 months is recognized as clinically important difference
- **Integrated Alzheimer's Disease Rating Scale (iADRS)**
  - Combines scores of ADAS-Cog and AD Cooperative Study – instrumental activities of daily living (ADCS-iADL)
- **Clinical Dementia Rating Scale (CDR)**
  - Interview of patient and caregiver
  - Based on a scale of 0–3: no dementia (CDR = 0), questionable dementia (CDR = 0.5), MCI (CDR = 1), moderate cognitive impairment (CDR = 2), and severe cognitive impairment (CDR = 3)

Hutchison LC, et al. *ASHP Publications* 2017.

Diagnosis

- Mental status examination
- Imaging
  - MRI is often used as a first step to exclude other causes of cognitive impairment
  - Aß-PET imaging
    - Aß-PET markers that allow the direct visualization of Aß plaque accumulation
    - Roughly correlates with the overall severity of cognitive impairment in AD, supporting the use of clinical severity as a proxy of AD pathology
- CSF biomarkers
  - Decreases in $A\beta_{42}$ and increases in phosphorylated tau (p-tau181)
- Definitive diagnosis made after death

2020 Alzheimer's disease facts and figures. Alzheimer's Dement., 16: 391-460.

Assessment- Technician

- Choose the best definitions of both dementia and AD
  - A. Dementia is an early stage of memory loss and AD is the most common type of dementia
  - B. Dementia is defined as memory loss that does not interfere with most ADLs and AD is an early form of dementia
  - C. Dementia is defined as cognitive impairment that has become severe enough to compromise social and/or occupational functioning and AD is the most common type of dementia
  - D. Dementia and AD is defined as an acutely disturbed state of mind characterized by restlessness, illusions, and incoherence of thought and speech

Management of AD

Classes of AD therapies

Cholinesterase inhibitors

NMDA receptor antagonist

Anti-amyloid therapy

Cholinesterase Inhibitors (CI)

- MOA: increase cholinergic transmission by inhibiting centrally-acting acetylcholinesterase at the synaptic cleft
- First-line therapy for mild to moderate AD
- Clinical trials
  - Slight improvement in cognitive function, behavior, and ADLs
  - No current evidence that CI are neuroprotective or disease modifying effects

Cholinesterase Inhibitors	Initial Dose	Formulations
Donepezil (Aricept®)	5 mg daily	Tablet, ODT
Galantamine (Razadyne®)	IR: 4 mg BID ER: 8 mg daily	ER capsule Oral solution Tablet
Rivastigmine (Exelon®)	Oral: 1.5 mg BID TD patch: 4.6 mg/24hour	Capsule Transdermal patch

Winslow BT, Onysko MK, Stob CM, Hazlewood KA. *Am Fam Physician*. 2011;83(12):1403-1412.

Cholinesterase Inhibitors

- Most common ADRs: GI (upset stomach, nausea, diarrhea, anorexia)
  - Dose-related
  - Resolves with time or dose reduction
- Significant ADRs: bradycardia and/or heart block in patients with or without a history of cardiac disease
  - Avoid in older adults with syncope due to bradycardia

Winslow BT, Onysko MK, Stob CM, Hazlewood KA. *Am Fam Physician*. 2011;83(12):1403-1412.

Memantine (Namenda®)

- MOA: NMDA receptor antagonist, prevents overstimulation of glutamate receptors to reduce neuronal excitotoxicity
- Place in therapy:
  - Second-line therapy for mild AD patients who do not tolerate CI's
  - Initial therapy for moderate/severe AD patients
  - Add-on therapy for moderate/severe AD patients on CI's
- Clinical trials:
  - Modest improvement in cognition and ability to do ADLs
  - May slow the clinical deterioration in moderate/severe AD
- Reported ADRs: dizziness, headache, constipation, somnolence
  - More tolerable than CI's
- Starting dose: IR: 5 mg daily, ER: 7 mg daily
- Formulations: ER capsule, oral solution, tablet, available in combination with donepezil

Winslow BT, Onysko MK, Stob CM, Hazlewood KA. *Am Fam Physician*. 2011;83(12):1403-1412.

Assessment- Technician

- Which of following is **NOT** a medication indicated for treatment of AD?
  - A. Rivastigmine
  - B. Galantamine
  - C. Donepezil
  - D. Selegiline

Pharmacological Approaches

Mild-Moderate AD

- Cholinesterase inhibitor (donepezil, rivastigmine, and galantamine)

Moderate-Severe AD

- Cholinesterase inhibitor and/or memantine

Winslow BT, Onysko MK, Stob CM, Hazlewood KA. *Am Fam Physician*. 2011;83(12):1403-1412.

Anti-Amyloid Therapies

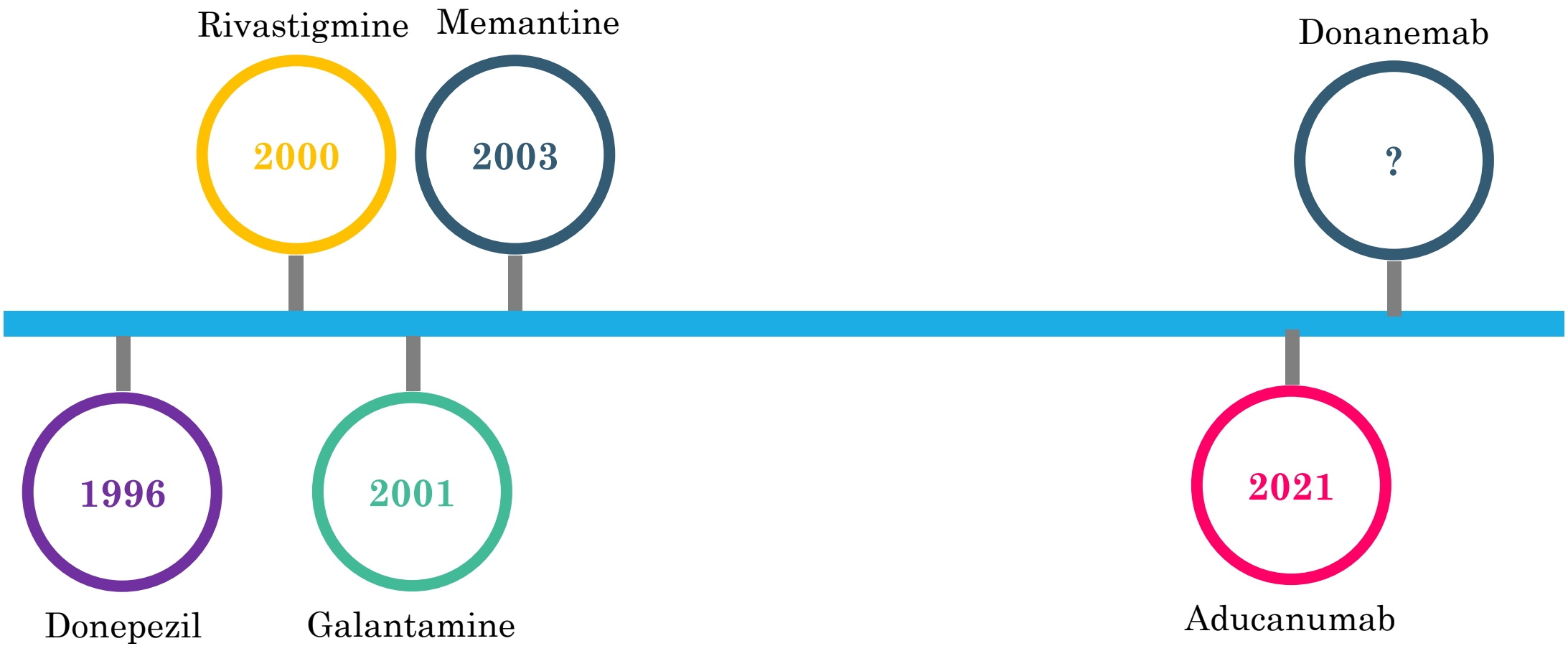
Aducanumab

- Monoclonal antibody
- FDA approved June 2021

Donanemab

- Monoclonal antibody
- Currently in phase 3 clinical trials

FDA Approval Timeline



Aducanumab (Aduhelm™)

- MOA: human, immunoglobulin gamma 1 monoclonal antibody directed against aggregated soluble and insoluble forms of Aß plaques in the brain
- Indication: treatment of AD, treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease
- First AD drug with potential disease-modifying mechanism
  - Targets the fundamental pathophysiology of the disease
  - Up until 2021, current therapies for AD could only improve cognitive symptoms of AD for a certain period of time

Aduhelm (aducanumab-avwa) [prescribing information]. Cambridge, MA: Biogen Inc; July 2021.

Aducanumab Administration

- Monitoring:
  - Prior to initiating treatment: obtain brain MRI (within one year)
  - During treatment: obtain MRI prior to the 7th and 12th infusions

IV Infusion every 4 weeks	Dose (given over 1 hour)
Infusion 1 and 2	1 mg/kg
Infusion 3 and 4	3 mg/kg
Infusion 5 and 6	6 mg/kg
Infusion 7 and beyond	10 mg/kg

Aduhelm (aducanumab-avwa) [prescribing information]. Cambridge, MA: Biogen Inc; July 2021.

Aducanumab Warnings

- **Amyloid-related imaging abnormalities (ARIA)**
  - Changes on MRI that are due to clearance of amyloid
  - Two types
    - Amyloid-related imaging abnormality edema/effusion (ARIA-E)
    - Amyloid-related imaging abnormality hemorrhage/hemosiderin deposition (ARIA-H)
  - ARIA-E is more commonly seen than ARIA-H during anti-amyloid treatment
    - Temporary swelling in areas of the brain
    - Typically does not cause symptoms and resolves over time
  - Enhanced clinical vigilance for ARIA is recommended during the first 8 doses
  - Symptoms: headache, confusion, dizziness, vision changes, or nausea
    - If patient experiences symptoms, MRI testing is indicated

Aduhelm (aducanumab-avwa) [prescribing information]. Cambridge, MA: Biogen Inc; July 2021.

Aducanumab Preparation

- Dosage forms
  - Single-dose vial (100 mg/mL)
    - 170 mg/1.7 mL
    - 300 mg/3 mL
- Dilution
  - Calculate dose, number of vials needed, and volume based on patient's actual body weight
  - Check that the solution is clear to opalescent and colorless to yellow solution
  - Using aseptic technique, remove cap from vial and insert syringe needle into vial through rubber stopper
  - Withdraw required volume from vial and add to an infusion bag of 100 mL of NS
  - Gently invert the infusion bag to mix completely

Aduhelm (aducanumab-avwa) [prescribing information]. Cambridge, MA: Biogen Inc; July 2021.

Aducanumab Storage

- Storage:
  - Store in original carton until use to protect from light
  - Store in a refrigerator at 2C to 8C
  - After dilution, immediate use is recommended
  - If not administered immediately, store the diluted solution refrigerated for up to 3 days or at room temperature for up to 12 hours

Aduhelm (aducanumab-avwa) [prescribing information]. Cambridge, MA: Biogen Inc; July 2021.

FDA Approval of Aducanumab

- Accelerated approval pathway
  - Drugs for a **serious or life-threatening illness** that provides a meaningful therapeutic advantage over existing treatments
    - Allows earlier access to the treatment for patients suffering from the disease
  - Based on a drug's effect on a **surrogate endpoint** that is reasonably likely to predict a clinical benefit
    - Surrogate endpoint: reduction of amyloid beta plaque in the brain
  - Required **post-approval trial** to verify that drug provides the expected clinical benefit
    - If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug

U.S. Food and Drug Administration. *FDA Grants Accelerated Approval for Alzheimer's Drug*. 2021 [online]

Aducanumab: Clinical Trials

- Objective: to evaluate the efficacy of monthly doses of aducanumab in slowing cognitive and functional impairment in patients with AD with mild cognitive impairment or mild dementia
- Efficacy was evaluated in two identically designed phase 3 trials
  - EMERGE (NCT02484547)
  - ENGAGE (NCT02477800)
  - **EMERGE and ENGAGE trials were terminated early based on futility analysis**

Biogen. ClinicalTrials.gov identifier: NCT02477800. Updated September 2, 2021. Accessed October 31, 2021.
Biogen. ClinicalTrials.gov identifier: NCT02484547. Updated September 2, 2021. Accessed October 31, 2021.

EMERGE and ENGAGE

- Trial design:
  - Double-blind, randomized, placebo-controlled studies
  - Intent-to-Treat (ITT) population was defined as all randomized participants who had received at least one dose of study treatment (aducanumab or placebo)
  - Planned duration: 78 weeks
- Recruitment:
  - EMERGE: 180 study locations in 13 countries
  - ENGAGE: 181 study locations in 14 countries

Biogen. ClinicalTrials.gov identifier: NCT02477800. Updated September 2, 2021. Accessed October 31, 2021.
Biogen. ClinicalTrials.gov identifier: NCT02484547. Updated September 2, 2021. Accessed October 31, 2021.

EMERGE and ENGAGE

- Key inclusion criteria
  - Age 50 to 85 years
  - Must meet all of the following clinical criteria for MCI due to AD or mild AD and must have:
    - Clinical Dementia Rating (CDR)-Global Score of 0.5.
    - MMSE score between 24 and 30
  - Must have a positive amyloid PET scan
  - Stable dose of AD medications for at least 8 weeks prior to screening

Biogen. ClinicalTrials.gov identifier: NCT02477800. Updated September 2, 2021. Accessed October 31, 2021.
Biogen. ClinicalTrials.gov identifier: NCT02484547. Updated September 2, 2021. Accessed October 31, 2021.

EMERGE and ENGAGE

- Key exclusion criteria
  - Any medical or neurological condition (other than AD) that might be a contributing cause of the subject's cognitive impairment
  - **Stroke, TIA, or unexplained loss of consciousness in the past 1 year**
  - Clinically significant unstable psychiatric illness in past 6 months
  - History of **unstable angina, myocardial infarction, advanced chronic heart failure, or clinically significant conduction abnormalities** within 1 year prior to screening
  - **Renal or hepatic impairment**
  - HIV infection
  - Significant systematic illness or infection in past 30 days
  - Relevant brain hemorrhage, bleeding disorder and cerebrovascular abnormalities
  - **Any contraindications to brain MRI or PET scans**
  - Alcohol or substance abuse in past 1 year
  - **Taking blood thinners (except for aspirin at a prophylactic dose or less)**

Biogen. ClinicalTrials.gov identifier: NCT02477800. Updated September 2, 2021. Accessed October 31, 2021.
Biogen. ClinicalTrials.gov identifier: NCT02484547. Updated September 2, 2021. Accessed October 31, 2021.

EMERGE and ENGAGE

- Interventions (randomized 1:1:1)
  - **Aducanumab**
    - Low dose (IV infusion every 4 weeks for 18 months)
      - 3 mg/kg for ApoE ε4 carriers
      - 6 mg/kg for non-carriers
    - High dose (IV infusion every 4 weeks for 18 months)
      - 10 mg/kg for non-carriers
      - 6 mg/kg for ApoE ε4 carriers (protocol was later modified - adjusted to 10 mg/kg)
  - **Placebo**
- Both studies included an initial titration period of up to 6 months to the maximum target dose
- Dose modification or discontinuation criteria for ARIA-E or ARIA-H occurrence

Aduhelm (aducanumab-avwa) [prescribing information]. Cambridge, MA: Biogen Inc; July 2021.

EMERGE and ENGAGE

- Primary outcome
  - Change from baseline in **Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB)** score at week 78

CDR Sum of Boxes Range	Staging Category
0	Normal
0.5-4.0	Questionable cognitive impairment
0.5-2.5	Questionable impairment
3.0-4.0	Very mild dementia
4.5-9.0	Mild dementia
9.5-15.5	Moderate dementia
16.0-18.0	Severe dementia

- Secondary outcomes
  - Change from baseline in score at week 78
    - **MMSE**
    - **ADAS-Cog 13**
    - Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory- Mild Cognitive Impairment Version (**ADCS-ADL-MCI**)

Biogen. ClinicalTrials.gov identifier: NCT02477800. Updated September 2, 2021. Accessed October 31, 2021.
Biogen. ClinicalTrials.gov identifier: NCT02484547. Updated September 2, 2021. Accessed October 31, 2021.

EMERGE and ENGAGE

- N = 1605
- Power = 90%
- Difference of 0.5 in change from baseline CDR-SB at week 78
  - Approximately 25% reduction assuming the placebo mean change in CDR-SB is 2 at week 78
- Statistical analysis
  - Mixed model repeated measures (MMRM) model
- Interim Analysis – Futility Assessment
  - Planned to occur after approximately 50% of patients completed week 78 visit

Biogen. ClinicalTrials.gov identifier: NCT02477800. Updated September 2, 2021. Accessed October 31, 2021.
Biogen. ClinicalTrials.gov identifier: NCT02484547. Updated September 2, 2021. Accessed October 31, 2021.

EMERGE and ENGAGE

- Results
  - EMERGE and ENGAGE trials were terminated early based on futility analysis
- EMERGE
  - 1,643 patients were randomized
  - 1,638 patients received study drug or placebo
- ENGAGE
  - 1,653 patients were randomized
  - 1,647 patients received study drug or placebo
- Study was terminated early based on futility
  - EMERGE: 49% completed week 78 visit
  - ENGAGE: 57% completed week 78 visit

Biogen. ClinicalTrials.gov identifier: NCT02477800. Updated September 2, 2021. Accessed October 31, 2021.
Biogen. ClinicalTrials.gov identifier: NCT02484547. Updated September 2, 2021. Accessed October 31, 2021.

EMERGE and ENGAGE

	EMERGE			ENGAGE		
Baseline demographics	**Placebo (n=548)**	**Low dose (n=543)**	**High dose (n=547)**	**Placebo (n=545)**	**Low dose (n=547)**	**High dose (n=555)**
Age in years, mean ± SD	70.8 ± 7.4	70.6 ± 7.5	70.6 ± 7.4	69.8 ± 7.7	70.4 ± 7.0	70.0 ± 7.7
Female, n (%)	290 (52.9%)	269 (49.5%)	284 (51.9%)	287 (51.9%)	284 (52.6%)	292 (52.6%)
White, n (%)	431 (78.6%)	432 (79.6%)	422 (77.1%)	413 (75.8%)	412 (75.3%)	413 (74.4%)
Education years, mean ± SD	14.5 ± 3.7	14.5 ± 3.6	14.5 ± 3.6	14.7 ± 3.7	14.6 ± 3.8	14.6 ± 3.7
ApoE ε4 carriers, n (%)	368 (67.2%)	362 (66.7%)	365 (66.7%)	376 (69.0%)	391 (71.5%)	378 (68.1%)
Baseline MMSE ≥24 – 26 ≥27 – 30	 296 (54.0%) 252 (46.0%)	 314 (57.8%) 228 (42.0%)	 296 (54.1%) 250 (45.7%)	 284 (52.1%) 258 (47.3%)	 282 (51.6%) 264 (48.3%)	 302 (54.4%) 252 (45.4%)

Biogen. ClinicalTrials.gov identifier: NCT02477800. Updated September 2, 2021. Accessed October 31, 2021.
Biogen. ClinicalTrials.gov identifier: NCT02484547. Updated September 2, 2021. Accessed October 31, 2021.

EMERGE and ENGAGE

- Treatment compliance
  - Due to dose modification for ARIA and early termination, some patients received fewer target doses
  - EMERGE
    - Compliance with study treatment was 96.2%
    - Percent of patients who received all 14 doses of 10 mg/kg
      - ApoE ε4 carriers: 9%
      - Non-carriers: 37.2%
  - ENGAGE
    - Compliance with study treatment was 96.4%
    - Percent of patients who received all 14 doses of 10 mg/kg
      - ApoE ε4 carriers: 6.1%
      - Non-carriers: 33.5%

Biogen. ClinicalTrials.gov identifier: NCT02477800. Updated September 2, 2021. Accessed October 31, 2021.
Biogen. ClinicalTrials.gov identifier: NCT02484547. Updated September 2, 2021. Accessed October 31, 2021.

EMERGE and ENGAGE

- Primary outcome: change from baseline in CDR-SB at Week 78

EMERGE	Adjusted mean	95% CI	Difference from placebo	% difference vs placebo	p-value
Placebo (N = 288)	1.74	1.513 – 1.963			
Low Dose (N = 290)	1.47	1.247 – 1.701	-0.26	-15%	0.0901
High Dose (N = 299)	1.35	1.124 – 1.573	-0.39	-22%	0.0120

ENGAGE	Adjusted mean	95% CI	Difference from placebo	% difference vs placebo	p-value
Placebo (N = 333)	1.56	1.344 – 1.768			
Low Dose (N = 331)	1.38	1.164 – 1.590	-0.18	-12%	0.2250
High Dose (N = 295)	1.59	1.370 – 1.805	0.03	2%	0.8330

Biogen. ClinicalTrials.gov identifier: NCT02477800. Updated September 2, 2021. Accessed October 31, 2021.
Biogen. ClinicalTrials.gov identifier: NCT02484547. Updated September 2, 2021. Accessed October 31, 2021.

EMERGE and ENGAGE

- Secondary outcomes

EMERGE	Change from baseline	Difference from placebo	% difference vs placebo	p-value
MMSE				
Placebo	-3.3			
Low Dose	-3.3	-0.1	3%	0.7578
High Dose	-2.7	0.6	-18%	0.0493
ADAS-Cog13				
Placebo	5.16			
Low Dose	4.46	-0.7	-14%	0.1962
High Dose	3.76	-1.4	-27%	0.0097
ADCS-ADL-MCI				
Placebo	-4.3			
Low Dose	-3.5	0.7	-16%	0.1515
High Dose	-2.5	1.7	-40%	0.0006

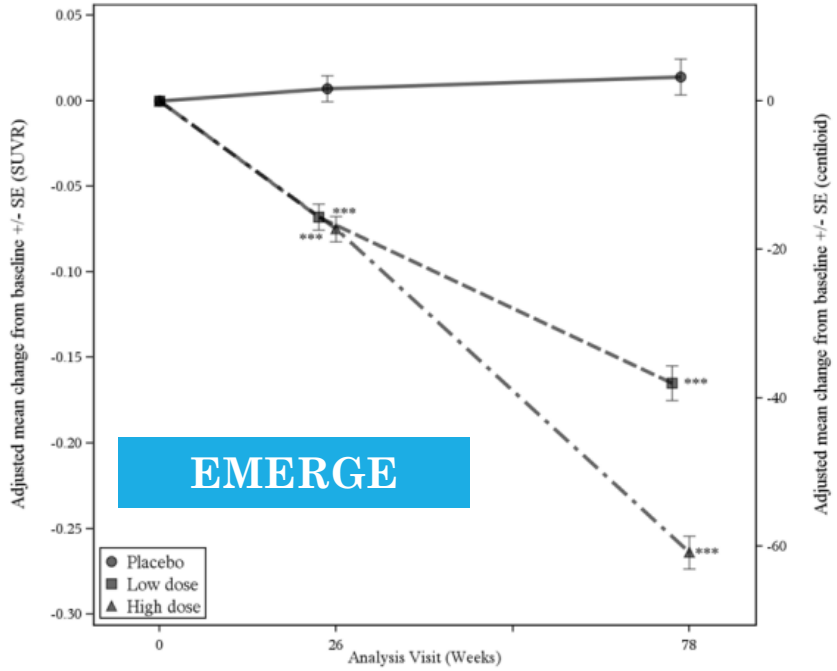
ENGAGE	Change from baseline	Difference from placebo	% difference vs placebo	p-value
MMSE				
Placebo	-3.5			
Low Dose	-3.3	0.2	-6%	0.4795
High Dose	-3.6	-0.1	3%	0.8106
ADAS-Cog13				
Placebo	5.14			
Low Dose	4.558	-0.583	-11%	0.2536
High Dose	4.552	-0.588	-11%	0.2578
ADCS-ADL-MCI				
Placebo	-3.8			
Low Dose	-3.1	0.7	-18%	0.1225
High Dose	-3.1	0.7	-18%	0.1506

Biogen. ClinicalTrials.gov identifier: NCT02477800. Updated September 2, 2021. Accessed October 31, 2021.
Biogen. ClinicalTrials.gov identifier: NCT02484547. Updated September 2, 2021. Accessed October 31, 2021.

EMERGE and ENGAGE

- Reduction in amyloid beta plaque

Figure 1: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 1

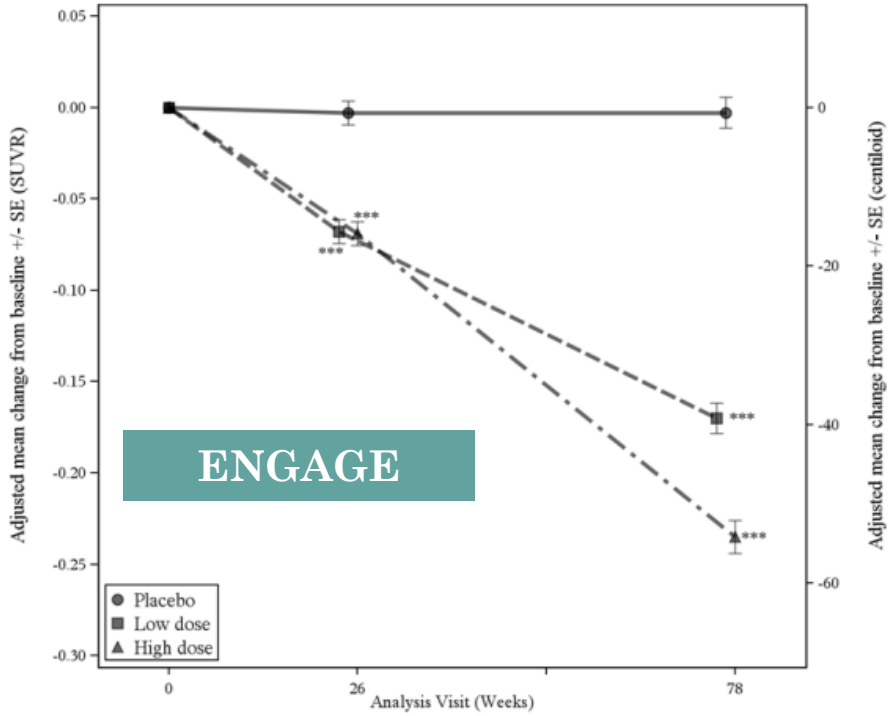


Number of subjects

Placebo	159	129	93
Low dose	159	129	100
High dose	170	138	109

*** p<0.001

Figure 3: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 2



Number of subjects

Placebo	204	168	124
Low dose	198	169	138
High dose	183	156	112

*** p<0.001

Aduhelm (aducanumab-avwa) [prescribing information]. Cambridge, MA: Biogen Inc; July 2021.

EMERGE and ENGAGE

Adverse reactions	EMERGE High dose N = 547	ENGAGE High dose N = 558	Placebo N = 1087
ARIA-E	33.5%	35.0%	3%
Headache	19.5%	20.6%	16%
ARIA-H	19.4%	18.3%	7%
Fall	13.4%	14.9%	12%
Diarrhea	7.7%	9.3%	7%

- Incidence of ARIA-E was highest in the high dose group and ApoE ε4 carriers
  - Most ARIA-E occurred during dose titration or shortly after attaining target dose
- Immunogenicity
  - 0.6% of patients developed neutralizing antibody in both studies

Biogen. ClinicalTrials.gov identifier: NCT02477800. Updated September 2, 2021. Accessed October 31, 2021.
Biogen. ClinicalTrials.gov identifier: NCT02484547. Updated September 2, 2021. Accessed October 31, 2021.

EMERGE and ENGAGE

- Conclusions
  - Two identically designed phase 3 clinical trials produced different results
    - In EMERGE, high dose aducanumab reduced clinical decline as measured by primary and secondary endpoints
    - In ENGAGE, aducanumab did not reduce clinical decline
  - Aducanumab successfully reduced brain amyloid plaque levels
  - In both trials, the most common adverse events was ARIA-E
- Limitations
  - Results applicable to AD with MCI
  - ARIA may have lead to unblinding
- Discussions
  - Results for placebo and low dose were consistent between two studies
  - Differences in number of doses in the high dose group is thought to be one of the major contributors
    - Patients in ENGAGE who had the opportunity for 14 doses of 10 mg/kg had clinical efficacy consistent with EMERGE
  - FDA approved based on plaques reductions, possible clinical effect, and urgent need of medicine in this area

Aducanumab Treatment Cost

- Aducanumab original WAC: approximately $56,000/year
  - As of January 1, 2022, WAC reduced to approximately $28,200/year
- Currently, coverage for the drug is determined at the local level by Medicare administrative contractors
- Centers for Medicare & Medicaid Services (CMS) proposed National Coverage Determination decision
  - Cover FDA approved monoclonal antibodies that target amyloid for the treatment of AD through coverage with evidence development (CED)
    - FDA-approved drugs would be covered only if they are enrolled in CMS approved clinical trials
  - Eligible to receive coverage of related services (PET scans if required by clinical trial)
  - Final decision expected April 11, 2022

CMS Proposes Medicare Coverage Policy for Monoclonal Antibodies Directed Against Amyloid for Treatment of Alzheimer's Disease | CMS. www.cms.gov. Accessed March 15, 2022.

Assessment- Pharmacist

- What is the mechanism of action of aducanumab?
  A. Removal of amyloid-beta plaques in the brain
  B. Inhibiting hydrolysis of acetylcholine
  C. Blocking NMDA receptors
  D. Blocking dopamine D2 receptors in the brain

Assessment- Technician

- Which diluent does aducanumab need to be mixed in?
  A. 0.9% sodium chloride
  B. 5% dextrose
  C. 0.45% sodium chloride 5% dextrose
  D. Lactated ringers

Assessment- Pharmacist

- A clinician plans to start treatment with aducanumab for a patient diagnosed with AD. What is the next best step in management?
  - A. Cerebrospinal fluid analysis
  - B. Obtain brain MRI
  - C. Obtain complete blood count
  - D. Start aducanumab

Assessment - Pharmacist

- Which of the following a symptom of ARIA?
  A. Nausea
  B. Dizziness
  C. Visual changes
  D. Headache
  E. All of the above

Emerging AD Therapies

Donanemab

- MOA: humanized IgG1 monoclonal antibody directed at the N-terminal Aß pyroglutamate epitope that is present only in established plaques
  - Induce clearance of existing Aß plaques with the intent of slowing the progressive decline in cognitive function associated with AD
- In June 2021, was granted Breakthrough Therapy designation by the FDA
  - Designed to expedite the development and review of drugs that are intended to treat a serious condition and may demonstrate substantial improvement over available therapy
    - Surrogate endpoints: endpoint that is considered reasonably likely to predict a clinical benefit
- Currently undergoing phase 3 trials

Lilly's donanemab receives U.S. FDA's Breakthrough Therapy designation for treatment of Alzheimer's disease | Eli Lilly and Company. investor.lilly.com. Accessed December 3, 2021.

Donanemab Clinical Trials

- TRAILBLAZER-ALZ
  - Objective: To evaluate the safety and efficacy of donanemab in patients with early symptomatic Alzheimer's disease
  - Trial Design:
    - Phase 2, multicenter, randomized, double-blind, placebo-controlled
    - Modified intention-to-treat principle
      - Included data from participants who had a baseline and at least one postbaseline iADRS score
    - Recruitment: 56 sites in US and Canada

Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384:1691-704.

TRAILBLAZER-ALZ

- Inclusion criteria:
  - Age 60 to 85 years
  - Early symptomatic AD (mild cognitive impairment due to AD)
  - **OR**
  - Mild AD with dementia
    - Mini-Mental State Examination (MMSE) score of 20 to 28
  - PET scan with evidence of pathologic tau deposition

- Exclusion criteria:
  - Tau standardized uptake value ratio > 1.46 or < 1.10
  - Received treatment with a stable dose of AChEI and/or memantine for less than 2 months prior
  - Contraindications to MRI
  - Serious or unstable CV, hepatic, renal, respiratory disease, or history of cancer within last 5 years
  - Presence of ARIA-E

Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384:1691-704.

TRAILBLAZER-ALZ

- Interventions
  - **Donanemab** 700mg for 3 doses then 1400 mg after
    - Administered IV every 4 weeks for up to 72 weeks
    - If amyloid plaque level was 11 to < 25 centiloids , the dose was lowered to 700mg
    - If amyloid plaque level was < 11 centiloids on any one scan or was 11 to less than 25 centiloids on two consecutive scans, donanemab was switched to placebo
    - If evidence of ARIA-E was seen on MRI within the first 3 doses of 700 mg – dose was not increased
  - **Placebo**

Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384:1691-704.

TRAILBLAZER-ALZ

- Primary Endpoint: change from baseline to 76 weeks in the score on the Integrated Alzheimer's Disease Rating Scale (iADRS)
  - Two components: ADAS-Cog13 and ADCS-iADL
  - Scores range from 0 to 144 with lower scores indicating a greater cognitive deficit and greater impairment of ADLs
- Secondary Endpoint: change from baseline in scores on Clinical Dementia Rating Scale (CDR), ADAS-Cog13 , ADCS-iADL, and MMSE and change in the amyloid and tau burden

Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384:1691-704.

TRAILBLAZER-ALZ

- Statistical Analysis
- Enrollment of 250 participants with 200 participants expected to complete the trial
  - Power = 84%
  - Decrease in iADRS score of approximately 6 points in the donanemab group and 12 points in placebo groups = 50% difference over 18 months
  - Primary and secondary outcomes were analyzed using MMRM
  - Fisher's exact test was used for categorical data
  - Covariance model analysis was used for postbaseline continuous data
  - Bayesian disease progression model was used to assess cognitive and functional decline

Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384:1691-704.

TRAILBLAZER-ALZ: Results

- Enrollment
  - 1955 patients assessed for eligibility
  - 257 were enrolled
  - 131 assigned to donanemab
    - 94 completed the trial
    - 37 discontinued trial (20 had adverse event)
  - 126 assigned to placebo
    - 93 completed the trial
    - 32 discontinued trial (6 had adverse event)

Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384:1691-704.

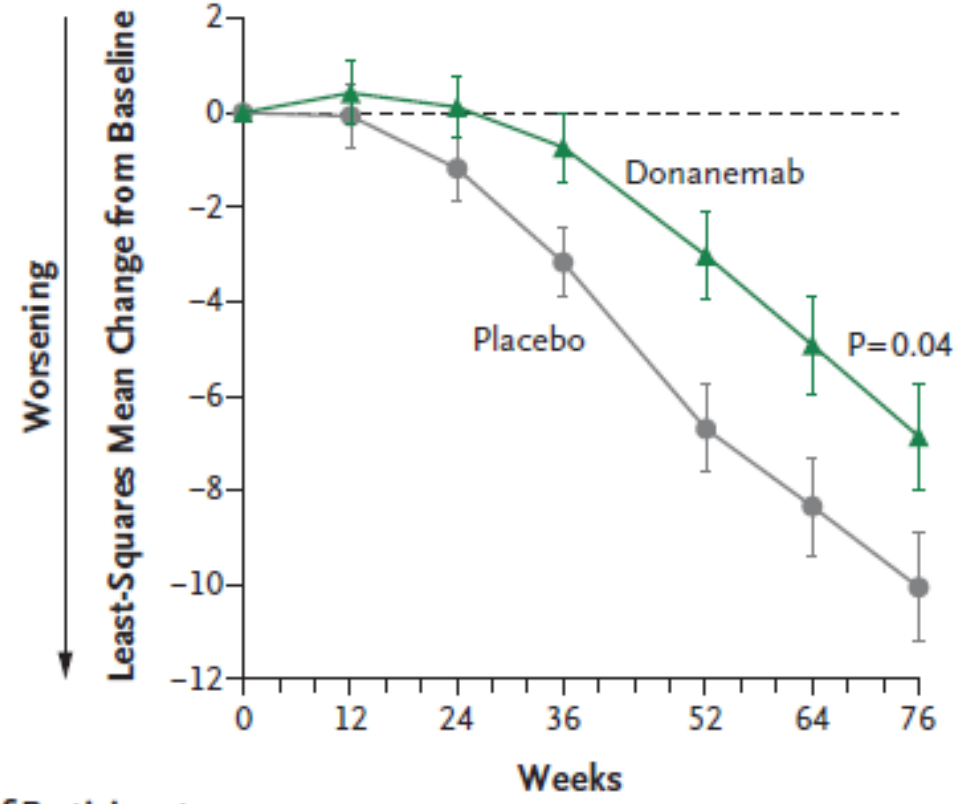
TRAILBLAZER-ALZ: Results

Baseline Demographics	Donanemab	Placebo	Total
Mean Age – yr	75.0	75.4	75.2
Female sex	51.9%	51.6%	53.3%
Race White	93.1%	96%	94.9%
ApoE ε4 carriers	72.5%	74.2%	73.0%
Use of CI	59.5%	58.7%	59.6%
iADRS score	106.2±13.0 (60.0-130.0)	105.9±13.2 (67.0-139.0)	106.2±13.0 (60.0-139.0)
MMSE score	23.6±3.1 (14.0-29.0)	23.7±2.9 (16.0 – 29.0)	23.5±3.1 (13.0 – 30.0)
Amyloid plaque level – centiloids	107.6 (41.0-251.4)	101.1 (38.7 – 225.2)	104.2 (38.7-251.4)
Tau load	0.47 (0.1-1.2)	0.46 (0.2-0.9)	0.46 (0.1-1.2)

Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384:1691-704.

TRAILBLAZER-ALZ: Results

A Primary Outcome: iADRS Score



No. of Participants

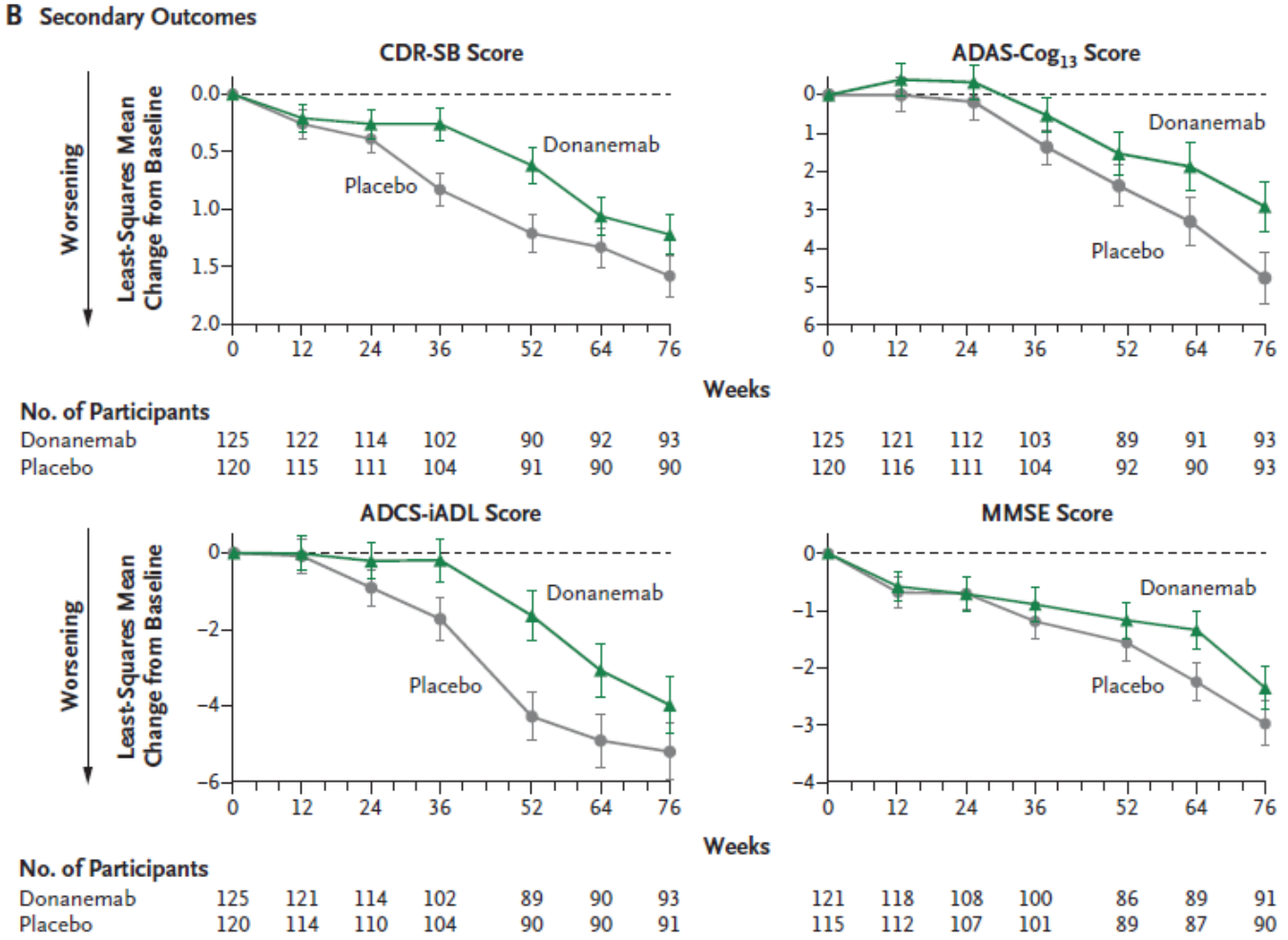
Donanemab	125	120	112	102	88	89	93
Placebo	120	113	110	103	90	90	91

Difference in Least-Squares Mean Change

	Donanemab vs. placebo	95% CI
	points	
Wk 36	2.44±0.96	0.55–4.33
Wk 52	3.67±1.26	1.19–6.15
Wk 64	3.42±1.42	0.63–6.21
Wk 76	3.20±1.56	0.12–6.27

Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384:1691-704.

TRAILBLAZER-ALZ: Results

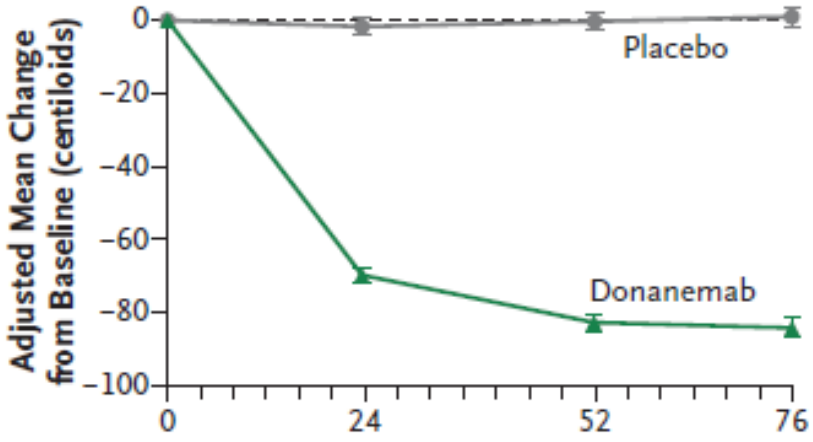


Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384:1691-704.

TRAILBLAZER-ALZ: Results

- **Biomarkers**
  - 76 weeks: 67.8% of donanemab patients had amyloid negative status
  - Percentage of patients who had sufficient lowering of the amyloid plaque level to switch to placebo infusion at 28 weeks = 27.4% and 56 weeks = 54.7%
  - No significant differences in global tau load

A Amyloid Plaque Level on Florbetapir PET



No. of Participants				
Donanemab	121	115	92	90
Placebo	112	111	91	91

	Difference in Adjusted Mean Change		Amyloid-Negative Status, Donanemab
	Donanemab vs. placebo	95% CI	
	centiloids		*no. (%)*
Wk 24	−67.83±3.16	−74.04 to −61.61	46 (40.0)
Wk 52	−82.30±3.41	−89.02 to −75.59	55 (59.8)
Wk 76	−85.06±3.87	−92.68 to −77.43	61 (67.8)

Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384:1691-704.

TRAILBLAZER-ALZ: Results

- **Adverse events**
  - Most cases of ARIA-E occurred at or by week 12
  - Antidrug antibodies were detected during the intervention period in approximately 90% of the participants who were treated with donanemab

Adverse events	Donanemab	Placebo	p-value
AE that lead to discontinuation of intervention	30.5%	7.2%	<0.001
AE that lead to discontinuation of trial	15.3%	4.8%	0.007
ARIA-E Symptomatic	26.7% 6.1%	0.8% 0.8%	<0.001
Infusion related reactions	7.6%	0%	0.002

Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384:1691-704.

TRAILBLAZER-ALZ

- Conclusions
  - Donanemab resulted in modestly less cognitive and functional decline than placebo in early symptomatic AD
  - ARIA was a common adverse event
- Limitations
  - Excluded patients with serious CV, hepatic, renal, respiratory disease, and history of cancer within last 5 years
  - Antidrug antibodies were developed by 90% of the donanemab group
  - Minimal clinically important difference on iADRS scale has not been established
- Discussion
  - Longer and larger trials are required to study the efficacy and safety of donanemab in early Alzheimer's disease
  - Currently undergoing phase 3 trial

Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384:1691-704.

Summary

	Aducanumab	Donanemab
MOA	monoclonal antibody directed against aggregated soluble and insoluble forms Aß plaques in the brain	monoclonal antibody directed at the N-terminal Aß pyroglutamate epitope that is present only in established plaques
Dosing	IV every 4 weeks Titration starting at 1 mg/kg with target dose 10 mg/kg	IV every 4 weeks 700 mg x 3 doses 1400mg after
Inclusion criteria	Age 50 to 85 years MCI due to AD or mild AD MMSE 24 to 30	Age 60 to 85 years MCI due to AD or mild AD MMSE 20 to 28
Trial Duration	78 weeks	76 weeks
Primary endpoints Difference vs placebo	CDR-SB EMERGE: -0.39 (p=0.012) ENGAGE: 0.03 (p=0.883)	iADRs 3.2 (p=0.04)
ARIA-E incidence	33.5 – 35.0 %	26.7%
FDA approved	Yes	No

The Future of Alzheimer's Disease

- Approval of aducanumab and other anti-amyloid therapies will open a new phase of research into AD
  - Provides with an opportunity to learn about AD pathogenesis
  - The role of biomarkers in clinical trials of dementia paves the way for new treatments
- In 2021, there were 126 agents in 152 trials assessing new therapies for AD
  - 28 treatments in Phase 3 trials, 74 in Phase 2, and 24 in Phase 1
  - Majority of drugs in trials (82.5%) target the underlying biology of AD with the intent of disease modification

Cummings, J, Lee, G, Zhong, K, et al. *Alzheimer's Dement*. 2021; 7:e12179.

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Thank you!

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