AD=Alzheimer's disease.

Accreditation and Acknowledgment

ACCME: Forefront Collaborative designates this activity for a maximum of 0.5 *AMA PRA Category 1 Credit*™; physicians should claim only the credit commensurate with the extent of their participation in the activity.

Forefront Collaborative is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The activity is provided by Forefront Collaborative and supported by an educational grant from Biogen.

AMA=American Medical Association. PRA=Physician's Recognition Award.

Alzheimer's Biopathology and Its Therapeutic Targeting

Introducing a Patient With MCI Due to AD

- 67-year-old man
- Retired; former high-level executive
- Presented with slowly progressive memory and word finding difficulties for three years
- He is independent in daily activities, although
  - It takes him longer to pay bills
  - He is more reliant on his calendar for remembering appointments according to his wife
- History of hypertension
- MMSE 27/30 (all memory) and CDR 0.5
- Medications: antihypertensives
- Brain MRI: subtle hippocampal atrophy
- Enrolled in IDEAS: florbetapir PET scan +

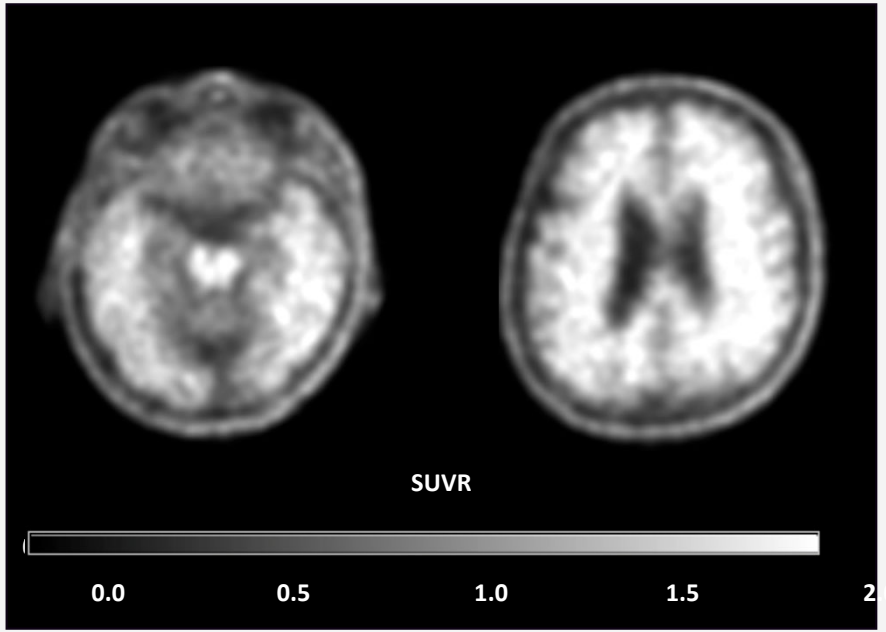


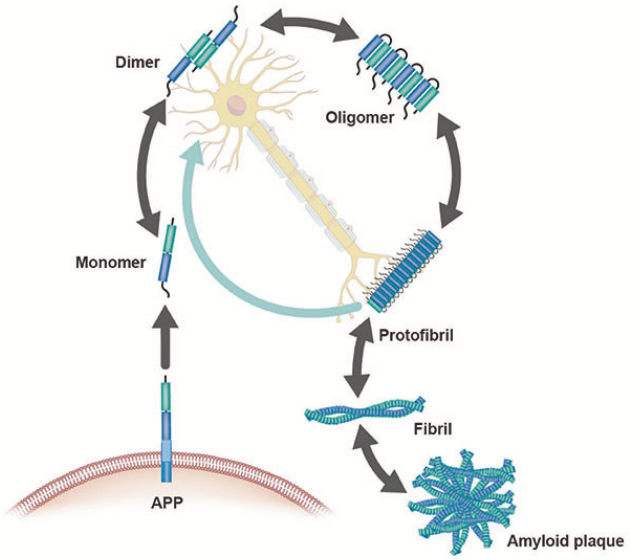
Image courtesy of Sharon J. Sha, MD, MS

CDR=Clinical Dementia Rating. IDEAS=Imaging Dementia—Evidence for Amyloid Scanning Study. MCI=mild cognitive impairment. MMSE=mini-mental state examination. MRI=magnetic resonance imaging. PET=positron emission tomography. SUVR=standardized uptake value ratio.

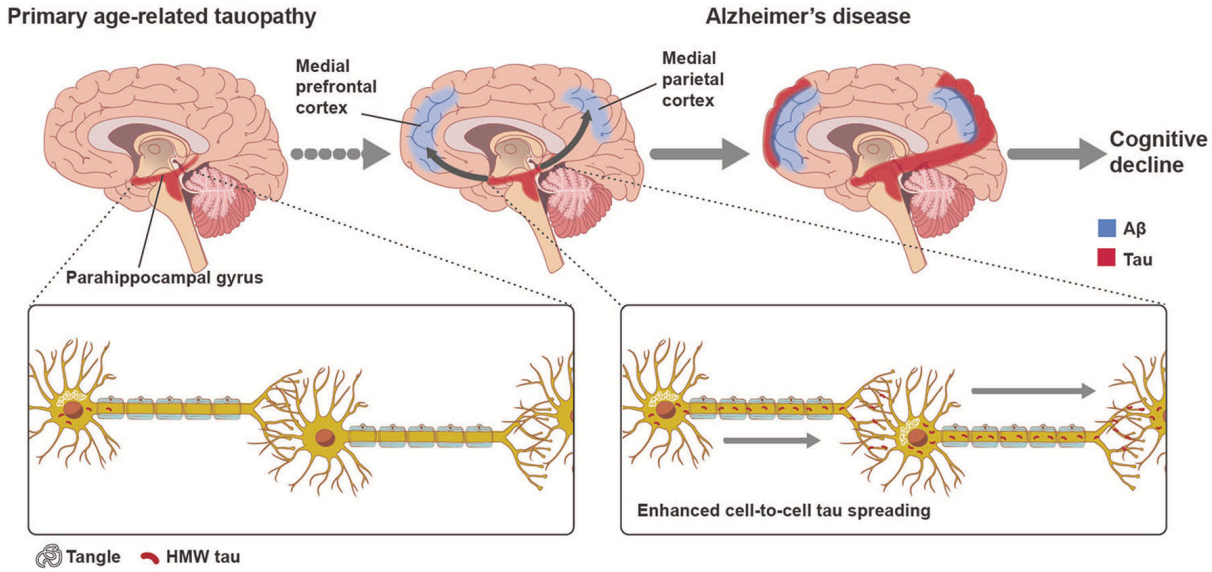
Hall JN, et al. *JAMA Neurol*. 2022; 79(1):87-89.

Amyloid-beta Plaques and Neurofibrillary (Tau) Tangles as Defining Hallmarks of AD (cont.)

Aβ Aggregation Species and Evidence of Reversible States: The Aβ Cycle



The Evidence-Driven Experimental Model of Aβ-tau Synergy

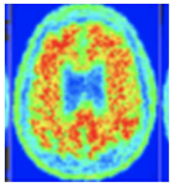


NIA-AA ATN Framework–Defining AD Biologically

A Aggregated Aβ representing neuritic amyloid plaques

- CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio
- Amyloid PET

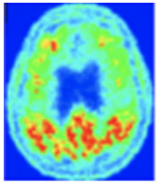
Amyloid PET



T Aggregated tau representing neurofibrillary tangles)

- CSF phosphorylated tau
- Tau PET

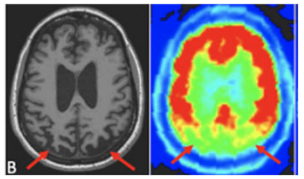
Tau PET



(N) Neurodegeneration or neuronal injury

- Anatomic MRI
- FDG PET
- CSF total tau

MRI FDG PET

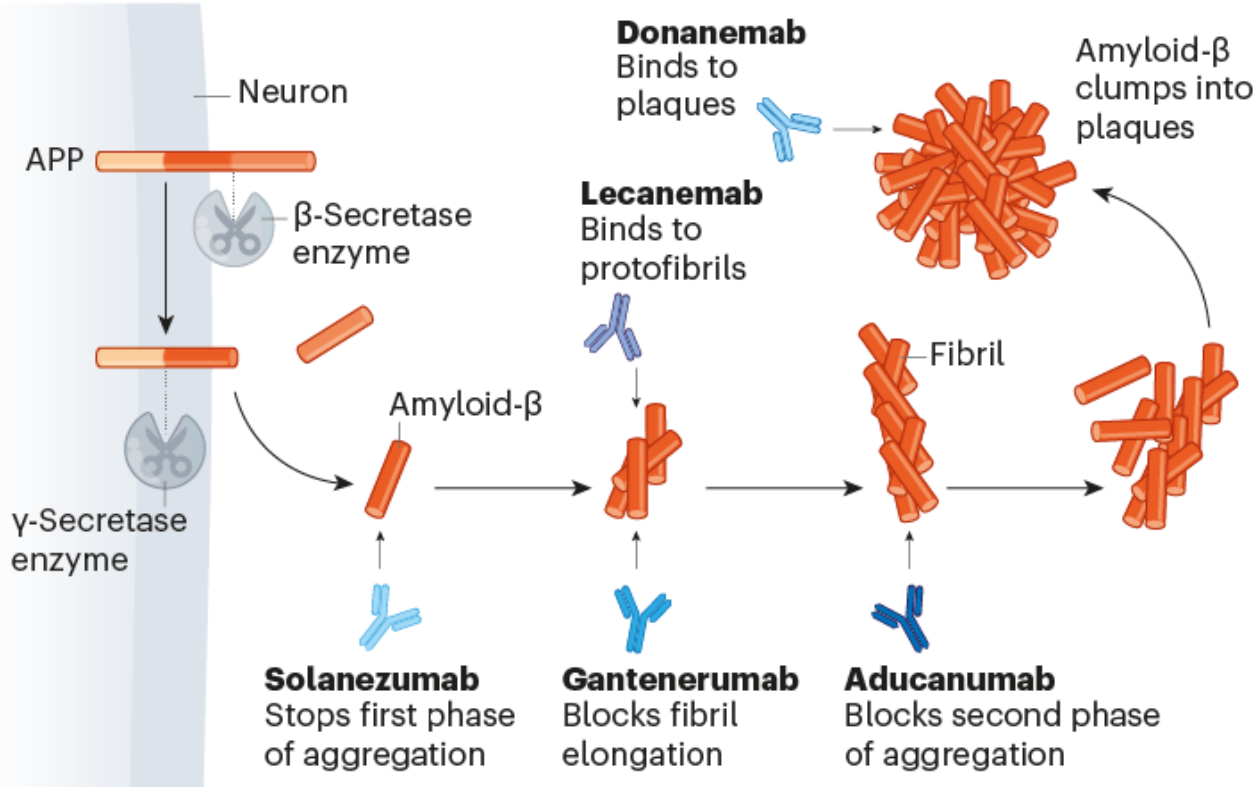


$A\beta_{40}$=40-amino acid form of beta amyloid. $A\beta_{42}$=42-amino acid form of beta amyloid. ATN=β amyloid deposition, pathologic tau, and neurodegeneration. CSF=cerebrospinal fluid. FDG=fluorodeoxyglucose. NIA-AA=National Institute on Aging – Alzheimer's Association.

1. Jack CR, et al. *Alz Dement*. 2018;14(4):535-562. 2. Dickerson B, Atri A. *Practical Neurology*. 2020;19(9):34-45.


New and Emerging
Treatment Landscape
in AD

Anti-amyloid Monoclonal Antibody (mAb) Treatment Under Investigation for AD



NOTE:

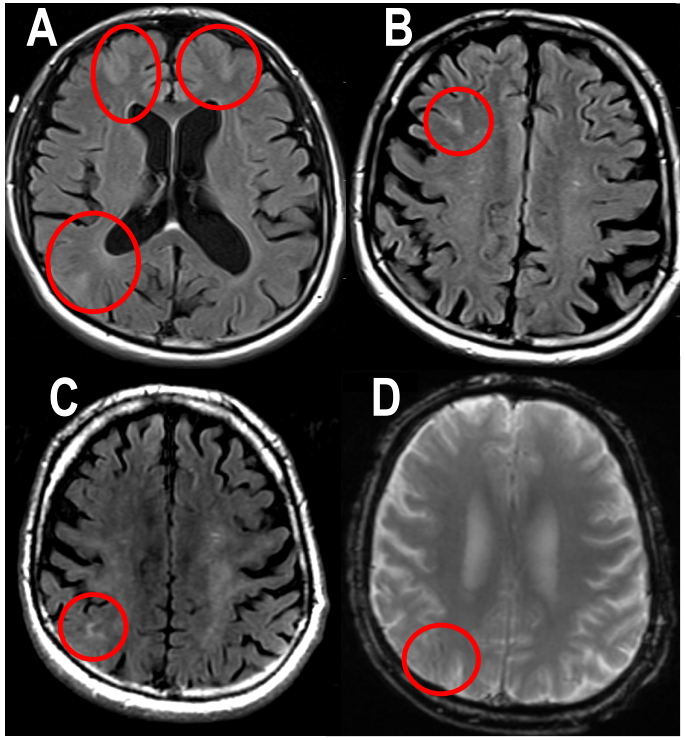
Donanemab, gantenerumab, lecanemab, and solanezumab are **not** FDA-approved.

Aducanumab received **accelerated** approval by the FDA for the treatment of MCI or mild dementia resulting from AD.

- Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s)

1. Nature.com website. Could drugs prevent Alzheimer's? These trials aim to find out. https://www.nature.com/articles/d41586-022-00651-0. Last updated March 9, 2022. Accessed April 22, 2022.
2. Drugs @ FDA website. Aducanumab Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s003lbl.pdf. Last updated July 2021. Accessed April 22, 2022.

Aducanumab: Side Effects Include ARIA-E

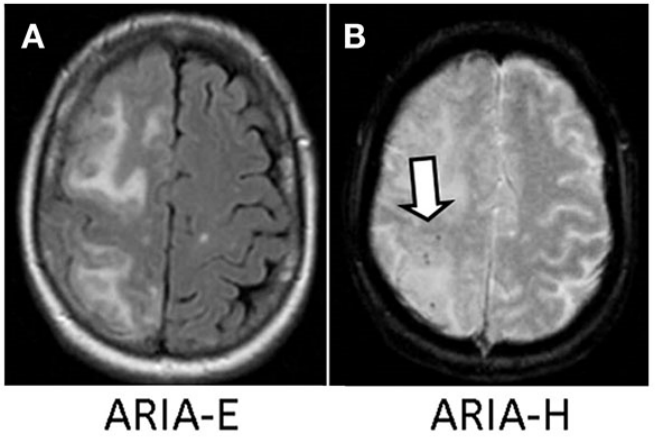


ARIA-E for 10 mg/kg: 35%

- 42% E4 carriers
- 20% noncarriers
- Usually within first 8 doses
- Majority asymptomatic (74%)
- Resolved (91%) within 20 weeks

ARIA-H: (microhemorrhage) 19%

ARIA-H superficial siderosis: 15%



MRI images demonstrating ARIA findings
A. ARIA #1: Axial FLAIR MRI-moderate ARIA-E leading to dose suspension; B. ARIA #2: Axial FLAIR MRI- mild ARIA-E without drug interruption;
C. ARIA #6: Axial FLAIR MRI- mild ARIA-E with dose suspension; D. ARIA #6: Axial GRE MRI-mild ARIA-H with dose suspension

ARIA=amyloid-related imaging abnormalities. ARIA-E=ARIA-edema. ARIA-H=ARIA-hemorrhage. FLAIR=fluid attenuated inversion recovery.

1. Hall JN, et al. *JAMA Neurol*. 2022;79(1):87-89. 2. Salloway S, et al. *JAMA Neurol*. 2022;79(1):13-21. 3. DiFrancesco JC, et al. *Front Neurol*. 2015;6:207.

Aducanumab Appropriate use Recommendations Update: Imaging, Laboratory, and Clinical Characterization of Patients Being Considered for Treatment

Participant Feature	Appropriate Use in Clinical Practice
Age	50-85; younger or older patients meeting all other criteria for treatment may be considered candidates for aducanumab
Diagnosis	MCI due to AD or mild AD dementia
Cognitive states	Mild decline of cognition with no or limited impairment of activities of daily living established by objective cognitive testing
Amyloid status	Amyloid positive PET (visual read) or CSF findings consistent with AD
Genetic testing	APOE genotype determined
Neurological examination	Non-AD neurological disorders excluded
Cardiovascular history	Stable cardiovascular conditions required
Medical history	Stable medical conditions required; patients with history of autoimmune disorders or seizures excluded
Psychiatric history	Stable psychiatrically
Clotting status	Patients with bleeding disorders or on anticoagulants excluded
Concomitant medications	Patients can be on standard of care with cholinesterase inhibitors and memantine
Laboratory studies	Normal serum vitamin B12 level, thyroid stimulating hormone (TSH), metabolic panel and liver function tests, complete blood count, comprehensive clotting studies and platelet count Normal erythrocyte sedimentaton rate and C-reactive protein
Baseline MRI	None of the following: • Acute or subacute hemorrhage • Macrohemorrhage • Cortical infarction larger than 1.5 cm • One lacunar infarction larger than 1.5 cm • More than four microhemorrhages • More than one area of superficial siderosis • Extensive white matter disease indicative of ischemic injury
Informed consent	Patient and care partner must understand the nature and requirements of therapy (e.g, monthly infusions to be performed indefinitely) and the expected outcome of therapy (removal of amyloid and slowing of decline of clinical features)

APOE=apolipoprotein E.

Cummings C, et al. *J Prev Alzheimers Dis*. Published online April 5, 2022. doi: 10.14283/jpad.2022.34

Aducanumab Appropriate Use Recommendations Update: Principal New Elements

- Recommend more emphasis on past medical conditions that may potentially place the patient at increased risk for ARIA or from complications potentially related to ARIA such as evidence of pre-existing autoimmune or inflammatory conditions, history of seizures, transient ischemic attacks, cerebrovascular disease, or extensive white matter changes in the brain
- Recommend APOE genotyping to allow better informed discussions with patients and their care partners concerning the risk for ARIA; these events occur more in patients heterozygous for the APOE4 than in noncarriers and more in those that are homozygous than in heterozygotes. ARIA may potentially be more likely to be recurrent, severe, or serious in individuals who are homozygous for the APOE4 allele.
- Recommend that MRIs be obtained routinely before the 5th, 7th, 9th, and 12th doses of aducanumab.
- Recommend stopping aducanumab therapy for any of the following:
  - o Any macrohemorrhage
  - o More than 1 area of superficial siderosis
  - o More than 10 microhemorrhages occurring since initiation of treatment
  - o More than 2 episodes of ARIA
  - o Severe symptoms of ARIA
  - o Development of any medical condition that requires anticoagulation (e.g., atrial fibrillation, deep vein thrombosis, pulmonary embolism, hypercoagulable state)
- For the most severe symptomatic cases of ARIA, recommend beginning high-dose glucocorticoid therapy; a regimen to be considered is methylprednisolone 1 gm intravenously per day for 5 days followed by oral prednisone, 60 mg per day, slowly tapered over weeks or months.
- For patients with seizures or electroencephalographic evidence of epileptiform activity, recommend treatment with anticonvulsants
- With progression to moderate/severe stages of dementia, recommend reconsideration of aducanumab therapy in the context of the patient's circumstances, clinical status and trajectory, perceived meaningfulness of continued treatment, patient and care partner preferences, and uncertainties regarding potential benefit as well as burden and risks
- Recommend greater equity of therapeutic opportunity

Cummings C, et al. *J Prev Alzheimers Dis*. Published online April 5, 2022. doi: 10.14283/jpad.2022.34