Prevent Defense: Anti-Amyloid Therapeutics for the Management of Alzheimer's Disease

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Disclosure Declaration

- The speaker has no relevant financial relationships in relation to this presentation.

- Use of brand/proprietary technology names are used for information only; use is not meant to imply endorsement.

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Learning Objectives

Describe the underlying mechanisms of anti-amyloid medications used in the management of Alzheimer's disease.

Differentiate efficacy and safety profiles of available anti-amyloid medications for Alzheimer's disease.

Explain the place in therapy anti-amyloid medications have in the management of Alzheimer's disease.

Identify anti-amyloid therapeutics currently in development.

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What is Alzheimer's Disease (AD)?

A type of dementia (syndrome) that also includes the following types: Vascular, Lewy Body, Frontotemporal and Mixed

Can include a collection of symptoms that include cognitive impairment and behavioral/psychological changes

Cognitive impairment is a normal part of aging, but mild cognitive impairment (MCI) is a known risk factor for dementia

Alzheimer's Association. What is Alzheimer's Disease. Available at: https://www.alz.org/alzheimers-dementia/what-is-alzheimers. Accessed March 21, 2024.

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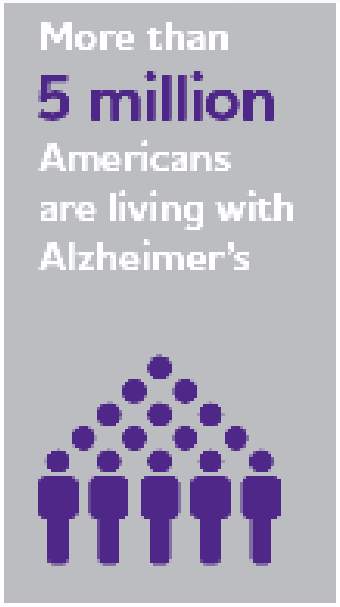
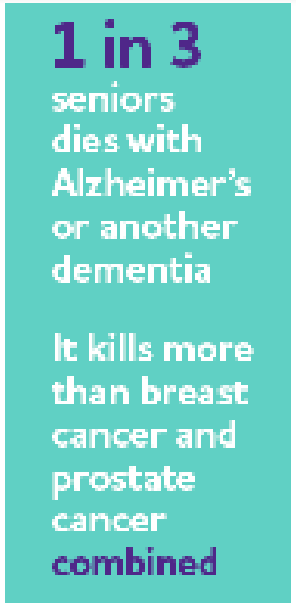
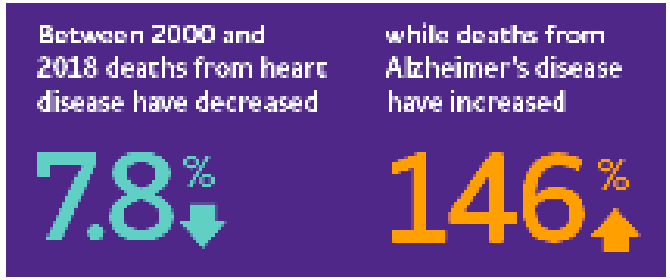
Epidemiology of AD

In 2020, Alzheimer's and other dementias will cost the nation $305 billion — By 2050, these costs could rise as high as $1.1 trillion

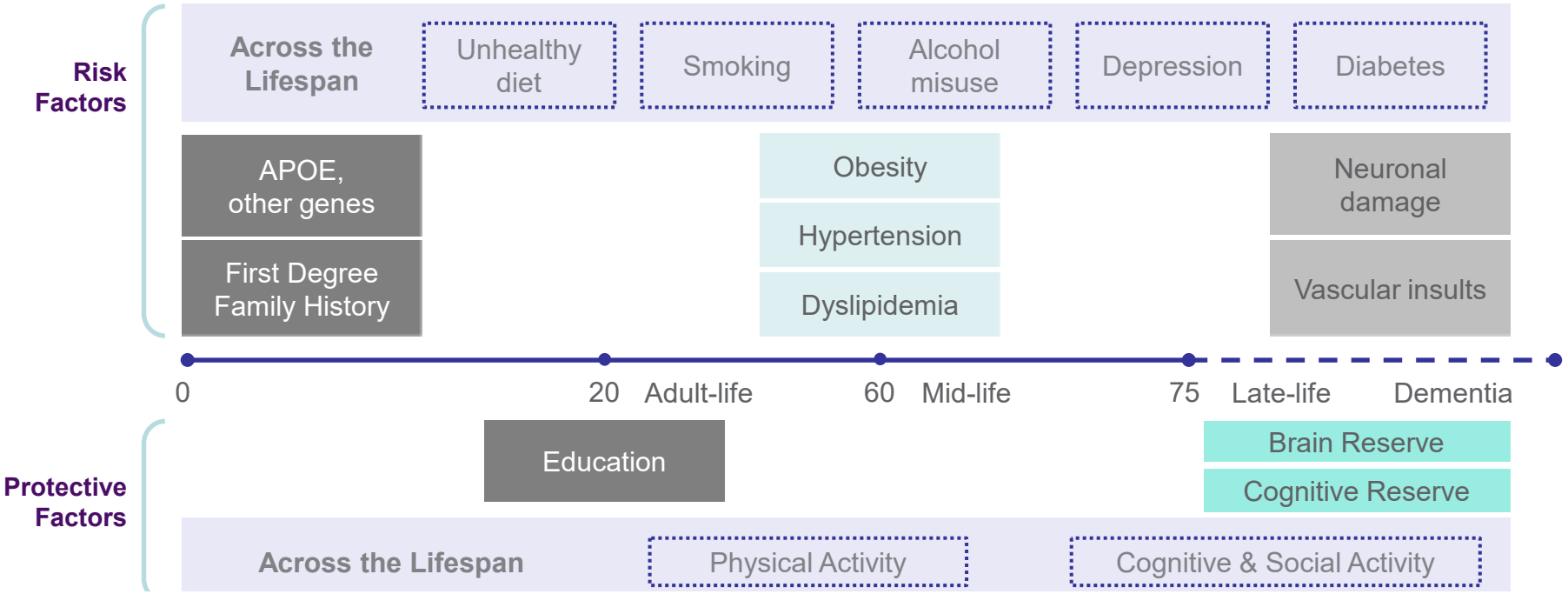






Alzheimer's Association. Alzheimer's Disease Facts and Figures (infographic). Available at: https://aaic.alz.org/downloads2020/facts2020_infographic.pdf. Accessed March 21, 2024.

Aging Process and the Brain



AD Risk
impact on neuron viability, inflammation, oxidative stress, glucose metabolism, endothelial cell damage, clearance of tau and b-amyloid from brain

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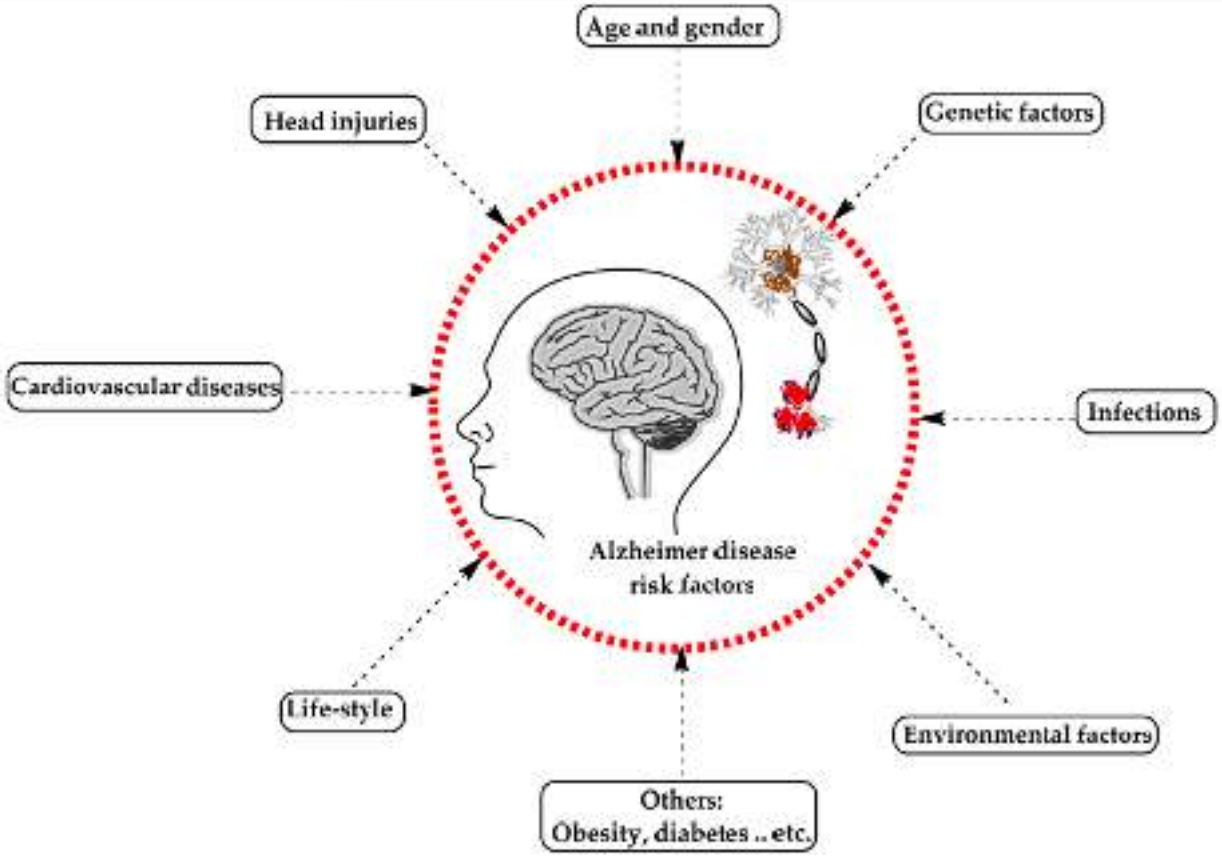
AD Risk Factors



Breijyeh Z, Karaman R. Comprehensive review on alzheimer's disease: Causes and treatment. *Molecules*. 2020;25(24). doi: 10.3390/molecules25245789.

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AD Risk Factors – cont.

Genetic Risk Factors	Acquired Risk Factors	Environmental Risk Factors
▪ Autosomal dominant inheritance of mutations that alter amyloid beta protein… ▪ Amyloid beta precursor protein (APP), Presenilin 1 (PSEN1), Presenilin (PSEN2) ▪ APOE e4	▪ Hypertension ▪ Hyperlipidemia ▪ Cerebrovascular disease ▪ Atherosclerosis ▪ Type 2 DM ▪ Obesity ▪ Lifestyle and activity ▪ Brain trauma ▪ Medications	▪ Secondhand smoke ▪ Air pollution ▪ Pesticides

Ballard C, et al. Alzheimer's disease. Lancet. 2011; 377:1019-31

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Genetics of AD

Familial Genes
APP
PSEN1
PSEN2
SorL1

Risk Genes
APOE
GSK3 – Beta
DYRK1A
Tau
TOMM40
CLU
PICALM

Ballard C, et al. Alzheimer's disease. Lancet. 2011; 377:1019-31

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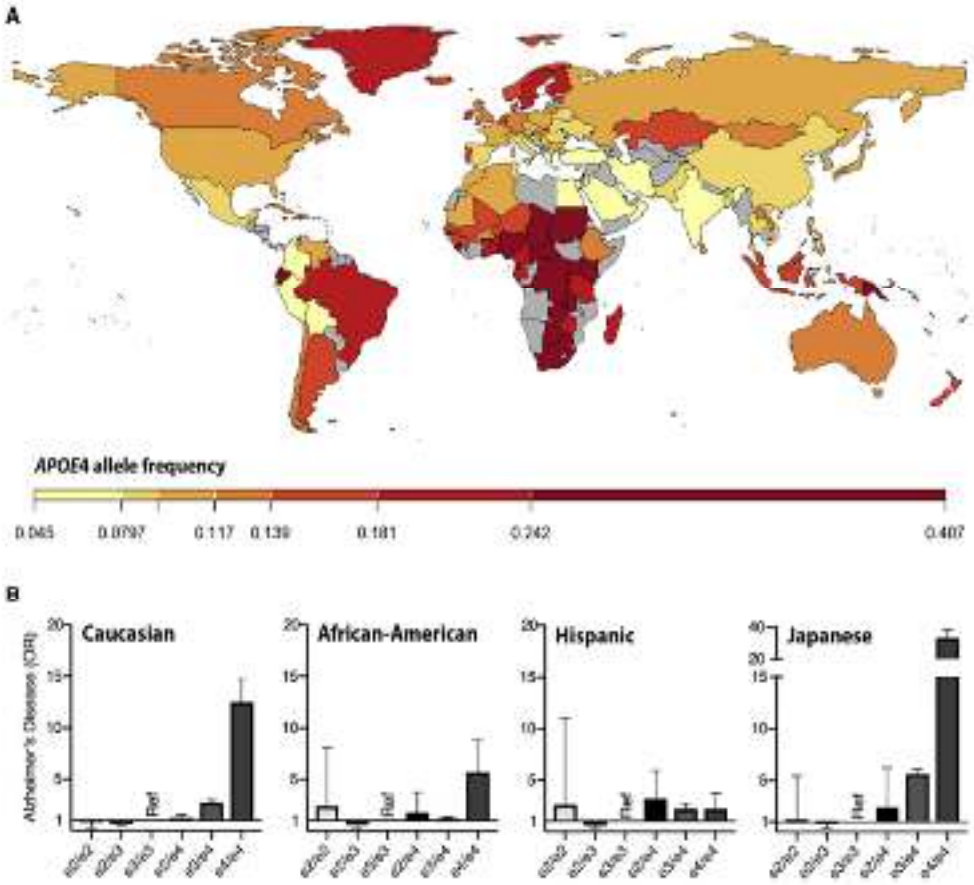
Genetics of AD – cont.

APOE
- AA: 1.93 (1.72-2.17)
- EUR: 3.32 (3.20-3.45)
- JAP: 5.5 (4.4-6.9)*

ABCA7
- AA: 1.41 (1.21-1.65)
- EUR: 1.13 (1.09-1.18)
- JAP: NS

SORL1
- AA: NS
- EUR: 0.81 (0.76–0.88)
- JAP: 0.75 (0.66–0.85)*



- Miyashita A, et al. (2013) Correction: *SORL1* Is Genetically Associated with Late-Onset Alzheimer's Disease in Japanese, Koreans and Caucasians. PLOS ONE 8(7).
- Belloy ME, et al. A Quarter Century of APOE and Alzheimer's Disease: Progress to Date and the Path Forward. Neuron. 2019 Mar 6;101(5):820-838.

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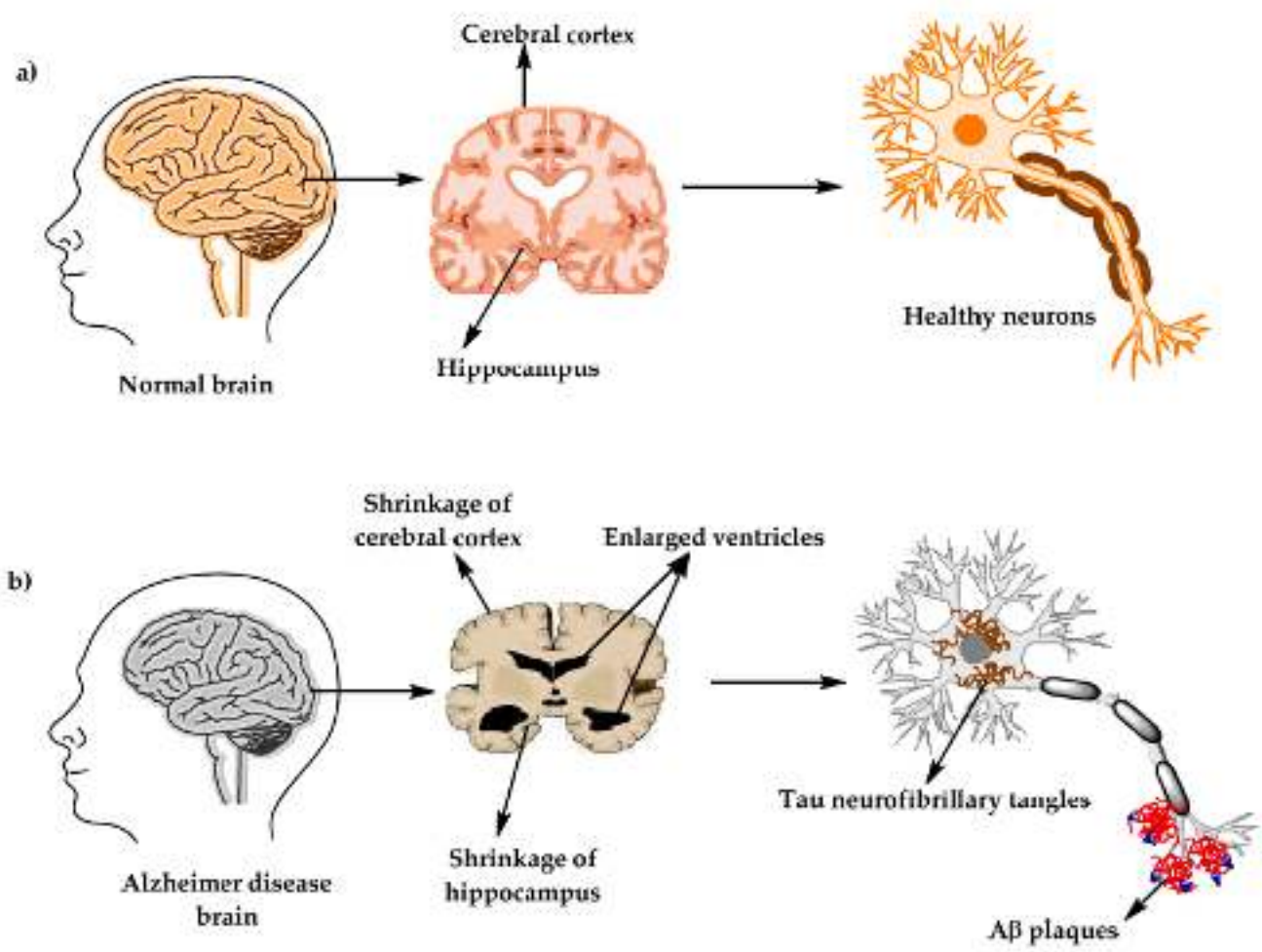
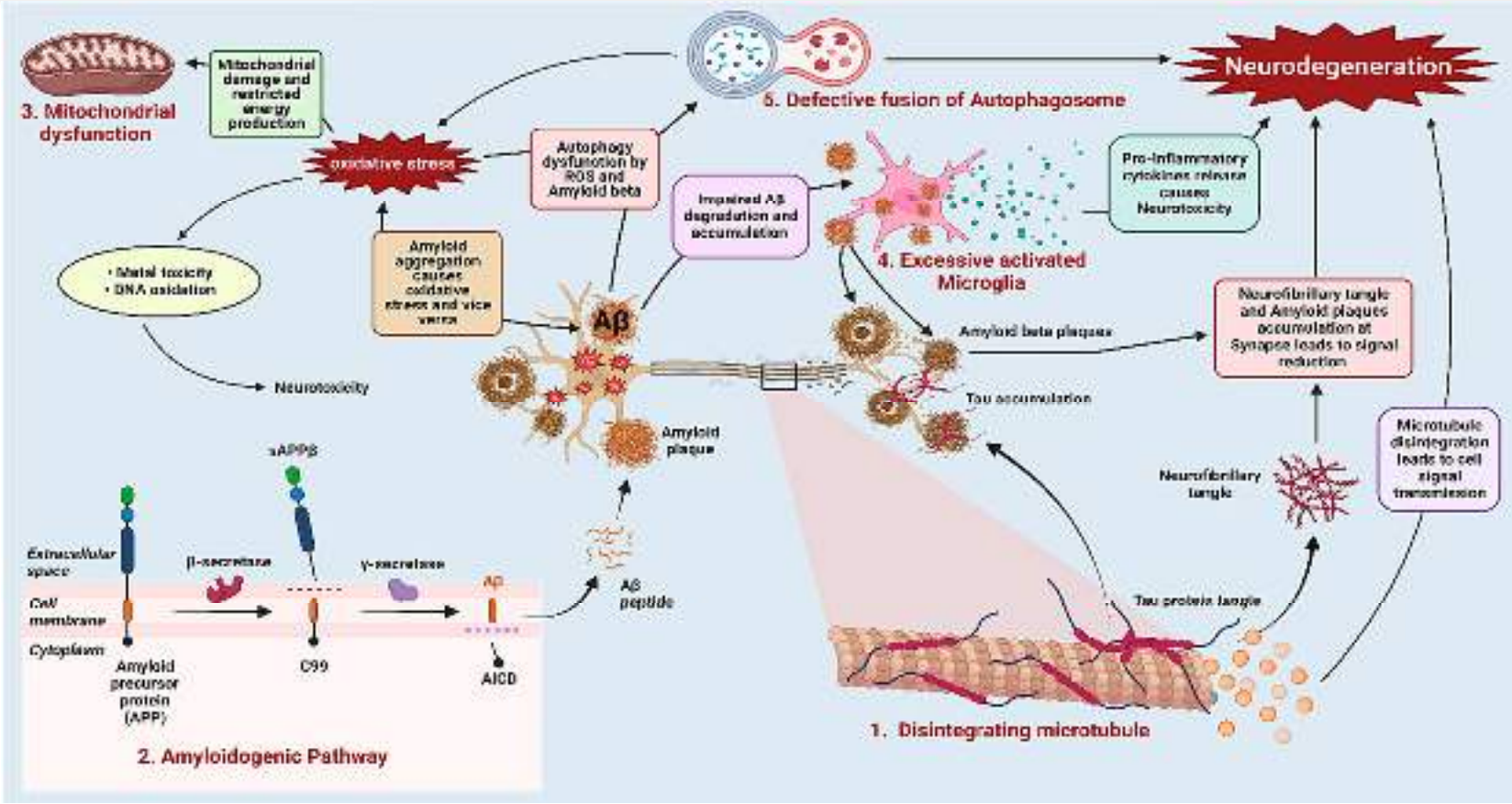
AD Pathology



Breijyeh Z, Karaman R. Comprehensive review on alzheimer's disease: Causes and treatment. *Molecules*. 2020;25(24). doi: 10.3390/molecules25245789.

Pathogenesis of AD



Singh B, et al. Alzheimer's disease current therapies, novel drug delivery systems and future directions for better disease management. *J Controlled Release*. 2024; 367:402.

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AD Pharmacotherapy

Dementia Symptoms

- **Cholinesterase inhibitors**
  - Donepezil, galantamine, rivastigmine
- **NMDA receptor antagonist**
  - Memantine

Neuropsychiatric symptoms

- **Atypical antipsychotics**
  - Aripiprazole, quetiapine, risperiodone, olanzapine
- **Antidepressants**
  - Citalopram, sertraline
- **Anticonvulsants**
  - Carbamazepine

Ballard C, et al. Alzheimer's disease. Lancet. 2011; 377:1019-31

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AD Treatment Pathway

Classification	Genetic Factors	Age Onset	Clinical Features	Risk Factors	Top Treatments
Early-onset	Yes	40s–50s	Plaques of amyloid and tau proteins	Family history	Acetylcholinesterase inhibitors (Donepezil, Galantamine, and Rivastigmine)
Late-onset	Yes (APOE)	≥65	(APOE) ε4 allele	Age ≥ 65 years, genetic and environmental factors	Acetylcholinesterase inhibitors (Donepezil, Galantamine, and Rivastigmine) and treatment of vascular risk factors and sleep and mood disorders
Familial	Yes (PSEN1, PSEN2, APP)	40s–50s	Mutations in PSEN1, PSEN2, and APP	Family history	Acetylcholinesterase inhibitors (Donepezil, Galantamine, and Rivastigmine)

Hajjo R, et al. A review of the recent advances in alzheimer's disease research and the utilization of network biology approaches for prioritizing diagnostics and therapeutics. *Diagnostics*. 2022;12(12).

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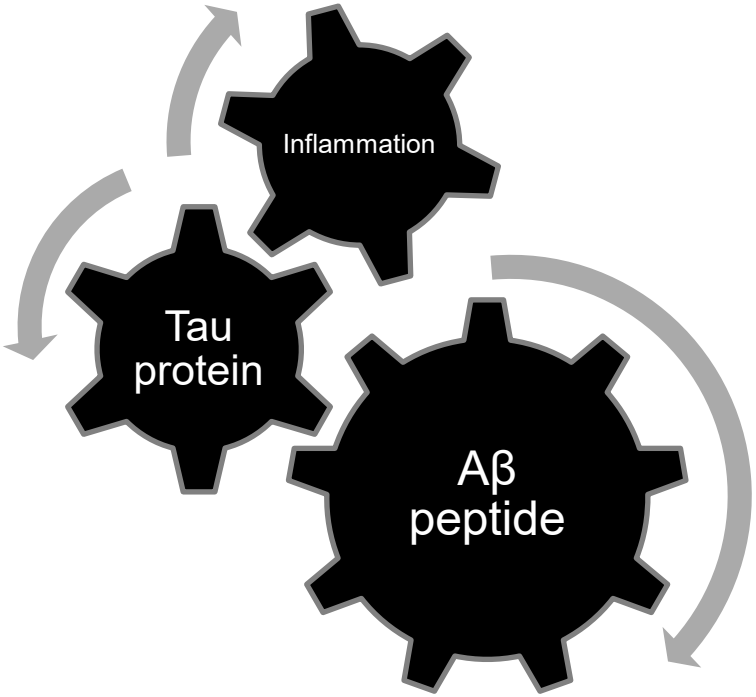
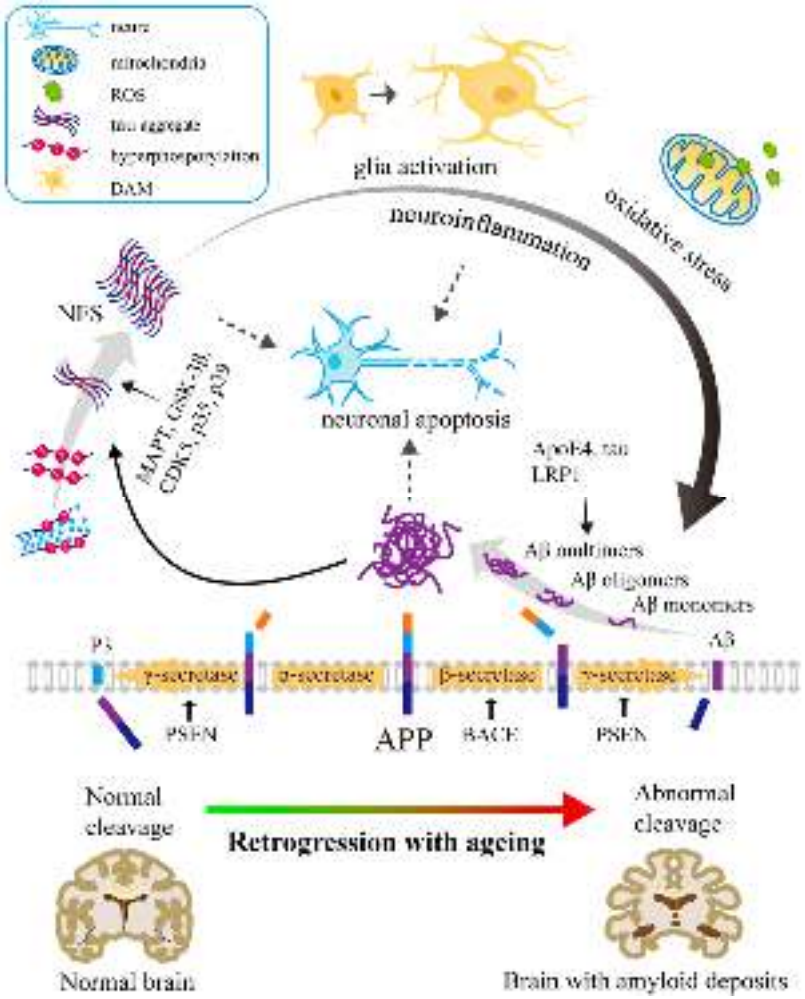
Pathogenic Targets of AD





Gu X, et al. Monoclonal antibody therapy for alzheimer's disease focusing on intracerebral targets. *BST*. 2024;18(1):49.

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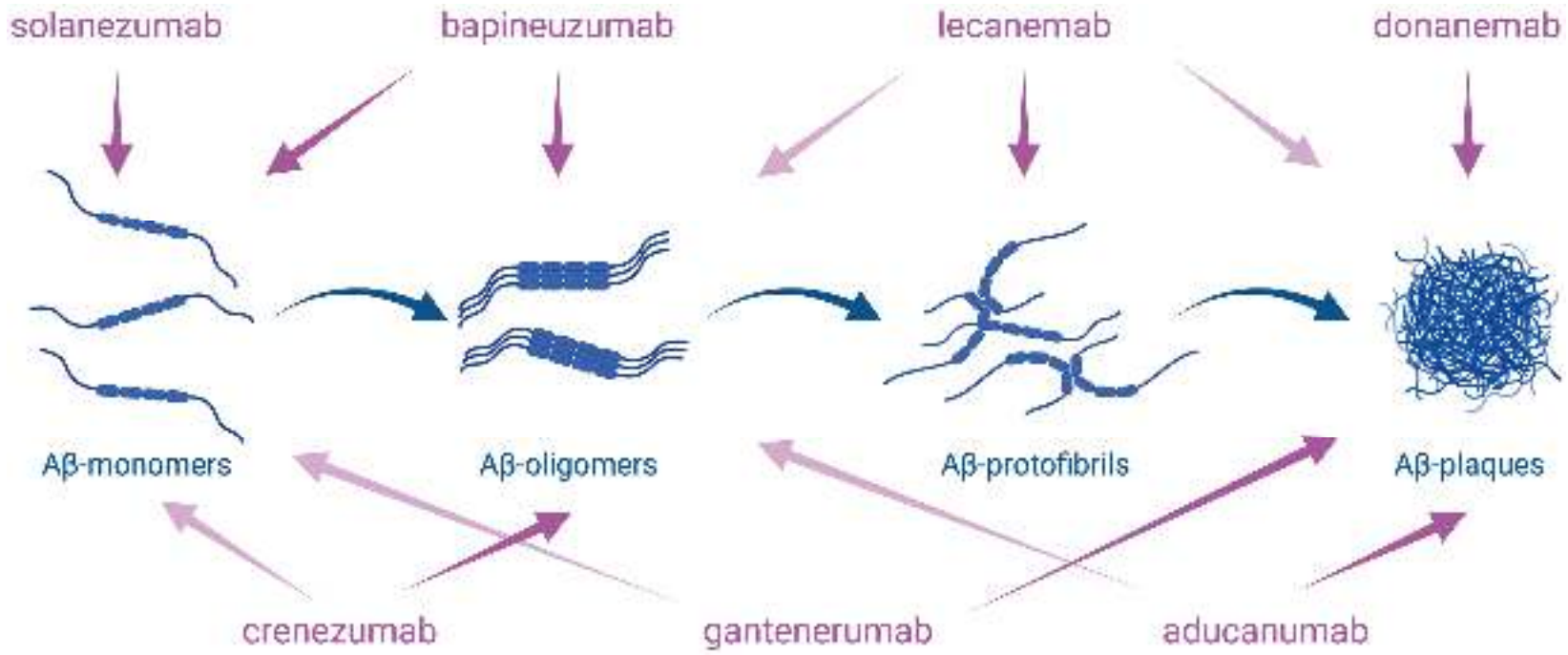
Amyloid Beta (Aβ) Targets



Perneczky R, et al. Anti-amyloid antibody treatments for alzheimer's disease. *Euro J of Neurology*. 2023;31(2).

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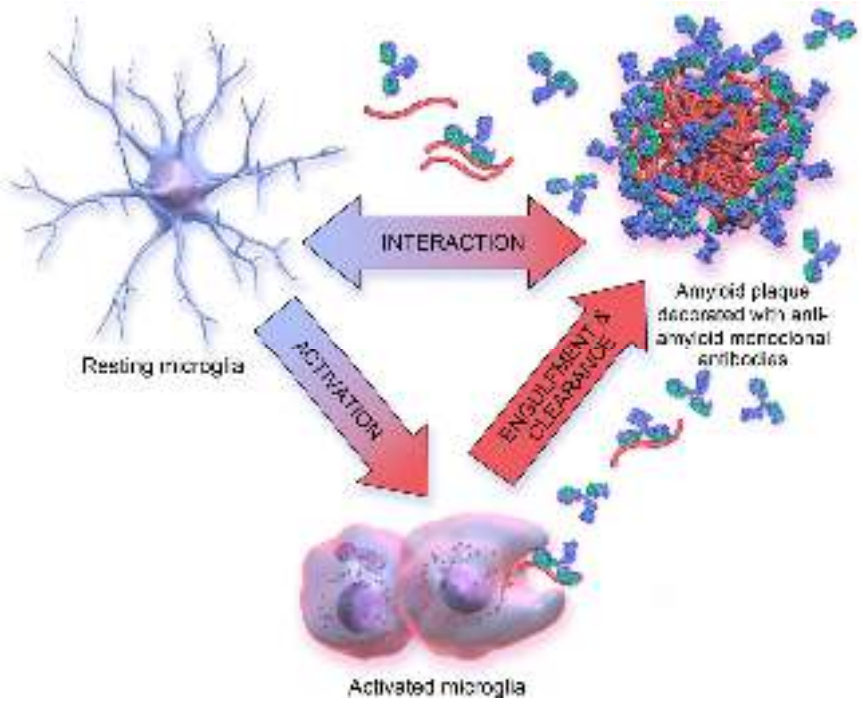
MOA | Anti-Amyloid Monoclonal Antibodies

- Amyloid beta (Aβ) plaque reduction via activation of microglia with phagocytosis of fibrillar Aβ and degradation through the endosomal/ lysosomal system

- Each approve mAb targets a different constellation of Aβ species



Cummings J, et al. Anti-amyloid monoclonal antibodies for the treatment of alzheimer's disease. *BioDrugs*. 2023;38(1):5.

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Learning Assessment – Question 1

Which of the following amyloid beta (Aβ) species is targeted by current generation monoclonal antibodies?

a. Amyloid beta (Aβ) monomers

b. Amyloid beta (Aβ) oligomers

c. Amyloid beta (Aβ) protofibrils

d. Amyloid beta (Aβ) plaques

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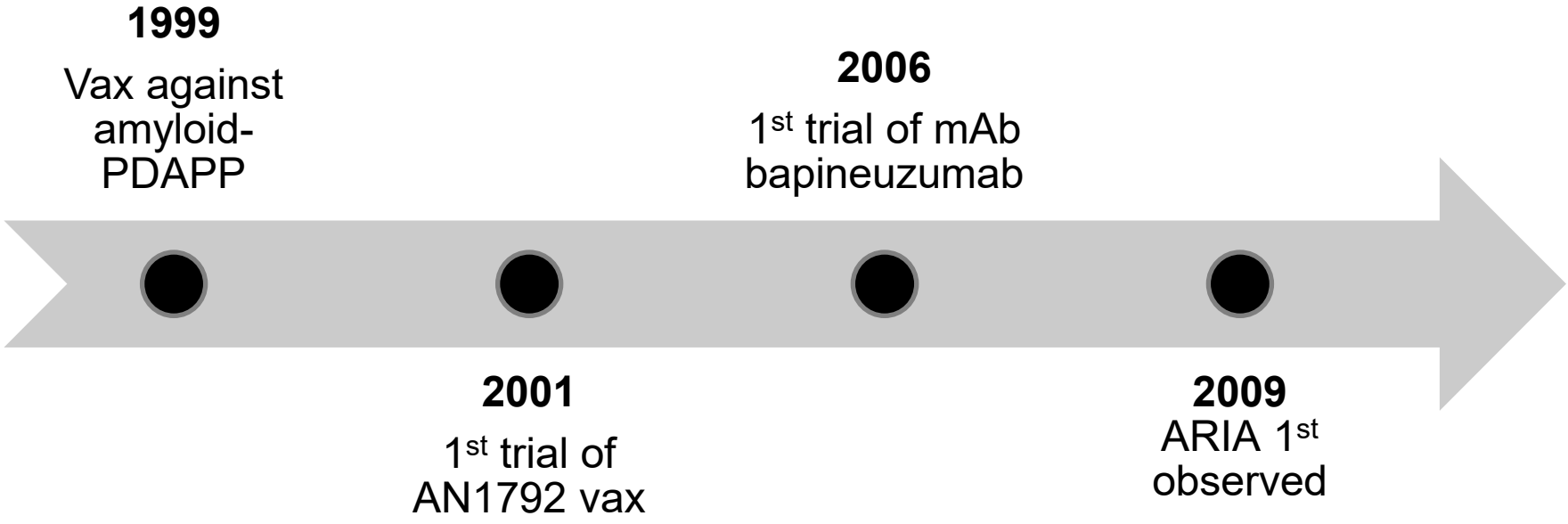
History of Monoclonal Antibody (mAb) Immunotherapy



Cummings J, et al. Anti-amyloid monoclonal antibodies for the treatment of alzheimer's disease. *BioDrugs*. 2023;38(1):5.

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Anti-Amyloid mAb Clinical Trials

Agent	Major Target(s)	Study Phase	Subjects	1º Efficacy Endpoint	1º TEAE
Aducanumab	Aβ multimers	3	Early AD	Slowing cognitive decline	ARIA
Lecanemab	Aβ oligomers	3	Early AD	Improved markers of amyloid	ARIA
Donanemab	Aβ plaque	3	Early AD	Slowing cognitive decline; reduced Aβ plaque	ARIA with microhemorrhages and hemosiderin
Gantenerumab	Aβ multimers or monomers	3	Early AD	Reduced Aβ plaque	ARIA
Remternetug	Aβ (promulgated)	3	Early AD	Reduced Aβ plaque	ARIA

- Gu X, et al. Monoclonal antibody therapy for alzheimer's disease focusing on intracerebral targets. *BST*. 2024;18(1):49.
- Cummings J, et al. Anti-amyloid monoclonal antibodies for the treatment of alzheimer's disease. *BioDrugs*. 2023;38(1):5.

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Select Anti-Amyloid Monoclonal Antibodies

Aducanumab-avwa (Aduhelm®)	Lecanemab (Leqembi®)	Donanemab
• Biogen • ENGANGE, EMERGE • FDA approval (accelerated) June 2021	• Esai & Biogen • CLARITY AD • FDA approval (accelerated) January 2023	• Eli Lilly • TRAILBLAZER – ALZ 2 • FDA decision delayed, March 2024 (accelerated pathway)

- Cummings J, et al. Anti-amyloid monoclonal antibodies for the treatment of alzheimer's disease. *BioDrugs*. 2023;38(1):5.
- Food and Drug Administration. Drugs@FDA. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed 20 March 2024.

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Aducanumab Clinical Program

Agent	Trial NCT	Phase	Status	No. of participants	Treatment duration (weeks)	Baseline MMSE (range)	Primary outcome	Secondary clinical outcomes	Biomarker outcomes
Aducanumab	03639987	II	Terminated	52	54	24 and 30	ARIA	10 measures about the onset of ARIA	PET ARIA
Aducanumab	02477800	III	Terminated [2]	1653	78	24 and 30	CDR-SB	MMSE; ADAS-Cog 13; ADCS-ADL-MCI	Amyloid PET SUVR, amyloid PET centiloid, CSF p-tau and t-tau, plasma p-tau
Aducanumab	02484547	III	Terminated [2]	1638	78	24 and 30	CDR-SB	MMSE; ADAS-Cog 13; ADCS-ADL-MCI	Amyloid PET SUVR, amyloid PET centiloid, CSF p-tau and t-tau, plasma p-Tau
Aducanumab	04241068	III	Active, not recruiting	1696	100	NA	No. of participants with AEs, SAEs, AEs leading to treatment discontinuation or study withdrawal, ARIA-E, ARIA-H	NA	PET ARIA

Cummings J, et al. Anti-amyloid monoclonal antibodies for the treatment of alzheimer's disease. *BioDrugs*. 2023;38(1):5.

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Lecanemab Clinical Program

Agent	Trial NCT	Phase	Status	No. of participants	Treatment duration (weeks)	Baseline MMSE (range)	Primary outcome	Secondary clinical outcomes	Biomarker outcomes
Lecanemab	01767311	IIb	Active, not recruiting [3]	856	76 (261 extension)	22–30	ADCOMS (12-month)	ADCOMS (18-month); CDR-SB; ADAS-Cog	Amyloid PET; vMRI; CSF ($A\beta_{1-42}$, t-tau, p-tau)
Lecanemab	03887455	III	Active, not recruiting [4]	1795	76 (300 extension)	22–30	CDR-SB	ADAS-Cog14; ADCOMS; ADCS-ADL-MCI	Amyloid PET; Tau PET; vMRI; CSF ($A\beta_{1-42}$, t-tau, p-tau, neurogranin, NfL, $A\beta_{1-40}$); plasma ($A\beta_{42/40}$ ratio, p-tau, GFAP, NfL)
Lecanemab	04468659	III	Recruiting	1400	216	27–30	PACC5	CFI	Amyloid PET; Tau PET
Lecanemab + E2814	05269394	II/III	Recruiting	168	208	NA	Tau PET	CDR-SB; CCS	Amyloid PET; CSF (NfL, p-tau217/t-tau ratio)

Cummings J, et al. Anti-amyloid monoclonal antibodies for the treatment of alzheimer's disease. *BioDrugs*. 2023;38(1):5.

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Donanemab Clinical Program

Agent	Trial NCT	Phase	Status	No. of participants	Treatment duration (weeks)	Baseline MMSE (range)	Primary outcome	Secondary clinical outcomes	Biomarker outcomes
Donanemab	03367403	II	Completed [5]	272	76	20–28	iADRS	ADAS-Cog13; CDR-SB; MMSE; ADCS-iADL	Amyloid PET; Tau PET; vMRI
Donanemab	04437511 [66]	III	Active, not recruiting	1800	76	20–28	iADRS	MMSE; ADAS-Cog13; CDR-SB; ADCS-iADL	Amyloid PET; Tau PET; vMRI; serum concentration; ADA
Donanemab	05026866	III	Recruiting	3300	182	NA	CDR-GS	ISLT; CPAL; iDSSTm; Category fluency; FNAME; BPS-O; CBB; CDR-SB; CFI; MoCA	Serum concentration; ADAs
Donanemab	05108922	III	Active, not recruiting	200	72	20–30	Plaque clearance	None	Amyloid PET
Donanemab	05508789	III	Recruiting	1500	76	20–28	iADRS	CDR-SB; ADAS-Cog; ADCS-iADL; MMSE; QoL; RUD-Lite; NPI	Amyloid PET; ADAs
Donanemab	05738486	III	Recruiting	800	76	20–28	ARIA-E	None	ARIA-E; ARIA-H; serum concentration; ADAs

Cummings J, et al. Anti-amyloid monoclonal antibodies for the treatment of alzheimer's disease. *BioDrugs*. 2023;38(1):5.

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FDA – Approved | Anti-Amyloid mAb

Generic Name	Indication(s)	Administration Considerations	Safety Considerations
Aducanumab	AD (Aβ confirmed) - patients with MCI or mild dementia	**ROA**: Infusion **Freq**: q 4 weeks **SOC**: outpt infusion **Other**: requires initial dose titration	**BBW**: Yes - ARIA **REMS**: No **Post-marketing**: ENVISION
Lecanemab	AD (Aβ confirmed) - patients with MCI or mild dementia	**ROA**: Infusion **Freq**: q 2 weeks **SOC**: outpt infusion **Other**: 10 mg/kg	**BBW**: Yes - ARIA **REMS**: No **Post-marketing**: Yes

- Aduhelm [package insert]. Bridgewater, NJ: Biogen, Inc. Revised August 2023.
- Leqembi [package insert]. Nutley, NJ: Esai, Inc. Revised July 2023.

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Anti-Amyloid Black Box Warning

WARNING: AMYLOID RELATED IMAGING ABNORMALITIES

See full prescribing information for complete boxed warning.

Monoclonal antibodies directed against aggregated forms of beta amyloid, including ADUHELM, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA is usually asymptomatic, although rarely serious and life-threatening events can occur. Serious intracerebral hemorrhage greater than 1 cm have occurred in patients treated with this class of medications. (5.1, 6.1)

ApoE ε4 Homozygotes

Patients treated with this class of medications, including ADUHELM, who are ApoE ε4 homozygotes have a higher incidence of ARIA, including symptomatic and serious ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. (5.1)

Consider the benefit of ADUHELM for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with ADUHELM. (5.1, 14)

Aduhelm [package insert]. Bridgewater, NJ: Biogen, Inc. Revised August 2023.

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Under FDA Review | Anti-Amyloid mAb

Generic Name	Indication(s)	Administration Considerations	Safety Considerations
Donanemab N3pG-Aβ Monoclonal Antibody, LY3002813	Early AD (Aβ confirmed)	**ROA**: Infusion **Freq**: q 4 weeks **SOC**: outpt infusion **Other**: requires dose titration after 3 months; not weight-based (700 – 1400 mg)	**BBW**: ? **REMS**: ? **Post-marketing**: Yes

Cummings J, et al. Anti-amyloid monoclonal antibodies for the treatment of alzheimer's disease. *BioDrugs*. 2023;38(1):5.

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Phase II – III

Primary Efficacy Outcomes

Agent	Trial NCT	Phase	Primary outcome	Biomarker outcomes
Aducanumab	02477800 (Study 301) ENGAGE [2]	III	High-dose CDR-SB: drug-pbo difference 0.03 (2%) [−0.26, 0.33]; $p = 0.833$	Amyloid PET SUVR: drug-pbo difference −0.232, $p < 0.0001$ Amyloid PET CL: drug-pbo difference −3.5, $p < 0.0001$ CSF p-tau (pg/mL): drug-pbo difference −13.19, $p = 0.3019$ CSF t-tau (pg/mL): drug-pbo difference −69.25, $p = 0.3098$
Aducanumab	02484547 (Study 302) EMERGE [2]	III	High-dose CDR-SB: drug-pbo difference −0.39 (−22%) [−0.69, −0.09]; $p = 0.012$	Amyloid PET SUVR: drug-pbo difference −0.278, $p < 0.0001$ Amyloid PET CL: drug-pbo difference −64.2, $p < 0.0001$ CSF p-tau (pg/mL): drug-pbo difference −22.44, $p = 0.0005$ CSF t-tau (pg/mL): drug-pbo difference −112.05, $p = 0.0088$
Donanemab	03367403 [5]	II	iADRS: drug-pbo difference 3.2 ± 1.56; $p = 0.04$	Amyloid PET: drug-pbo difference −85.06 CL
Donanemab	04437511 [66]	III	iADRS: Intermediate tau population: 40% less decline in drug vs. placebo; $p < 0.001$ Combined tau populations: 23% less decline in drug vs. placebo; $p < 0.001$	Amyloid PET: Intermediate tau population: 34% of participants achieving Aβ clearance at 6 months; 71% of participants achieving Aβ clearance at 12 months
Lecanemab	01767311 [3]	IIb	ADCOMS (12 months, 10BW): LS mean drug-pbo difference −0.046 (90% CI −0.079, −0.012); $p = 0.027$	Amyloid PET (18 months, 10 mg/kg combined); LS mean drug-pbo difference −0.253; $p < 0.001$
Lecanemab	03887455 [4]	III	CDR-SB: drug-pbo difference −0.45 (95% CI −0.67, −0.23); $p < 0.001$	Amyloid PET: drug-pbo difference −59.12 CL (95% CI −62.64, −55.6); $p < 0.001$

ADCOMS Alzheimer's Disease Composite Score, *BW* biweekly treatment, *CDR-SB* Clinical Dementia Rating–Sum of Boxes, *CL* centiloids, *CSF* cerebrospinal fluid, *iADRS* integrated Alzheimer's Disease Rating Scale, *LS* least squares, *pbo* placebo, *PET* positron emission tomography, *SUVR* standardized uptake value ratio

Cummings J, et al. Anti-amyloid monoclonal antibodies for the treatment of alzheimer's disease. *BioDrugs*. 2023;38(1):5.

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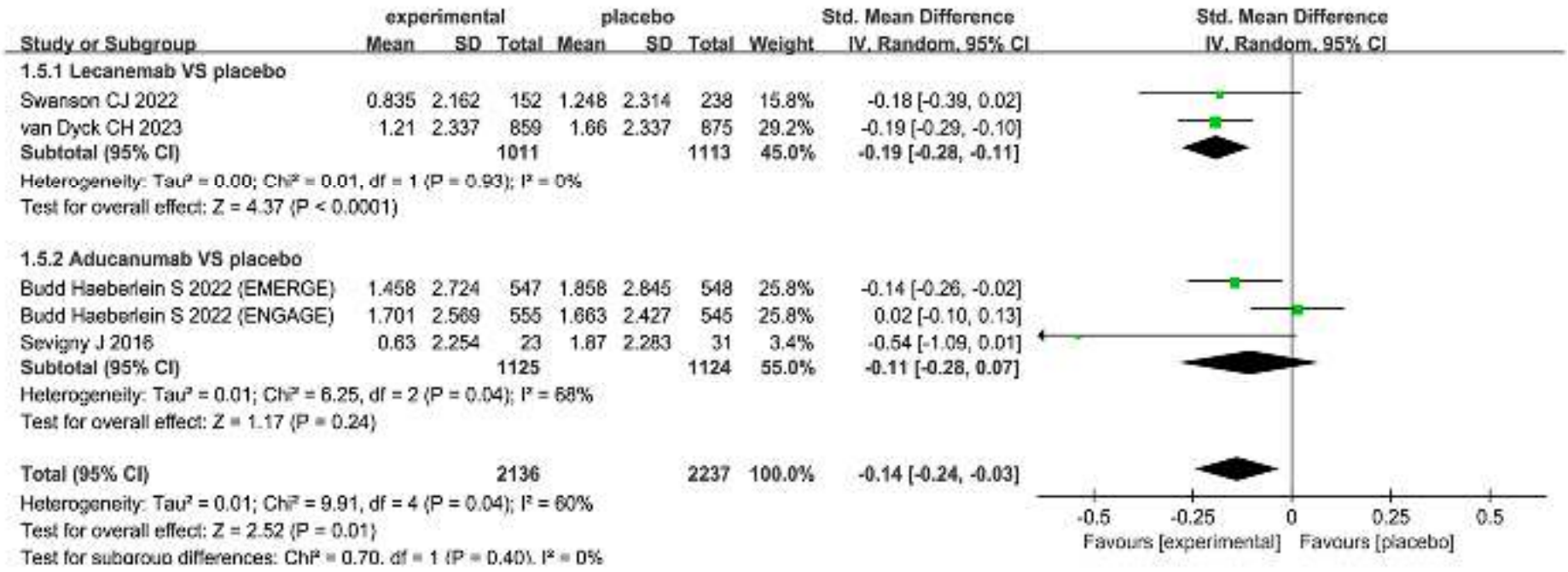
Comparative Effectiveness | Primary Outcome



Study or Subgroup	experimental Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.1 Lecanemab VS placebo								
Swanson CJ 2022	0.835	2.162	152	1.248	2.314	238	15.8%	-0.18 [-0.39, 0.02]
van Dyck CH 2023	1.21	2.337	859	1.66	2.337	875	29.2%	-0.19 [-0.29, -0.10]
Subtotal (95% CI)			**1011**			**1113**	**45.0%**	**-0.19 [-0.28, -0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%								
Test for overall effect: Z = 4.37 (P < 0.0001)								
1.5.2 Aducanumab VS placebo								
Budd Haeberlein S 2022 (EMERGE)	1.458	2.724	547	1.858	2.845	548	25.8%	-0.14 [-0.26, -0.02]
Budd Haeberlein S 2022 (ENGAGE)	1.701	2.569	555	1.663	2.427	545	25.8%	0.02 [-0.10, 0.13]
Sevigny J 2016	0.63	2.254	23	1.87	2.283	31	3.4%	-0.54 [-1.09, 0.01]
Subtotal (95% CI)			**1125**			**1124**	**55.0%**	**-0.11 [-0.28, 0.07]**
Heterogeneity: Tau² = 0.01; Chi² = 6.25, df = 2 (P = 0.04); I² = 68%								
Test for overall effect: Z = 1.17 (P = 0.24)								
Total (95% CI)			**2136**			**2237**	**100.0%**	**-0.14 [-0.24, -0.03]**
Heterogeneity: Tau² = 0.01; Chi² = 9.91, df = 4 (P = 0.04); I² = 60%								
Test for overall effect: Z = 2.52 (P = 0.01)								
Test for subgroup differences: Chi² = 0.70, df = 1 (P = 0.40), I² = 0%								

Wu W, et al. The FDA-approved anti-amyloid-β monoclonal antibodies for the treatment of alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. *Eur J Med Res*. 2023;28(1).

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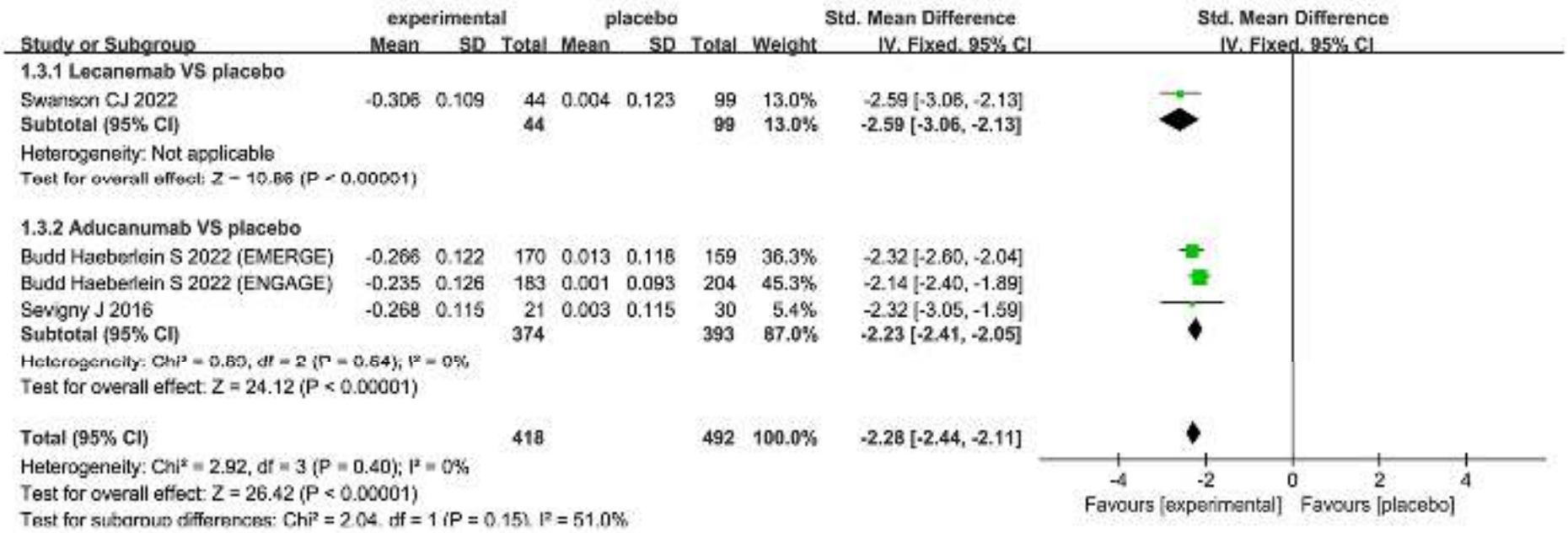
Comparative Effectiveness | Biomarker Outcome



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Phase II – III Primary Safety Outcome

Agent	Trial NCT	Phase	ARIA-E (%)	ARIA-H (%)	Symptomatic ARIA (%)	ARIA-E in *APOE* heterozygotes (%)	ARIA-E in *APOE*4 homozygotes (%)
Aducanumab (high dose)	02477800 [2]	III	35.9	18.8	20.8 (headache)	Carrier 42.1 Non-carrier 22.7	62.2
Aducanumab (high dose)	02484547 [2]	III	34.8	20.0	19.8 (headache)	Carrier 43.2 Non-carrier 17.9	58.7
Aducanumab (high dose)	02477800 and 02484547 [36]	III	35.2	19.1	26.0	35.9	66.0
Donanemab	03367403 [5]	II	26.7	30.5	6.1	30.9	44
Donanemab	04437511 [66]	III	24.0	31.4	6.1	NA	NA
Lecanemab	01767311 [3]	IIb	2.5 BW—1.9 5 MNTH—2.0 5 BW—3.3 10 MNTH—9.9 10 BW—9.9	2.5 BW—3.8 5 MNTH—13.7 5 BW—18.5 10 MNTH—11.1 10 BW—6.8	2.5 BW—1.9 10 MNTH—0.4 10 BW—1.2 (all ARIA-E)	2.5 BW—2.6 5 MNTH—2.5 5 BW—3.6 10 MNTH—10.2 10 BW—14.3	*APOE*4 heterozygotes and homozygotes were grouped in this study (*APOE*4 +)
Lecanemab	03887455 [4]	III	12.6	17.3	3.5	10.9	32.6

ARIA amyloid-related imaging abnormalities, *ARIA-E* amyloid-related imaging abnormalities, effusion/edema, *ARIA-H* amyloid-related imaging abnormalities, hemorrhagic, *APOE* apolipoprotein E, *BW* biweekly treatment, *MNTH* monthly treatment, *NA* not available

Cummings J, et al. Anti-amyloid monoclonal antibodies for the treatment of alzheimer's disease. *BioDrugs*. 2023;38(1):5.

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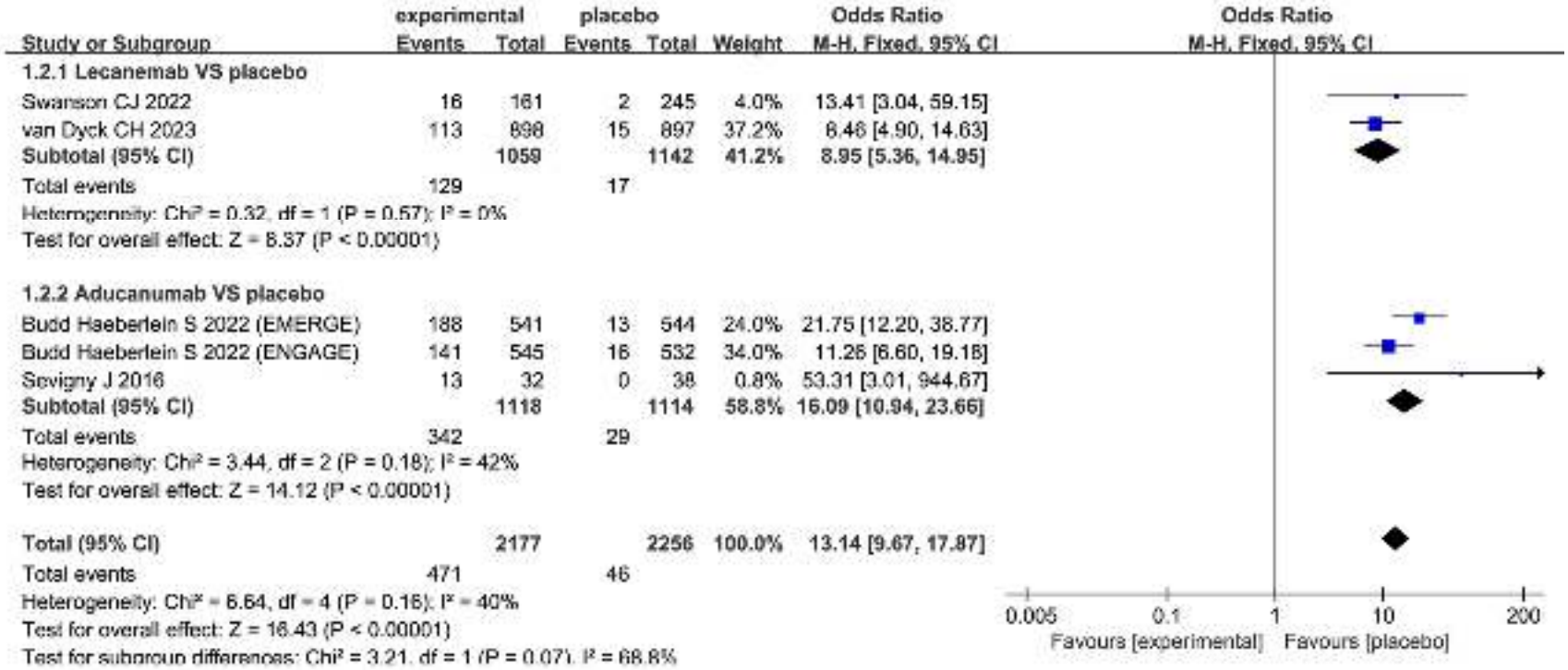
Comparative Effectiveness | Safety Outcome, ARIA-E



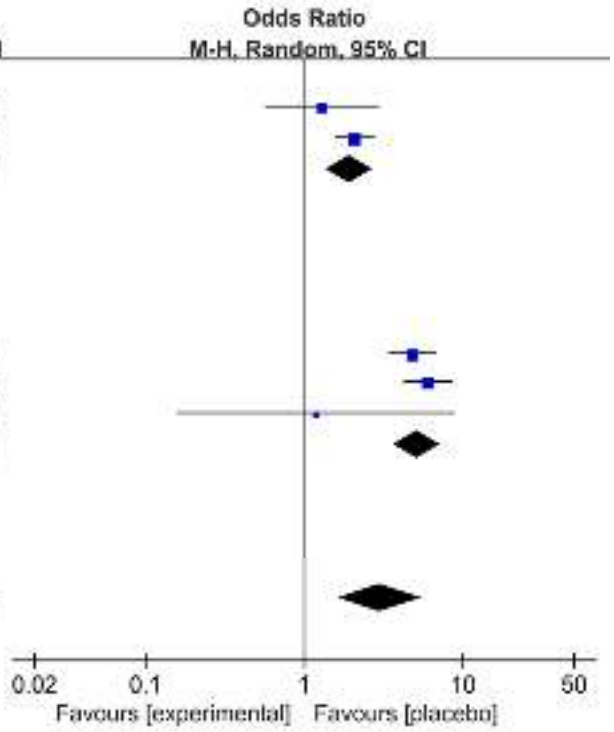
Study or Subgroup	experimental Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Lecanemab VS placebo						
Swanson CJ 2022	16	161	2	245	4.0%	13.41 [3.04, 59.15]
van Dyck CH 2023	113	898	15	897	37.2%	8.46 [4.90, 14.63]
Subtotal (95% CI)		1059		1142	41.2%	8.95 [5.36, 14.95]
Total events	129		17			
Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 8.37 (P < 0.00001)						
1.2.2 Aducanumab VS placebo						
Budd Haeberlein S 2022 (EMERGE)	188	541	13	544	24.0%	21.75 [12.20, 38.77]
Budd Haeberlein S 2022 (ENGAGE)	141	545	16	532	34.0%	11.26 [6.60, 19.18]
Sevigny J 2016	13	32	0	38	0.8%	53.31 [3.01, 944.67]
Subtotal (95% CI)		1118		1114	58.8%	16.09 [10.94, 23.66]
Total events	342		29			
Heterogeneity: Chi² = 3.44, df = 2 (P = 0.18); I² = 42%						
Test for overall effect: Z = 14.12 (P < 0.00001)						
Total (95% CI)		2177		2256	100.0%	13.14 [9.67, 17.87]
Total events	471		46			
Heterogeneity: Chi² = 6.64, df = 4 (P = 0.16); I² = 40%						
Test for overall effect: Z = 16.43 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.21, df = 1 (P = 0.07), I² = 68.8%						

Wu W, et al. The FDA-approved anti-amyloid-β monoclonal antibodies for the treatment of alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. *Eur J Med Res*. 2023;28(1).

RUTGERS HEALTH

Comparative Effectiveness | Safety Outcome, ARIA-H

Study or Subgroup	experimental Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Lecanemab VS placebo						
Swanson CJ 2022	11	161	13	245	17.9%	1.31 [0.57, 3.00]
van Dyck CH 2023	155	898	81	897	25.6%	2.10 [1.58, 2.80]
Subtotal (95% CI)		**1059**		**1142**	**43.5%**	**1.96 [1.41, 2.73]**
Total events	166		94			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.12$, df = 1 (P = 0.29); $I^2 = 11\%$						
Test for overall effect: Z = 3.98 (P < 0.0001)						
1.1.2 Aducanumab VS placebo						
Budd Haeberlein S 2022 (EMERGE)	181	541	51	544	25.0%	4.86 [3.46, 6.82]
Budd Haeberlein S 2022 (ENGAGE)	193	545	44	532	24.8%	6.09 [4.26, 8.67]
Sevigny J 2016	2	32	2	38	6.6%	1.20 [0.16, 9.04]
Subtotal (95% CI)		**1118**		**1114**	**56.5%**	**5.21 [3.74, 7.26]**
Total events	376		97			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.91$, df = 2 (P = 0.23); $I^2 = 31\%$						
Test for overall effect: Z = 9.77 (P < 0.00001)						
Total (95% CI)		**2177**		**2256**	**100.0%**	**2.99 [1.64, 5.43]**
Total events	542		191			
Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 31.59$, df = 4 (P < 0.00001); $I^2 = 87\%$						
Test for overall effect: Z = 3.59 (P = 0.0003)						
Test for subgroup differences: $Chi^2 = 16.81$, df = 1 (P < 0.0001), $I^2 = 94.1\%$						



Wu W, et al. The FDA-approved anti-amyloid-β monoclonal antibodies for the treatment of alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. *Eur J Med Res*. 2023;28(1).

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Learning Assessment – Question 2

Which of the following are the 1^{o} efficacy / safety outcome measures of the aducanumab and lecanemab pivotal trials?

a. iADRS / ARIA

b. CDR-GS / ARIA

c. CDR-SB / ARIA

d. MMSE / ARIA

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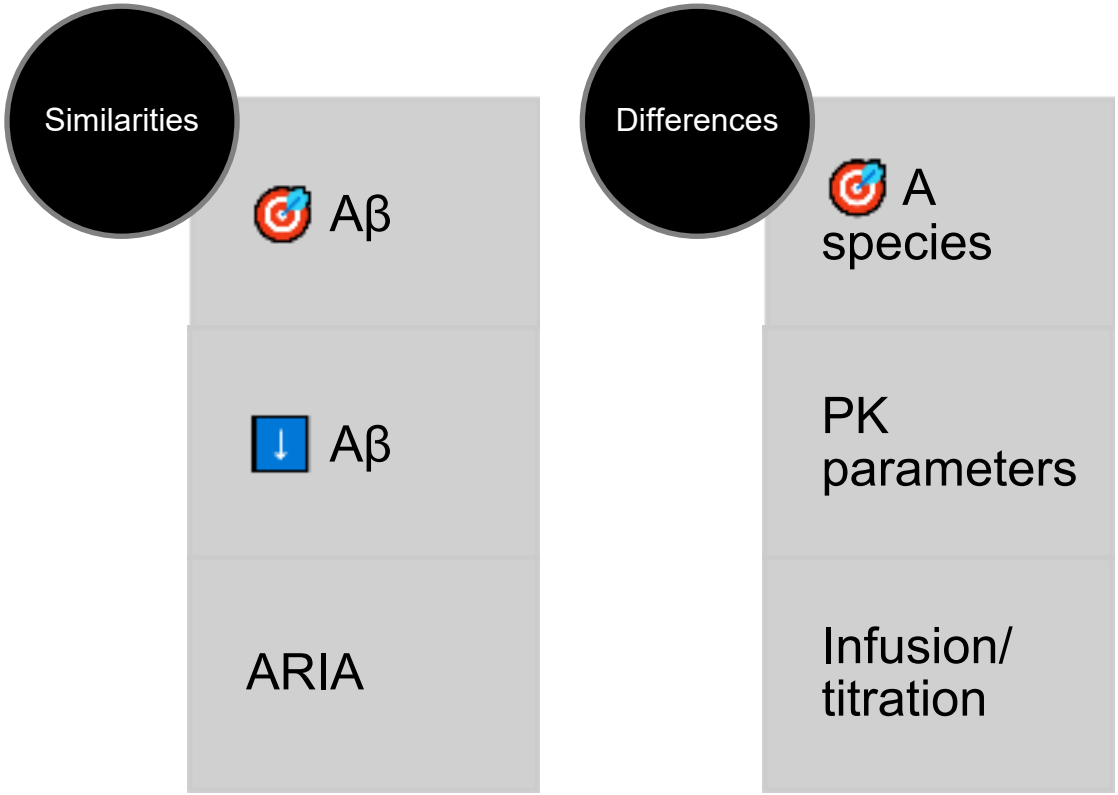
Anti-Amyloid mAb | Characteristics



Cummings J, et al. Anti-amyloid monoclonal antibodies for the treatment of alzheimer's disease. *BioDrugs*. 2023;38(1):5.

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Aducanumab Status

- **Futility Analysis Halted Trial:** Mar 2019
- **Expanded Data Analysis Reported CTAD:** Dec 2019
  - Reduction in clinical decline
  - Effects on cognition and function
  - Reduction in amyloid/tau biomarkers
- **Open Label Extension Studies Launced:** March 2020
- **FDA grants 'Priority Review':** Aug 2020
- **FDA Approval:** June 2021
- **Major US insurers refuse to cover**: Summer 2021
- **Manufacturer announces removal of drug from market**: **January 31, 2024**
- Patients may continue drug until: **November 1, 2024**

Alzforum. Therapeutics - ALZForum Web site. Available at: https://www.alzforum.org/therapeutics/search.

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Donanemab Status

Eli Lilly Announcement – March 8, 2024

- FDA action on Alzheimer drug, donanemab, delayed
- FDA convening panel of independent experts for discussion

Reason for Delay

- FDA seeks further understanding of safety and efficacy
- Focus on safety results in donanemab-treated patients
- Efficacy implications of novel trial design

Previous Expectations

- FDA was expected to approve the drug in the first quarter of 2024

Postponed Decision

- Approval decision delayed until at least later 2024
- Advisory panel meeting expected in Q1 or Q2 of 2024

Lilly Medical Affairs: update regarding donanemab (email communication, March 11, 2024)

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Anti-Amyloid mAb Clinical Trials

Drug	Study Phase	CADRO Target	Clinical Trial No.	Lead Sponsor	Est complete date
Aducanumab	3	Amyloid β	NCT04241068 NCT05310071	Biogen	Oct 2023 Dec 2025
Donanemab	3	Amyloid β	NCT04437511 NCT05026866 NCT05108922 NCT05508789	Eli Lilly	Apr 2023 Oct 2027 Sep 2022 Apr 2027
Lecanemab	3	Aβ oligomers	NCT01760005 NCT03887455 NCT04468659 NCT05269394	Wash U SOM Esai Esai Wash U SOM	Oct 2027 Sep 2027 Oct 2027 Jul 2027

Cummings J, et al. Alzheimer's disease drug development pipeline: 2023. *Transl Res & Clin Interv*. 2023; 9(2).

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New AD Targets

Drug Category	Classification	Why Suggested	Why Failed
Monoclonal Antibodies (mABs)	Disease-modifying	These antibodies target the amyloid protein, and they predominate drug discovery efforts [154]. Amyloid has been considered a promising drug target since it is located outside the nerve cells, and it is toxic to the brain's tissues [154].	The mABs have not succeeded in eradicating AD because cognitive impairment predisposing dementia does not associate with amyloid precipitation [154].
Gamma (γ-) Secretase Inhibitors	Disease-modifying	It was proposed that targeting γ-secretase might reduce amyloid production, particularly Aβ42 isoform [160–163]. Phase II trials showed a dose-dependent decrease in both Aβ isoforms (Aβ40 and Aβ42) without significant decrease in tau protein, though the magnetic resonance imaging (MRI) recorded a cerebral atrophy following such treatment [154,165]. Patients showed some improvement at the beginning of treatment.	No distinct response of improvement nor worsening could be traced after 3 months of treatment [154,162]. Side effects were reported with higher doses, such as skin rashes, nausea, and diarrhea, accompanied by higher rate of skin cancer [154,164]. Furthermore, the narrow therapeutic window impeded their proceeding to Phase III [154,165].
Tau Inhibitors	Disease-modifying	The tau protein appeared as a potential target for AD dementia since an irregular phosphorylation of tau results in neurofibrillary tangle formation [166–168]. Clinical studies reported that AD progress is related to tangle formation more than that of Aβ [156]. Initially, tau aggregation inhibitors (TAIs) showed better response.	After long-term treatment (approximately 15 months), TAIs failed in AD treatment. Moreover, 15% of patients showed minor improvement without any co-administered therapy [169].
Neurochemical Enhancers	Symptomatic	Idalopiridine that inhibits 5-hydroxytryptamine 6 (5-HT6) receptors and consequently enhances the release of acetylcholine in the brain, i.e., pro-cholinergic effector [182,183]. Encenicline incites cholinergic response through activating α-7 nicotinic acetylcholine receptors [185–187].	Further clinical studies declared that Idalopiridine does not show any promising effect in AD treatment [182,184]. Side effects of Encenicline were observed in Phase II trials at the maximum dose (2 mg) [185–187]. In addition, the Phase III trials, with doses of 2–3 mg, were terminated due to GI toxicity and eventually discontinued because there was no improvement in cognitive function [185–187].
Miscellaneous	Symptomatic	Dimebon is a histamine (H1) antagonist [188]. It affects α-adrenergic and serotonergic receptors, AMPA and NMDA glutamate receptors, and L-type voltage-gated calcium channels [189].	It exerted a better response in AD patients and one Phase II trial in Russia [189], but it failed in Phase III trials in Austria, Europe, New Zealand, and the US [189].

Hajjo R, at al. A review of the recent advances in alzheimer's disease research and the utilization of network biology approaches for prioritizing diagnostics and therapeutics. *Diagnostics*. 2022;12(12).

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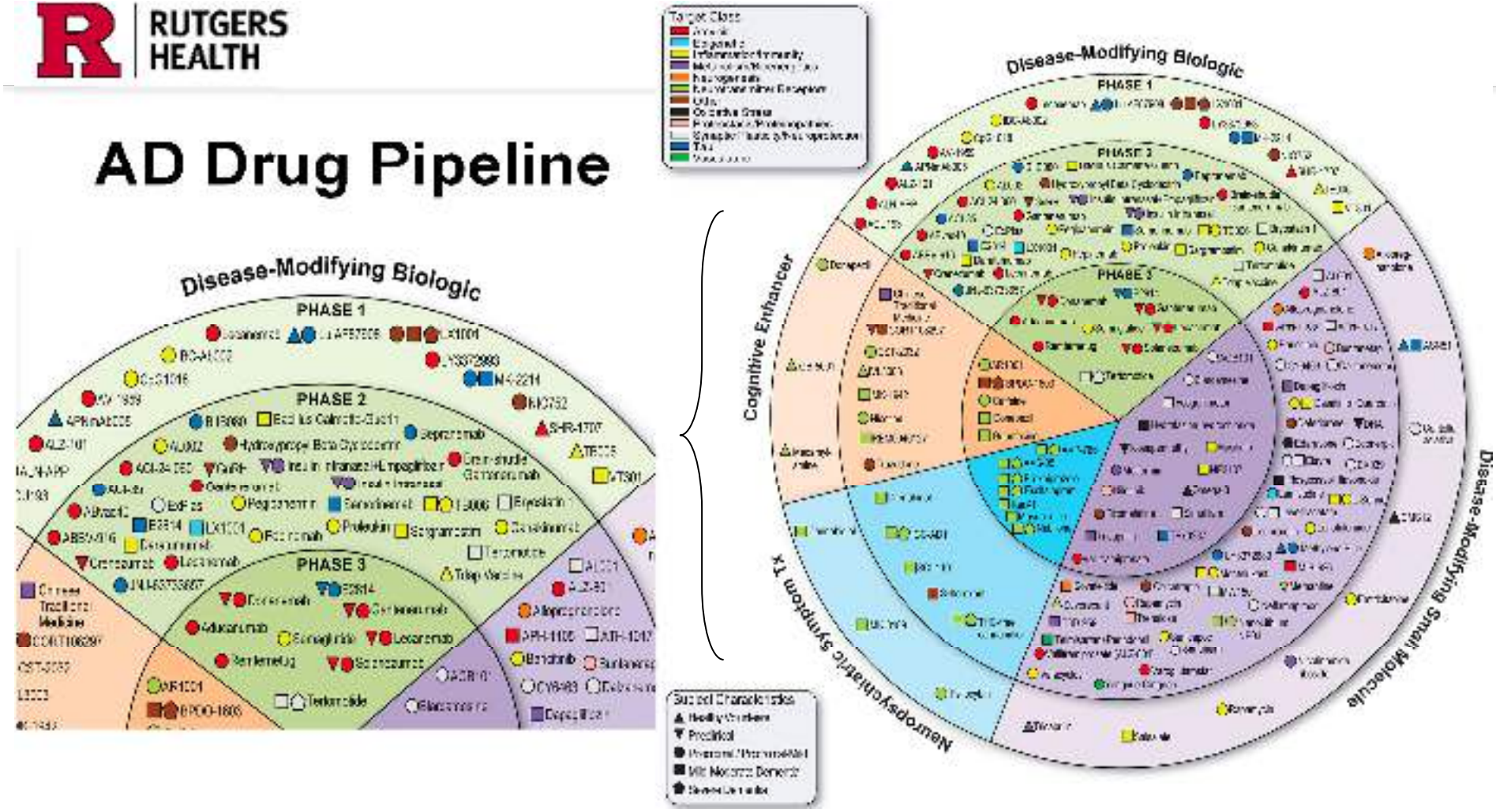
AD Drug Pipeline



Cummings J, et al. Alzheimer's disease drug development pipeline: 2023. *Transl Res Clin Interv*. 2023; 9(2).

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Learning Assessment – Question 3

FDA-approved Anti-amyloid mAb are currently recommended in which AD patient population?

a. Early AD

b. Mild AD

c. Preclinical AD

d. Mild-moderate AD

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AD Drug Pipeline | Development Status

Need for Diverse Participants

Cummings J, et al. Alzheimer's disease drug development pipeline: 2023. *Transl Res Clin Interv*. 2023; 9(2).

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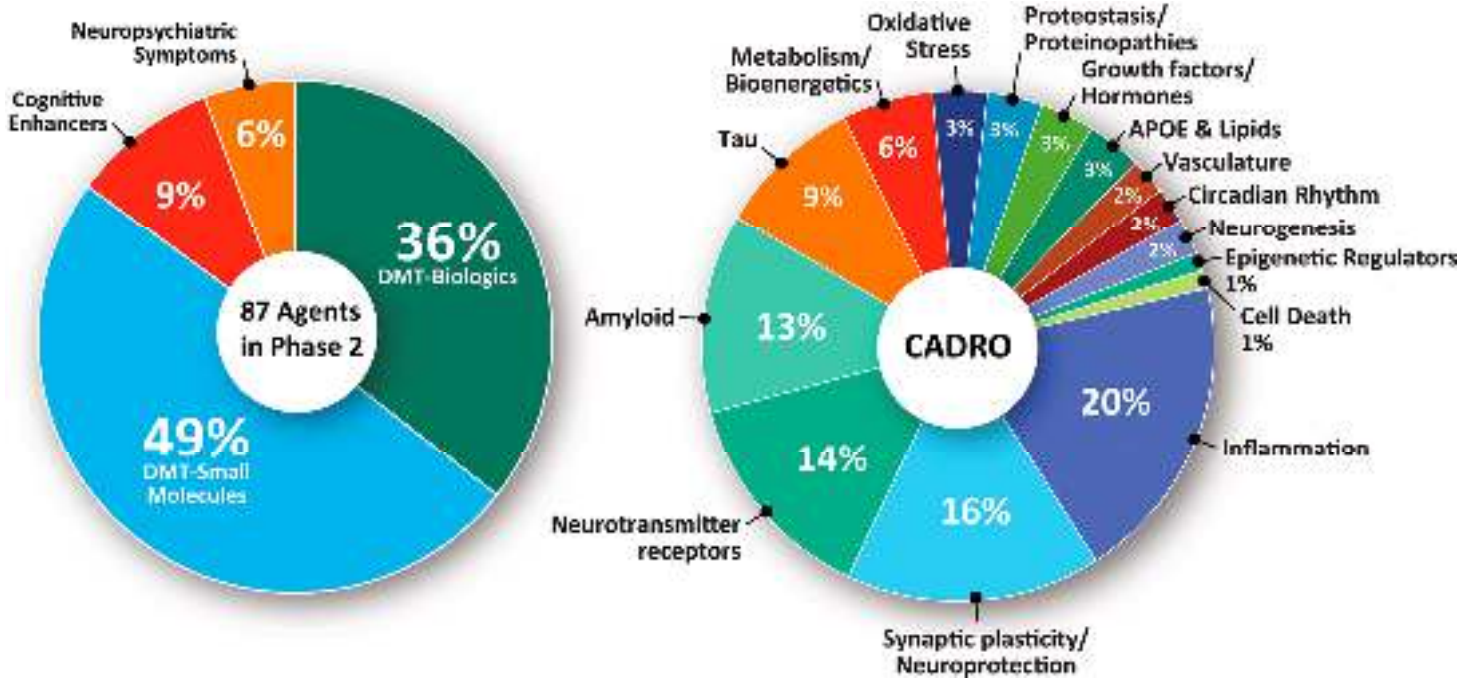
AD Drug Pipeline | MOA – Phase 2



CADRO: Common Alzheimer's Disease Research Ontology

Cummings J, et al. Alzheimer's disease drug development pipeline: 2023. *Transl Res & Clin Interv*. 2023; 9(2).

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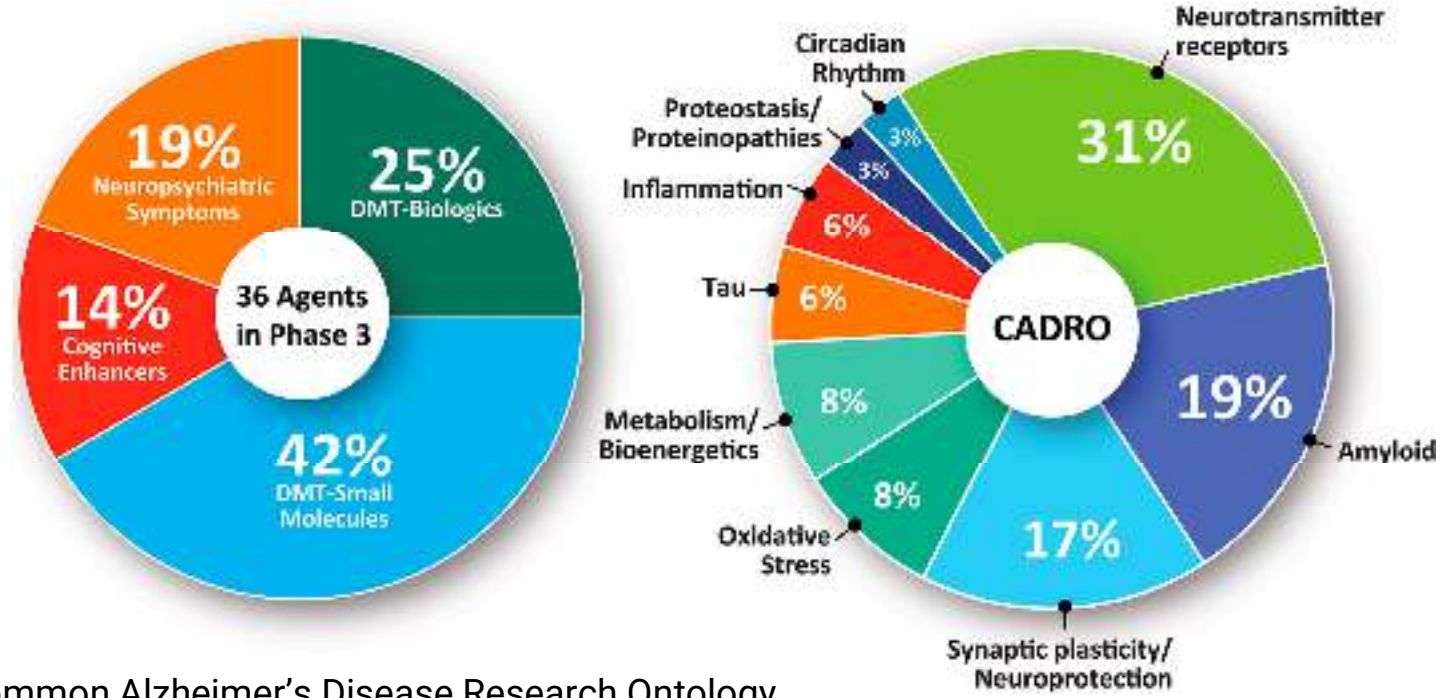
AD Drug Pipeline | MOA – Phase 3



CADRO: Common Alzheimer's Disease Research Ontology

Cummings J, et al. Alzheimer's disease drug development pipeline: 2023. *Transl Res & Clin Interv*. 2023; 9(2).

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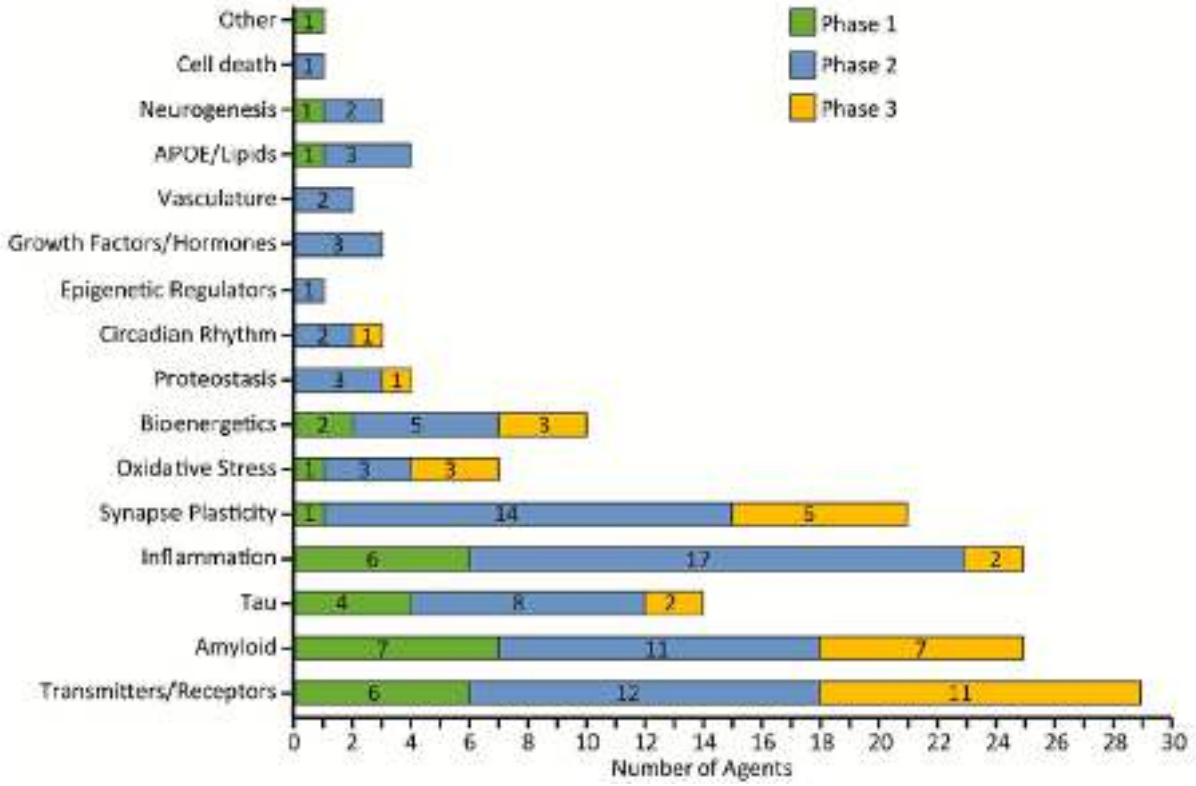
AD Drug Pipeline | MOA – Phase I, II, III



Cummings J, et al. Alzheimer's disease drug development pipeline: 2023. *Transl Res & Clin Interv*. 2023; 9(2).

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AD Drug Pipeline – 2024 Anticipated Data

AL002 (Alector/AbbVie)

- Monoclonal antibody targeting TREM2
- Activates TREM2 signaling to improve cell survival and activity
- Phase II testing ongoing, Phase III development rights held by AbbVie

Fosgonimeton (Athira)

- Modulates HGF system for neuroprotection and anti-inflammatory effects
- Initial Phase II trial in Parkinson's disease dementia showed mixed results
- Phase II/III trial for mild-to-moderate AD underway, topline data expected soon

ALZ-801 (Alzheon)

- Oral disease-modifying treatment targeting amyloid oligomers
- Phase II results showed preservation of hippocampus without increased risk of ARIA
- Phase III testing ongoing, positive data may lead to partnerships

BioSpace. Five Alzheimer's Data Readouts to Watch in 2024. Available at: https://www.biospace.com/article/five-alzheimer-s-data-readouts-to-watch-for-in-2024/. Accessed 10 February 2024.

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AD Drug Pipeline – 2024 Anticipated Data

PRX012 (Prothena)

- Next-generation anti-amyloid antibody with subcutaneous delivery
- Phase I trials ongoing, potential for best-in-class status
- Delayed clinical readouts, but continued interest

AXS-05 (Axsome Therapeutics)

- Symptom-treating drug for Alzheimer's-related agitation
- Repurposed antidepressant tested against agitation
- Positive Phase II and Phase III data, second Phase III study to read out soon

BioSpace. Five Alzheimer's Data Readouts to Watch in 2024. Available at: https://www.biospace.com/article/five-alzheimer-s-data-readouts-to-watch-for-in-2024/. Accessed 10 February 2024.

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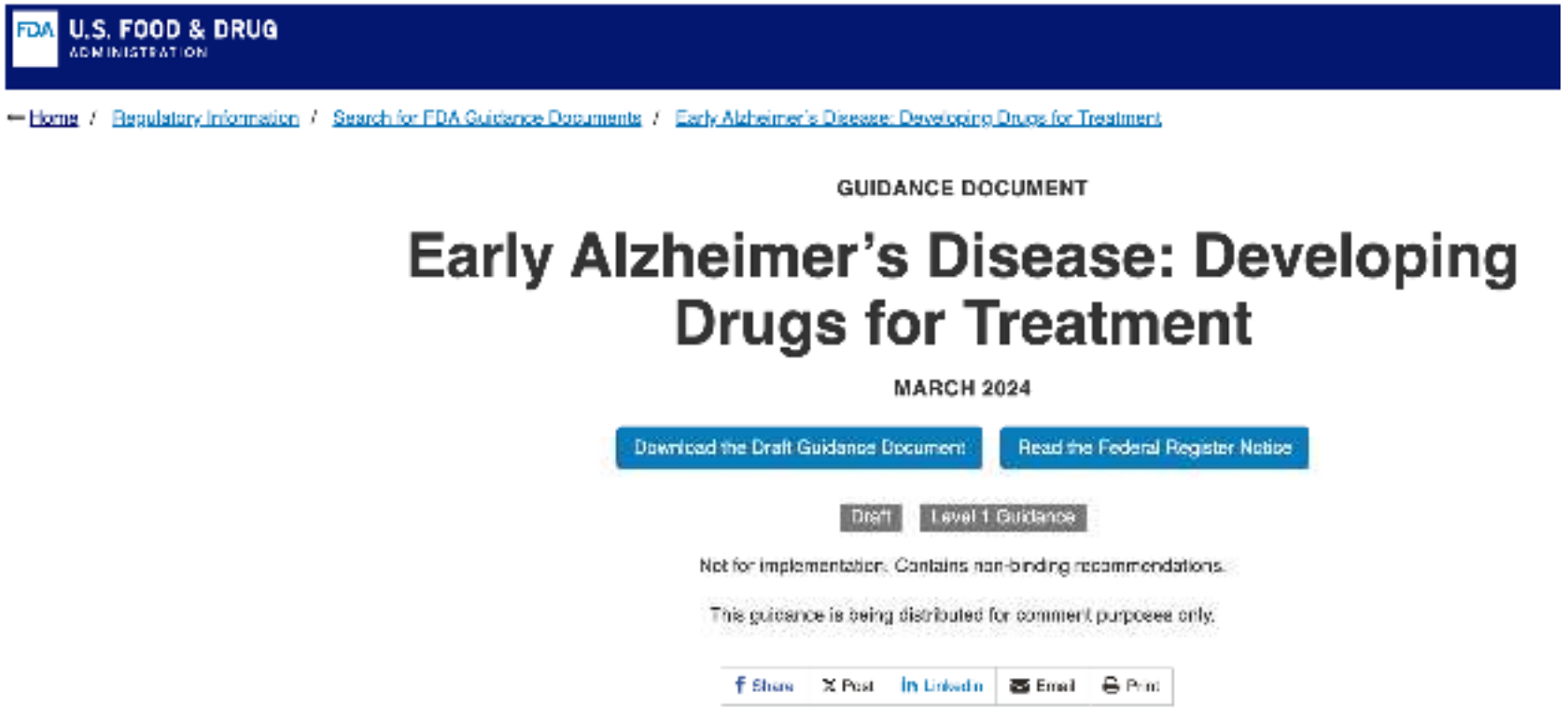
On the Horizon | Stem Cell Therapy

Agent	Phase	Clinical trial NCT#	Sponsor	Start date	Primary completion date
Allogenic human mesenchymal stem cells	Phase 2	NCT02833792	Stemedica Cell Technologies, Inc.	2016-06-01	2024-07-30
Amniotic and umbilical cord tissue	Phase 1	NCT03899298	R3 Stem Cell	2019-09-01	2024-03-20
Autologous adipose tissue derived mesenchymal stem cells	Phase 2	NCT04482413	Nature Cell Co. Ltd.	2023-02-01	2024-05-30
Human mesenchymal stem cells	Phase 1	NCT04040348	Bernard (Barry) Baumel	2019-10-08	2023-05-01
Human umbilical cord blood derived mesenchymal stem cells	Not applicable	NCT04954534	Samsung Medical Center	2021-07-12	2022-01-31
Lomecel-B (mesenchymal stem cells derived from bone marrow)	Phase 2	NCT05233774	Longeveron Inc.	2021-12-28	2023-09-29
SNK01 (autologous natural killer cells)	Phase 1	NCT04678453	NKGen Biotech, Inc.	2021-01-06	2022-12-01

Abbreviation: NCT#, National Clinical Trial number.

Cummings J, et al. Alzheimer's disease drug development pipeline: 2023. *Transl Res & Clin Interv*. 2023; 9(2).

On the Horizon | FDA Action



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GUIDANCE DOCUMENT

Early Alzheimer's Disease: Developing Drugs for Treatment

MARCH 2024

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Draft | Level 1 Guidance

Not for implementation. Contains non-binding recommendations.

This guidance is being distributed for comment purposes only.

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Search for FDA Guidance Documents

Submit Comments by 06/10/2024

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Learning Assessment – Question 4

Which of the following is a target of anti-amyloid mAb currently in the development pipeline?

a. Tau protein

b. Aβ oligomers

c. Stem cells

d. TREM2

Risk vs. Benefit vs. Cost

ICER Publishes Final Evidence Report on Lecanemab for Alzheimer's Disease

Press Release

Independent appeals panel revised the currently available evidence is not adequate to demonstrate a net health benefit for lecanemab when compared to supportive care.

ICER Publishes Evidence Report on Lecanemab for Alzheimer's Disease

Press Release

Currently available evidence is not sufficient to determine whether lecanemab provides a net health benefit over supportive care. The evidence appeals group would achieve incremental thresholds for cost-effectiveness at prices between $[illegible] per year.

ICER Releases Draft Evidence Report on Treatments for Alzheimer's Disease

Press Release

Public comment period now open until February 2, 2022. Requests to make oral comment during public meeting also being accepted.

Cost-Effectiveness and Value-Based Pricing of Aducanumab for Patients With Early Alzheimer Disease

Journal Article

Introduction: Aducanumab was granted accelerated approval despite conflicting evidence base, unanimous FDA Advisory Committee vote to reject approval, and widely criticized launch price of $56,000 per year. The objective of this analysis was to estimate its cost-effectiveness. Methods: We developed a Markov model to compare aducanumab in addition to supportive care to supportive [...]

ICER to Assess Treatments for Alzheimer's Disease

Press Release

Report will be subject of CTAF meeting in July 2022. Draft Scoping Document open to public comment until January 18, 2022.

Institute for Clinical and Economic Review (ICER). Alzheimer's Disease. Available at: https://icer.org/?s=Alzheimer. Accessed 20 March 2024.

Resources

Trial Match

ALZ.org/trialmatch

Alzheimer's Association

Science Hub app

ALZ Forum

alzforum.org

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Key Takeaways

Anti-amyloid mAb target high molecular weight fibrillar Aβ aggregates

Anti-amyloid mAb reduced Aβ demonstrated on amyloid imaging, but clinical benefits in early AD are modest at best

Anti-amyloid mAb are associated with amyloid-related imaging abnormalities (ARIA)

Numerous other anti-amyloid therapies are in various stages of development; novel and multimodal therapies are the future

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Prevent Defense: Anti-Amyloid Therapeutics for the Management of Alzheimer's Disease

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Thank You!