Sixth Annual Participant Appreciation Day Conference on Healthy Brain Aging

Victor W. Henderson, MD

Departments of Epidemiology & Population Health and of Neurology & Neurological Sciences
Director, Farrukh–Jamal Stanford Alzheimer's Disease Research Center

NIH National Institute on Aging
P30 AG066515

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Sixth annual participant appreciation day, Nov. 4, 2023

Sixth Annual Participant Appreciation Day Conference on Healthy Brain Aging

Healthy Brain Aging Study
Farrukh–Jamal Stanford Alzheimer's Disease Research Center (ADRC)
Lewy Body Scientific Partnership for Advancing Research and Knowledge
Stanford Clinical Trials Programs
Stanford Aging and Memory Study (SAMS)
Longitudinal Early-onset Alzheimer's Disease Study
Asian Cohort for Alzheimer's Disease (ACAD)

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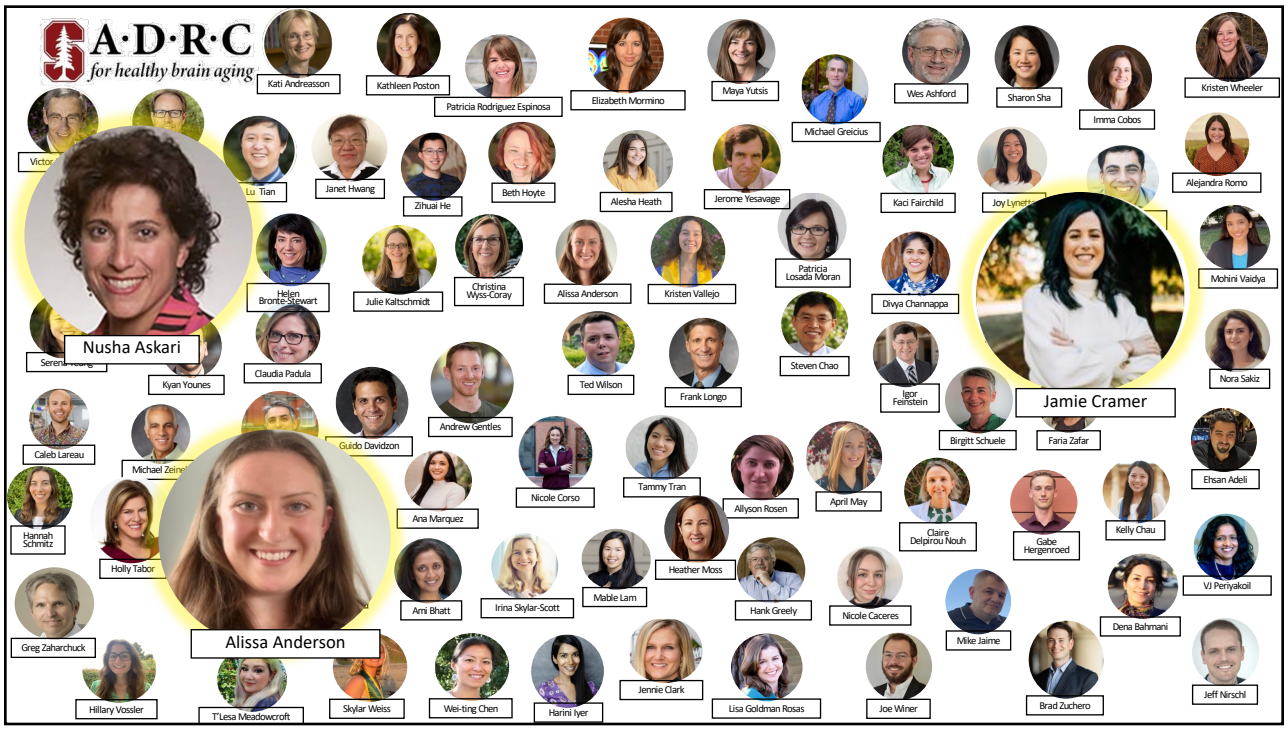
A·D·R·C
for healthy brain aging
Kati Andreasson
Kathleen Poston
Patricia Rodriguez Espinosa
Elizabeth Mormino
Maya Yutsis
Michael Greicius
Wes Ashford
Sharon Sha
Imma Cobos
Kristen Wheeler
Victor Henderson
Tony Wyss Coray
Lu Tian
Janet Hwang
Zihuai He
Beth Hoyte
Alesha Heath
Jerome Yesavage
Kaci Fairchild
Joy Lynette
Nima Aghaeepour
Alejandra Romo
Nusha Askari
Veronica Ramirez
Helen Bronte-Stewart
Julie Kaltschmidt
Christina Wyss-Coray
Alissa Anderson
Kristen Vallejo
Patricia Losada Moran
Divya Channappa
Hannes Vogel
Mohini Vaidya
Serena Yeung
Kyan Younes
Claudia Padula
Ted Wilson
Frank Longo
Steven Chao
Ryan Taylor
Igor Feirstein
Jamie Cramer
Nora Sakiz
Caleb Lareau
Michael Zeineh
Monther Abu-Remaileh
Guido Davidzon
Andrew Gentles
Birgitt Schuele
Faria Zafar
Ehsan Adeli
Hannah Schmitz
Holly Tabor
John Barry
Ana Marquez
Nicole Corso
Tammy Tran
Allyson Rosen
April May
Claire Delpirou Nouh
Gabe Hergenroed
Kelly Chau
VJ Periyakoil
Windy McNerney
Ami Bhatt
Irina Skylar-Scott
Mable Lam
Heather Moss
Hank Greely
Nicole Caceres
Mike Jaime
Dena Bahmani
Greg Zaharchuck
Alissa Anderson
Hillary Vossler
T'Lesa Meadowcroft
Skylar Weiss
Wei-ting Chen
Harini Iyer
Jennie Clark
Lisa Goldman Rosas
Joe Winer
Brad Zuchero
Jeff Nirschl

3


A·D·R·C
for healthy brain aging
Nusha Askari
Jamie Cramer
Alissa Anderson

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CAB (Community Advisory Board)

Stella De La Pena	Alzheimer's Association
Leslie DuBridge	Senior advocate
Denise Coley	Parkinson's disease advocate
Sandra Green	Alzheimer's Association
Sara Langer	Stanford ADRC participant volunteer
Kirk Leu	Caregiver
Ting Pun	Vi Senior Housing Community
Scott Roney	Veteran
Elissa Wellikson	Veteran
Sandra Winters	Senior Coastsiders
Benjamin Yen	Caregiver
Amy Yotopolous	Avenidas

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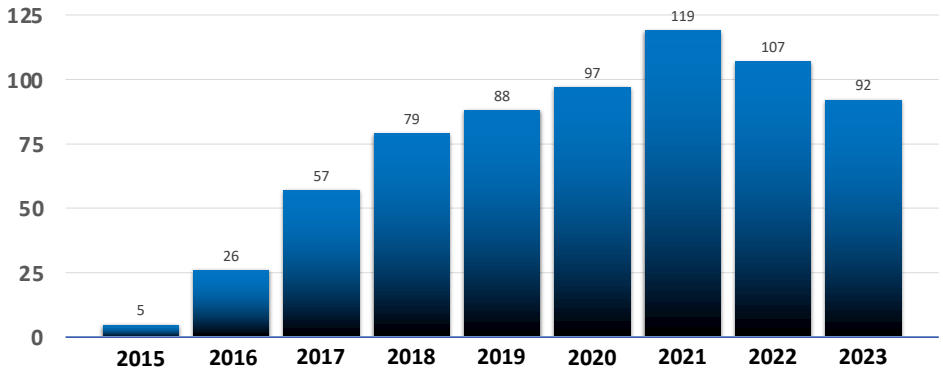
Sixth annual participant appreciation day, Nov. 4, 2023

579 scientific publications in the National Library of Medicine (PubMed Central) cite the Stanford ADRC NIH grant, July 2015 to October 2023



NIH National Institute on Aging

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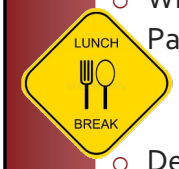
- New FDA-approved treatments for mild cognitive impairment and mild dementia due to Alzheimer's disease (**Victor Henderson**)
- Your genetics are driving advances in Alzheimer's disease (**Michael Greicius**)
- What your blood can tell us about age and disease (**Tony Wyss-Coray**)
- Why we ask for skin samples: Human stem cell models for Alzheimer's disease and Parkinson's disease / dementia with Lewy bodies research (**Birgitt Schuele**)



- Destimatizing the lumbar puncture: What is it and why does it matter (**Ryan Taylor**)
- Lumbar puncture: A personal perspective (**Celina Rodriguez**)
- JEDI: Justice, equity, diversity and inclusion in the ADRC (**Patricia Rodriguez Espinosa**)
- Stanford ADRC Community Advisory Board (**Lisa Goldman Rosas**)
- Breakout session: "We want to hear from you" (**Lisa Goldman Rosas**)

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Sixth annual participant appreciation day, Nov.4, 2023

New FDA-approved treatments for mild cognitive impairment and mild dementia due to Alzheimer's disease

Victor W. Henderson, MD

Departments of Epidemiology & Population Health and of Neurology & Neurological Sciences
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NIH National Institute on Aging
P30 AG066515

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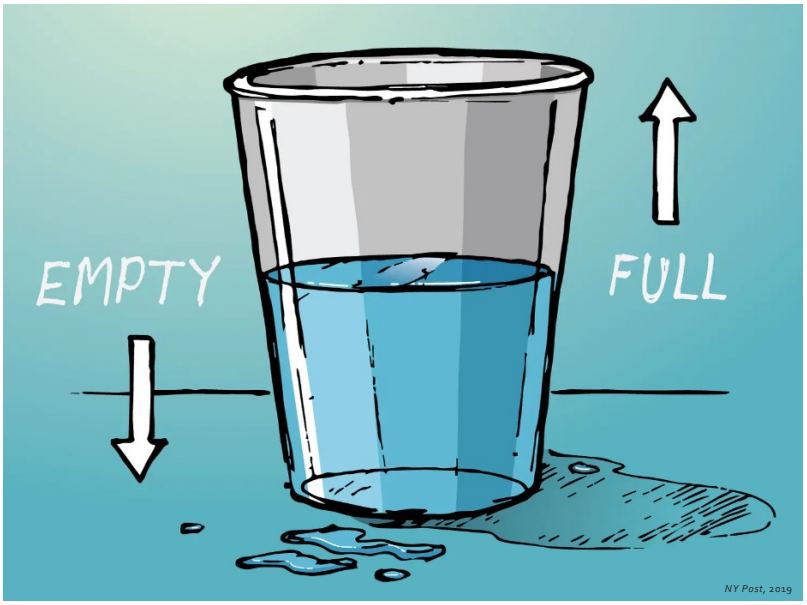
New FDA-approved treatments for mild cognitive impairment and mild dementia due to Alzheimer's disease



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Before now, there were no approved treatments for the early stages of Alzheimer's disease

But now there are FDA-approved treatments for both MCI and mild dementia associated with Alzheimer's disease biomarkers

- Aducanumab ⇢ Accelerated approval by the FDA, June 2021
- Lecanemab ⇢ Regular approval by the FDA, July 2023
- Donanemab ⇢ Under FDA review

These are IgG1 monoclonal antibodies that target β-amyloid and reduce brain amyloid

Rubin, *JAMA* 2023;330:1411

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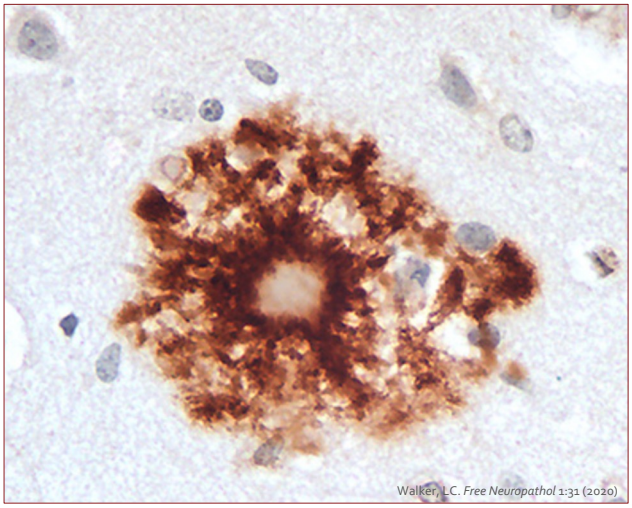
Amyloid Plaque



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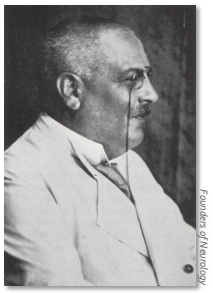
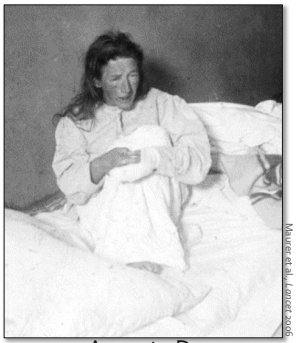
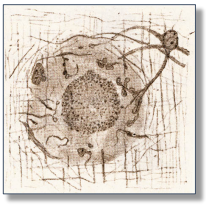
Plaques and tangles

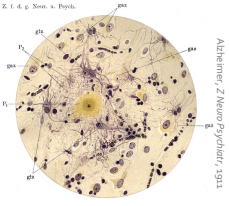


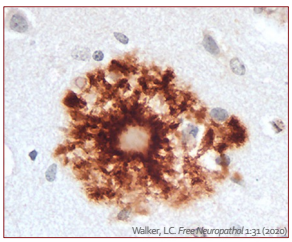
Alois Alzheimer



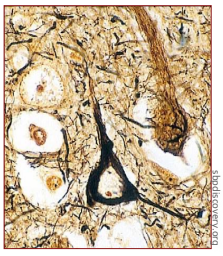
Auguste D.

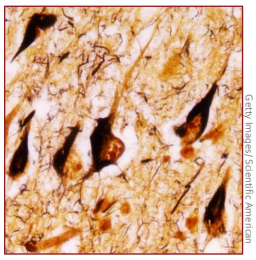






- Plaque cores: β-amyloid protein
- Neurofibrillary tangles: Tau protein (hyperphosphorylated)





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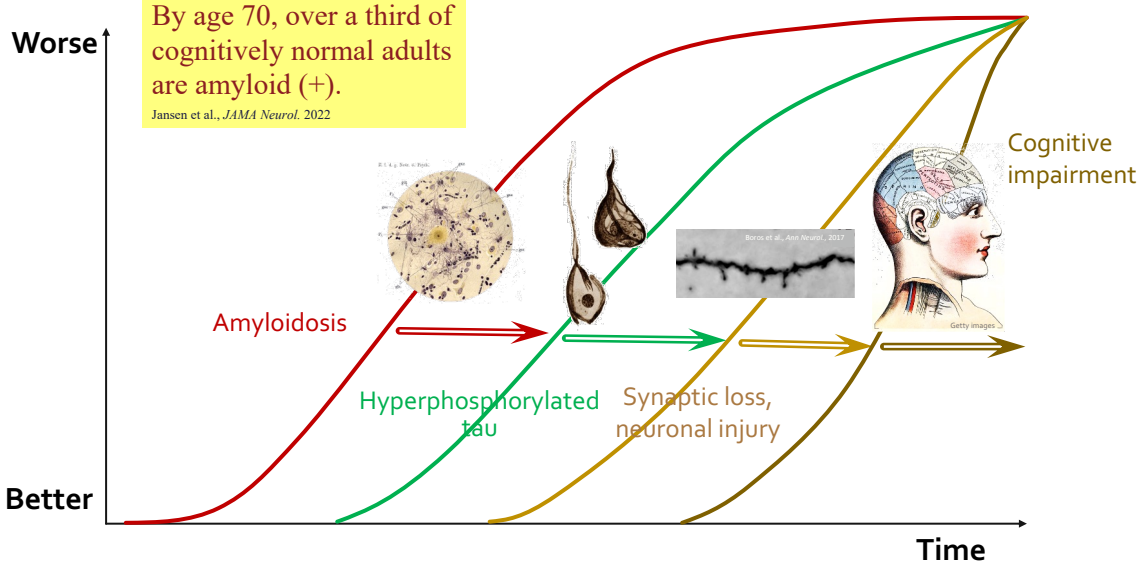
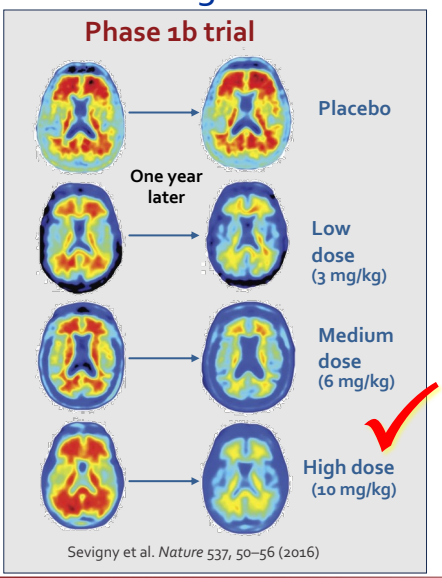
Amyloid hypothesis of Alzheimer's disease (early 1990s)

By age 70, over a third of cognitively normal adults are amyloid (+).
Jansen et al., *JAMA Neurol.* 2022



13

Aducanumab: Impressive amyloid reductions in a Phase-1b trial and two Phase-3 trials



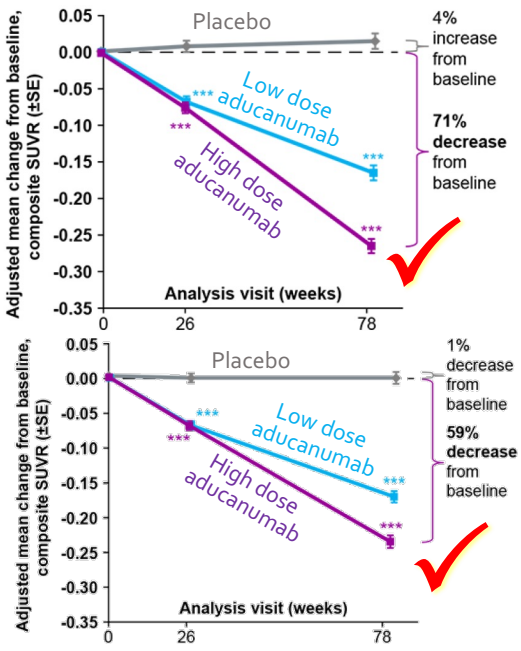
Sevigny et al. *Nature* 537, 50–56 (2016)

Phase 3 trial ENGAGE

Phase 3 trial EMERGE

SUVr = Standardized uptake value ratio

Haeberlein et al., *J Prev Alz Dis* 2022;2:197



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Clinical Dementia Rating (CDR) Sum of Boxes score

	NONE 0	QUESTIONABLE 0.5	MILD 1	MODERATE 2	SEVERE 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to taken to functions outside a family home	No pretense of independent function outside home Appears too ill to be be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

CDR sum of boxes ranges from 0 (best) to 18 (worst). Minimal clinically important difference estimated at 1-2 points.

Clinical Dementia Rating (CDR): based on cognition and function

Hughes et al, *Brit J Psychiatry*, 1982; Morris, *Neurology*, 1993

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Aducanumab: Unimpressive clinical results

80% MCI, 20% mild AD-dementia

- **EMERGE** phase 3 trial
  - 18 months, monthly influsions, n = 1638
  - Very small benefit
- **ENGAGE** phase 3 trial
  - 18 months, monthly infusions, n = 1647
  - No benefit

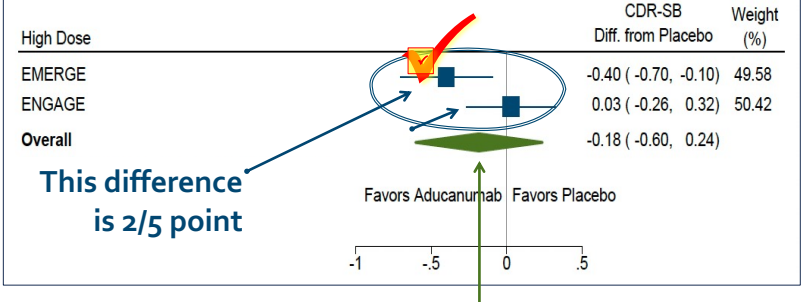
J Prev Alz Dis 2022;2(9):197-210
Published online March 18, 2022, http://dx.doi.org/10.14283/jpad.2022.30
Haeberlein et al.

Original Research

© The Author(s) 2022

Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease

Figure 3.1. Meta-Analysis of Difference in CDR-SB versus Placebo



This difference is 2/5 point

The overall mean difference is less than 1/5 point

Accelerated FDA approval in June 2021

Lin GA et al. Aducanumab for Alzheimer's Disease: Effectiveness and Value. Institute for Clinical and Economic Review, August 5, 2021. https://icer.org/assessment/alzheimers-disease-2021/. Accessed 15 Oct. 2021

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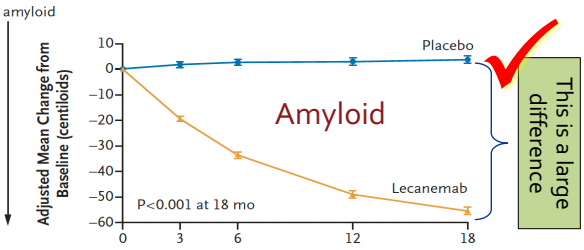
The NEW ENGLAND JOURNAL of MEDICINE

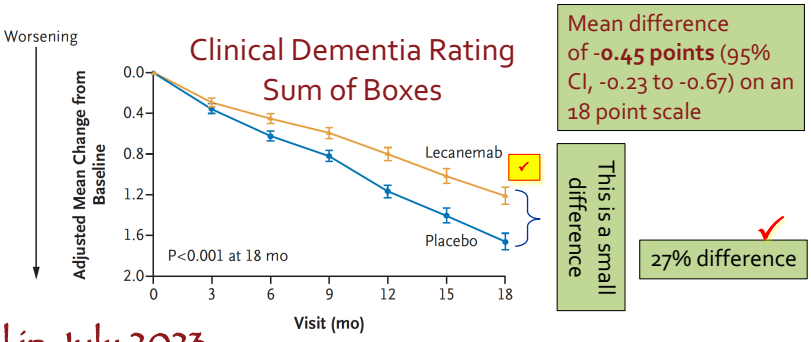
ORIGINAL ARTICLE

Lecanemab in Early Alzheimer's Disease

Van Dyck et al., *NEJM* 2023; 388:9-21

- Lecanemab infusions versus placebo every two weeks
- MCI (62%) or mild AD-dementia (38%), **n = 1795**
- Primary outcome: Change in CDR-Sum of Boxes at 18 months





Mean difference of **-0.45 points** (95% CI, -0.23 to -0.67) on an 18 point scale

27% difference

Regular FDA approval in July 2023

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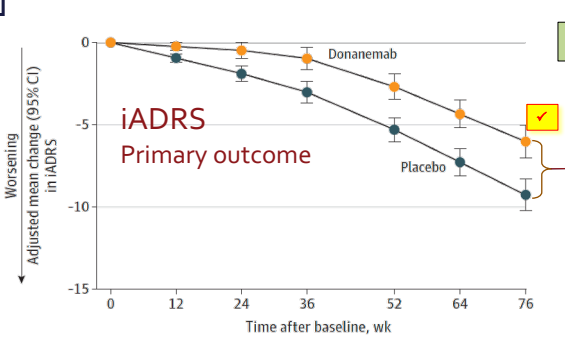
JAMA | Original Investigation

Donanemab in Early Symptomatic Alzheimer Disease
The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

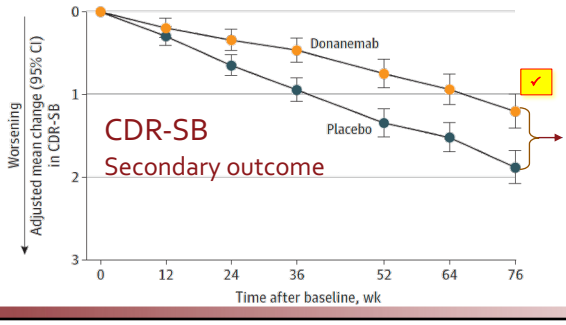
Sims et al., *JAMA* 2023;330:512

- Donanemab infusions versus placebo every 4 weeks
- MCI or mild AD-dementia, n = 1736
- Primary outcome: change in iADRS (Integrated Alzheimer's Disease Rating Scale) at 72 weeks



35% difference

Mean difference of **-3.3** points (95% CI, -1.9 to -4.6) on a 144 point scale



These are small differences

Mean difference of **-0.68** points (95% CI, -0.42 to -0.94) on an 18 point scale

37% difference

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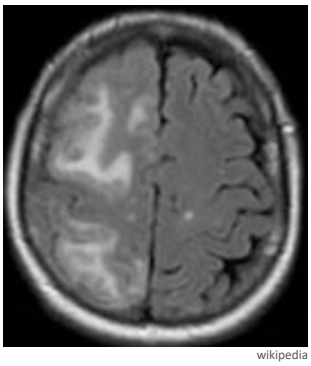
A·D·R·C for healthy brain aging

Amyloid Related Imaging Abnormalities (ARIA): Edema and Hemorrhage

ARIA-E

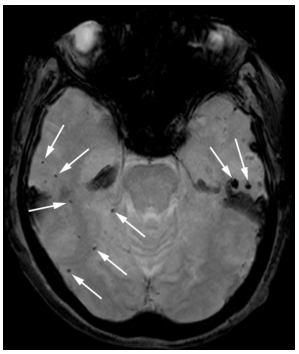
Edema



wikipedia

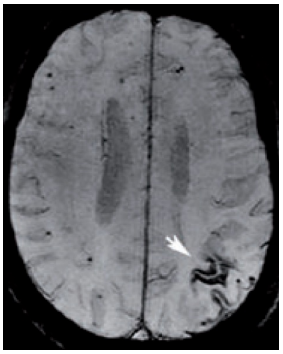
ARIA-H

Microhemorrhage



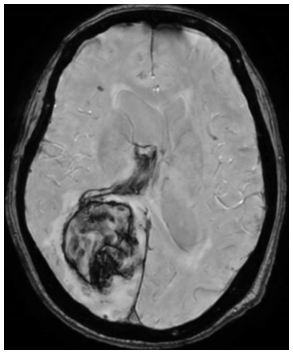
Piller, science.org, 21 Dec 2022

Superficial siderosis



Charidimou et al., Brain 2015;138:2126

Macrohemorrhage



Villain et al., *Rev Neurol* 2022;178:1-11

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Adverse events: Drug – placebo differences in phase-3 trials

Drug	ARIA-E	ARIA-H					
		Micro-hemorrhage	Superficial siderosis	Macro-hemorrhage			
Aducanumab* (ENGAGE)	**33%** (36% vs. 3%)	**13%** (19% vs. 6%)	**14%** (16% vs. 2%)	-			
Aducanumab* (EMERGE)	**32%** (35% vs. 2%)	**13%** (20% vs. 7 %)	**10%** (13% vs. 3%)	-			
Lecanemab (Clarity AD)	**11%** (13% vs. 2%)	**6%** (14% vs. 8%)	**3%** (6% vs. 3%)	5 drug / 1 placebo			
Donanemab (Trailblazer-Alz 2)	**22%** (24% vs. 2%)	**14%** (27% vs. 13%)	**13%** (16% vs. 3%)	3 drug / 2 placebo			

ARIA-E, Amyloid related imaging abnormality – edema. ARIA-H, Amyloid related imaging abnormality – hemorrhage.

*Results for high-dose aducanumab subgroup.

†Flu-like symptoms, nausea, vomiting, hyper- or hypotension, oxygen desaturation; transient decreased LC counts (38% vs. 2%) and increased leukocyte counts (22% vs. 1%)

§Percent difference; Alves et al., *Neurology* 2023;100:e2114

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Adverse events: Drug – placebo differences in phase-3 trials

Drug	ARIA-E	ARIA-H			Infusion reaction†	Death	
		Micro-hemorrhage	Superficial siderosis	Macro-hemorrhage			
Aducanumab* (ENGAGE)	**33%** (36% vs. 3%)	**13%** (19% vs. 6%)	**14%** (16% vs. 2%)			8 drug / 5 placebo	
Aducanumab* (EMERGE)	**32%** (35% vs. 2%)	**13%** (20% vs. 7 %)	**10%** (13% vs. 3%)				
Lecanemab (Clarity AD)	**11%** (13% vs. 2%)	**6%** (14% vs. 8%)	**3%** (6% vs. 3%)	5 drug / 1 placebo	**19%** (26% vs. 7%)	6 drug / 7 placebo	
Donanemab (Trailblazer-Alz 2)	**22%** (24% vs. 2%)	**14%** (27% vs. 13%)	**13%** (16% vs. 3%)	3 drug / 2 placebo	**8%** (9% vs. 1%)	16 drug / 10 placebo	

Opportunity for unblinding?

ARIA-E, Amyloid related imaging abnormality – edema. ARIA-H, Amyloid related imaging abnormality – hemorrhage.

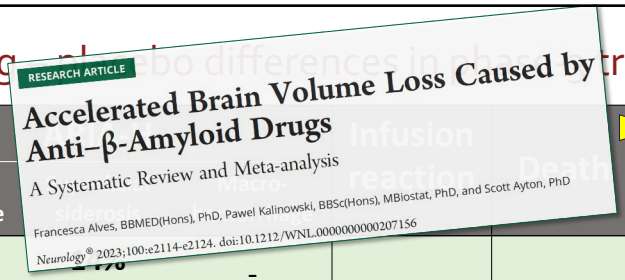
*Results for high-dose aducanumab subgroup.

†Flu-like symptoms, nausea, vomiting, hyper- or hypotension, oxygen desaturation; transient decreased LC counts (38% vs. 2%) and increased leukocyte counts (22% vs. 1%)

§Percent difference; Alves et al., *Neurology* 2023;100:e2114

21

Adverse events: Drug – placebo differences in phase-3 trials


RESEARCH ARTICLE

Accelerated Brain Volume Loss Caused by Anti–β-Amyloid Drugs

A Systematic Review and Meta-analysis

Francesca Alves, BBMED(Hons), PhD, Pawel Kalinowski, BBSc(Hons), MBiostat, PhD, and Scott Ayton, PhD

Neurology® 2023;100:e2114-e2124. doi:10.1212/WNL.0000000000207156

Drug	ARIA-E	ARIA-H			Infusion reaction†	Death	Brain volume loss§
		Micro-hemorrhage	Superficial siderosis	Macro-hemorrhage			
Aducanumab* (ENGAGE)	**33%** (36% vs. 3%)	**13%** (19% vs. 6%)	**14%** (16% vs. 2%)	-	-	8 drug / 5 placebo	**0%**
Aducanumab* (EMERGE)	**32%** (35% vs. 2%)	**13%** (20% vs. 7 %)	**10%** (13% vs. 3%)	-			**4%**
Lecanemab (Clarity AD)	**11%** (13% vs. 2%)	**6%** (14% vs. 8%)	**3%** (6% vs. 3%)	5 drug / 1 placebo	**19%** (26% vs. 7%)	6 drug / 7 placebo	**26%**
Donanemab (Trailblazer-Alz 2)	**22%** (24% vs. 2%)	**14%** (27% vs. 13%)	**13%** (16% vs. 3%)	3 drug / 2 placebo	**8%** (9% vs. 1%)	16 drug / 10 placebo	**23%**

ARIA-E, Amyloid related imaging abnormality – edema. ARIA-H, Amyloid related imaging abnormality – hemorrhage.

*Results for high-dose aducanumab subgroup.

†Flu-like symptoms, nausea, vomiting, hyper- or hypotension, oxygen desaturation; transient decreased LC counts (38% vs. 2%) and increased leukocyte counts (22% vs. 1%)

§Percent difference; Alves et al., *Neurology* 2023;100:e2114

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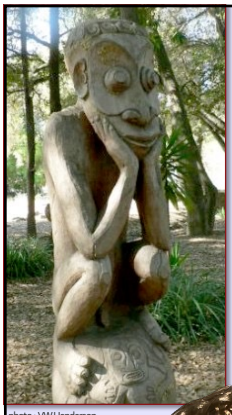

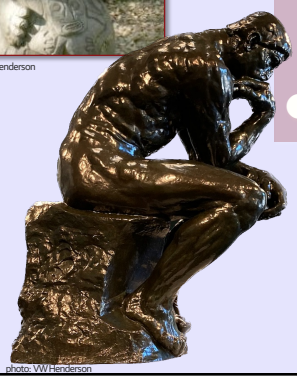

What are other considerations?

- Aducanumab, lecanemab, and (presumably) donanemab are expensive.
- Screening, treatment, and monitoring are resource intensive.
- There are equity concerns.

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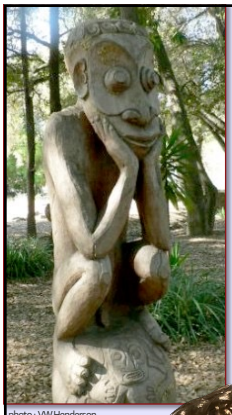

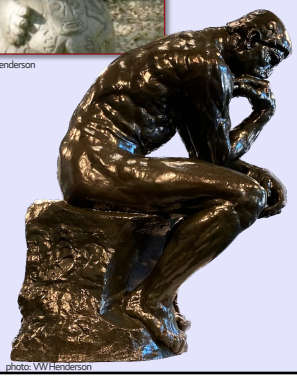

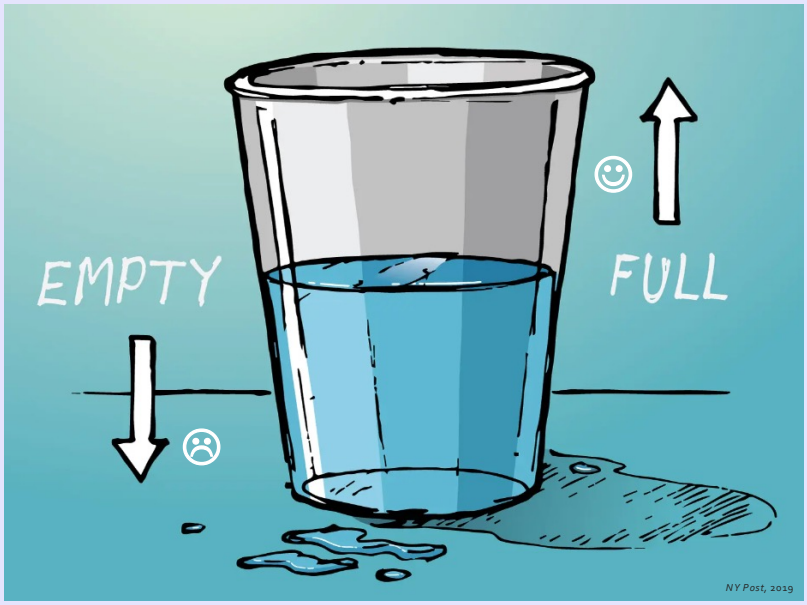

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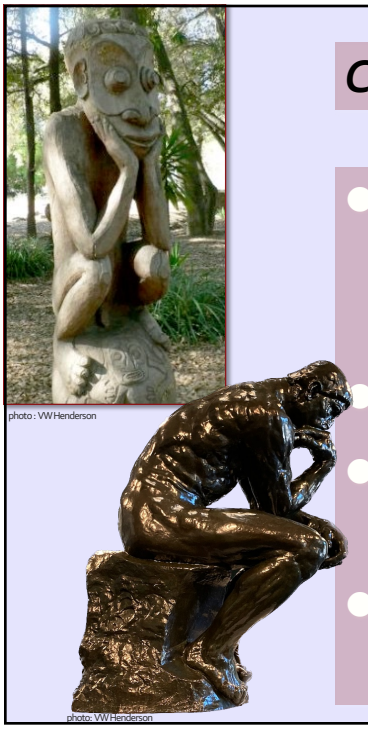

Concluding thoughts

- For the first time, there are approved treatments for mild cognitive impairment and mild dementia associated with an Alzheimer biomarker. ☺
- Patients worsen despite treatment. ☹
- The average difference in decline at 18 months is significant (e.g., 27% for lecanemab). ☺
- But the average clinical difference at 18 months is probably not noticeable. ☹

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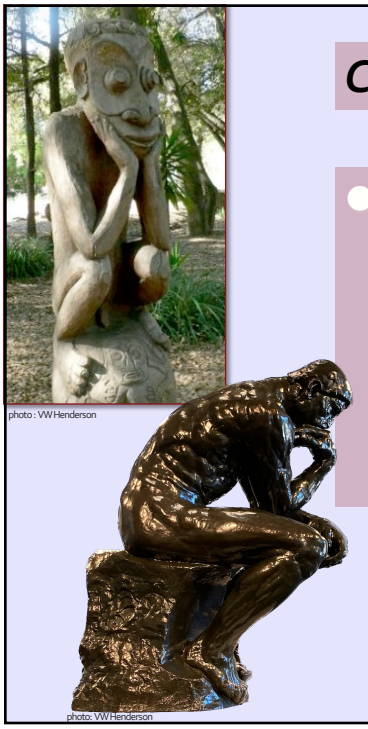

Concluding thoughts

- We don't yet know the long-term clinical outcomes.
  - There may be meaningful long-term benefit, or
  - There may be long-term harm, or
  - There may not be much of a difference.

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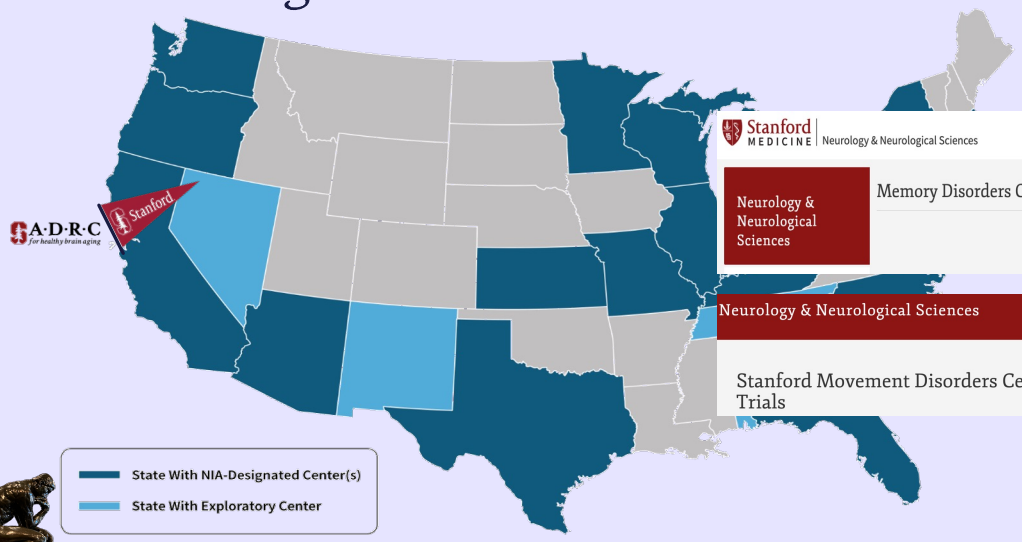
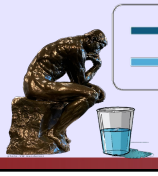
Alzheimer's Disease Research Centers are congressionally designated NIH Centers of Excellence





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Sixth annual participant appreciation day, Nov. 6, 2023

Thank You

New FDA-approved treatments for mild cognitive impairment and mild dementia due to Alzheimer's disease

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Departments of Epidemiology & Population Health and of Neurology & Neurological Sciences
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