3 November 2021, 14:00 – 14:20

4th annual Patient and Research Participant Appreciation Day (virtual)

Aducanumab: Is There a New Treatment for Alzheimer's Disease?

Potential COIs:

NIH grant support for Alzheimer's disease research; honoraria from the Institute for Clinical and Economic Review as an expert reviewer.

Victor W. Henderson, MD, MS
Departments Epidemiology & Population Health and of Neurology & Neurological Sciences
Director, Alzheimer's Disease Research Center

Pacific Udall Center
NIH Center of Excellence for Parkinson's Disease Research
A·D·R·C for healthy brain aging

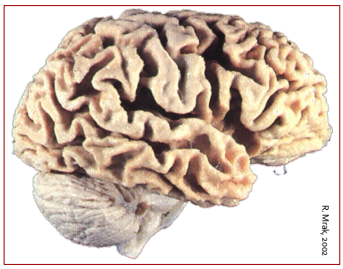
Current therapies

A·D·R·C for healthy brain aging

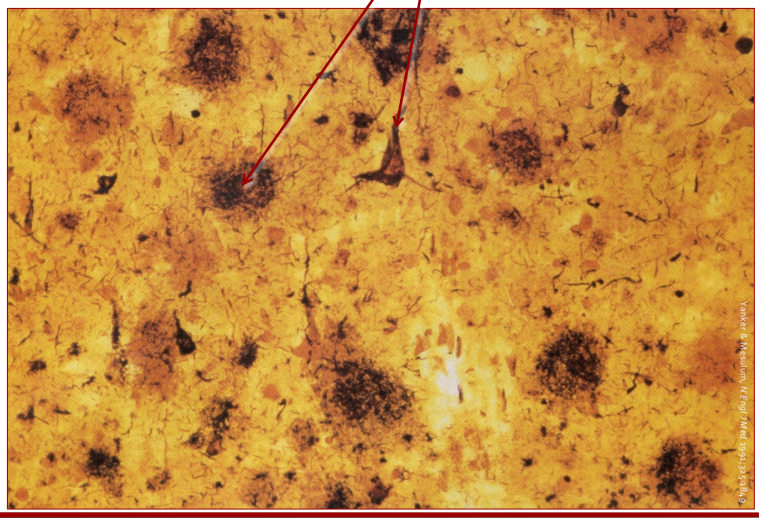
- **3 cholinesterase inhibitors**
  - **Donepezil** (Aricept, 1996)
  - **Galantamine** (Razadyne, 2000)
  - **Rivastigmine** (Exelon, 2001)
- **1 partial N-methyl-D-aspartate (NMDA) receptor antagonist**
  - **Memantine** (Namenda, 2003)

Alzheimer's disease

- Characterized by microscopic changes of neuritic plaques and neurofibrillary tangles.



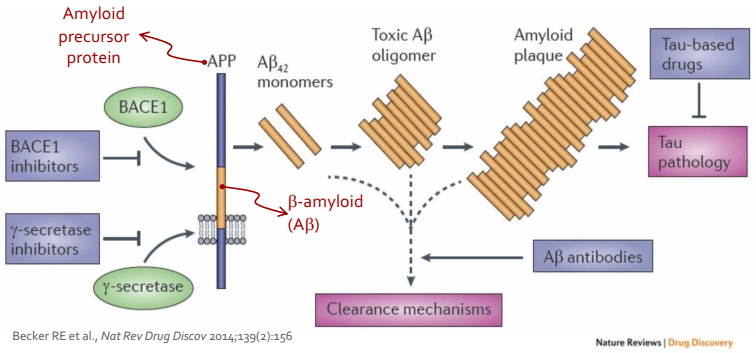
- Neuritic plaques → Beta amyloid (Aβ)
- Neurofibrillary tangles → Tau protein (hyperphosphorylated tau)



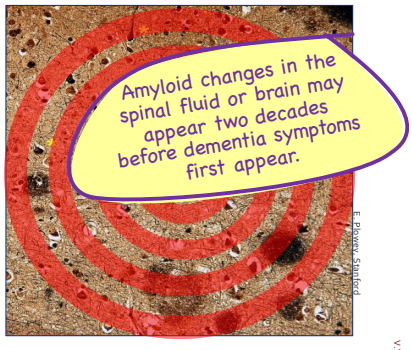
Epidemiology & Population Health
Neurology & Neurological Sciences

A·D·R·C for healthy brain aging

One way to prevent or treat Alzheimer's disease *might* be to target amyloid or tau in the brain.



Becker RE et al., *Nat Rev Drug Discov* 2014;139(2):156



V.W. Henderson, EPI 226, 19 Oct. 2021, 4

Amyloid changes come first

Tau changes come second

Time line

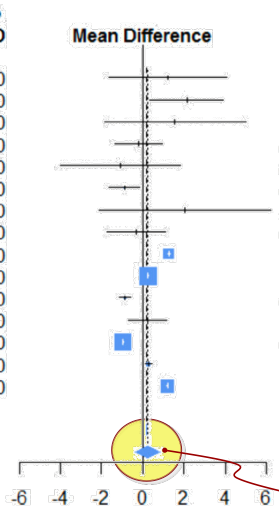
Other anti-amyloid clinical trails

Lu L, et al. *J Neurol Neurosurg Psychiatry* 2020;91:1316–1324.

Forest plot of anti-amyloidβ drugs on the Alzheimer's Disease Assessment Scale-cognitive subscale (RCTs)

Study	Aβ targeted drugs Total	Mean	SD	Placebo Total	Mean	SD	MD	95%-CI	Weight (fixed)	Weight (random)
Coric, Vladimir 2012	109	0.91	7.0400	32	-0.30	7.3500	1.21	[-1.66; 4.08]	0.0%	3.0%
Coric, Vladimir 2015	45	3.15	5.5600	114	1.02	4.0600	2.13	[0.34; 3.92]	0.0%	5.2%
Dodel, Richard 2013	20	1.89	6.6100	5	0.33	2.1200	1.56	[-1.88; 5.00]	0.0%	2.3%
Farlow M 2012	42	0.18	1.9200	10	0.40	1.6300	-0.22	[-1.39; 0.95]	0.0%	7.0%
Gilman S 2005	44	-3.80	7.8000	53	-2.70	6.5000	-1.10	[-3.99; 1.79]	0.0%	3.0%
Lannfelt L 2008	49	0.41	2.2000	29	1.30	1.0500	-0.89	[-1.61; -0.17]	0.1%	8.2%
Salloway, S2009 2009	87	-6.18	17.0400	78	-8.23	9.6900	2.05	[-2.13; 6.23]	0.0%	1.7%
Schwam EM 2014	80	-1.91	4.8300	93	-1.60	4.8200	-0.31	[-1.75; 1.13]	0.0%	6.1%
Doody RS 2013	980	7.65	0.5600	486	6.40	0.4900	1.25	[1.19; 1.31]	10.8%	9.3%
Egan MF 2018	1257	7.95	0.3600	644	7.70	0.3000	0.25	[0.22; 0.28]	36.4%	9.3%
Gauthier, S 2009	181	6.16	1.1400	97	7.03	1.1300	-0.87	[-1.15; -0.59]	0.4%	9.2%
Green RC 2009	787	6.68	9.8500	746	6.44	8.6900	0.24	[-0.69; 1.17]	0.0%	7.7%
Honig LS 2018	1057	4.03	0.3800	1072	4.99	0.4000	-0.96	[-0.99; -0.93]	30.9%	9.3%
Relkin NR 2017	267	3.88	0.9700	123	3.60	0.6400	0.28	[0.12; 0.44]	1.3%	9.3%
Egan MF 2019	969	6.40	0.4100	485	5.20	0.3600	1.20	[1.16; 1.24]	20.0%	9.3%
Fixed effect model	**5974**			**4067**			**0.17**	**[0.15; 0.19]**	**100.0%**	--
Random effects model							**0.20**	**[-0.40; 0.81]**	--	**100.0%**

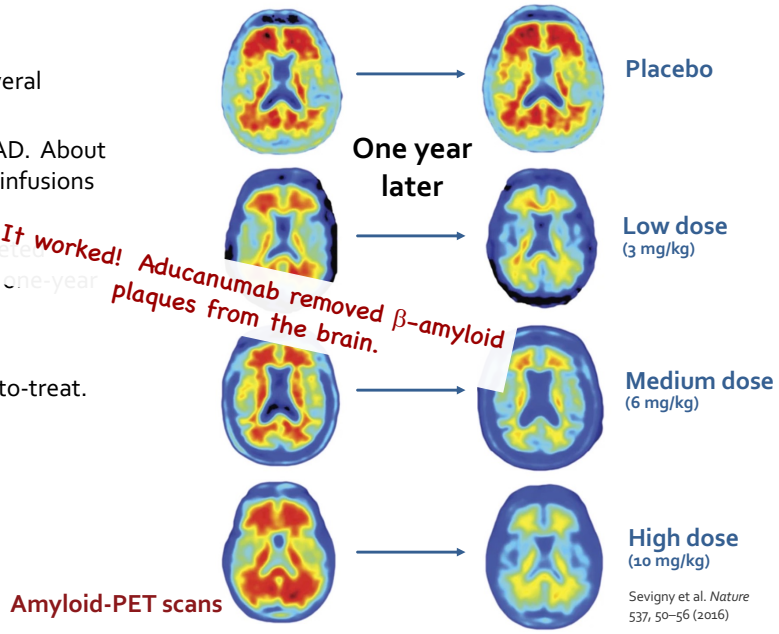
Heterogeneity: I^2 = 100%, τ^2 = 1.0282, p = 0



A four point difference may be clinically meaningful.

Small, phase-1b trial of aducanumab

- PRIME study: Small trial with several different doses of aducanumab.
- Patients with prodromal or mild AD. About one year of monthly intravenous infusions of aducanumab or placebo.
- 197 were randomized; 152 comp[illegible] treatment; 121 with baseline and [illegible]-year scans.
- High dropout rate.
- Analyses not based on intention-to-treat.



It worked! Aducanumab removed β-amyloid plaques from the brain.

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

Aducanumab Phase 3 Trial Design

ENGAGE (301): 46% from the U.S.
EMERGE (302): 40% from the U.S.

Studies	Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
Geography/ Sample size	3285 patients at 348 sites in 20 countries
Population	• Early Alzheimer's disease (MCI due to Alzheimer's disease + mild Alzheimer's disease dementia) – MMSE 24-30, CDR-G 0.5, RBANS ≤ 85, with confirmed amyloid pathology
Doses	• Two dosing regimens (low and high) and placebo; randomized 1:1:1
Primary endpoint	• CDR-SB at 18 months (CDR-SB = Clinical Dementia Rating, sum of boxes)
Other endpoints	• Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI • Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers

Lots of people were studied!

Countries with active sites included:
Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

CDR-SB (clinical dementia rating, sum of boxes)

	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

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

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

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

Results from ENGAGE and EMERGE

Table 3.2. CDR-SB Results from ENGAGE and EMERGE at Week 78, ITT Population[25,27]

	ENGAGE			EMERGE		
	Placebo (n=545)	ADU Low Dose (n=547)	ADU High Dose (n=555)	Placebo (n=548)	ADU Low Dose (n=543)	ADU High Dose (n=547)
Baseline CDR-SB, Mean	2.40	2.43	2.40	2.47	2.46	2.51
Adjusted Mean Change From Baseline at Week 78 (95% CI)	1.56 (1.23, 1.77)	1.38 (1.16, 1.59)	1.59 (1.37, 1.81)	1.74 (1.51, 1.96)	1.47 (1.25, 1.70)	1.35 (1.12, 1.57)
Difference vs. Placebo (95% CI)	--	-0.18 (-0.47, 0.11)	0.03 (-0.26, 0.33)	--	-0.26 (-0.57, 0.04)	-0.39* (-0.69, -0.09)
% Difference vs. Placebo	--	-12%	2%	--	-15%	-22%
p-value (vs. Placebo)	--	0.2250	0.8330	--	0.0901	0.0120

Very slightly better

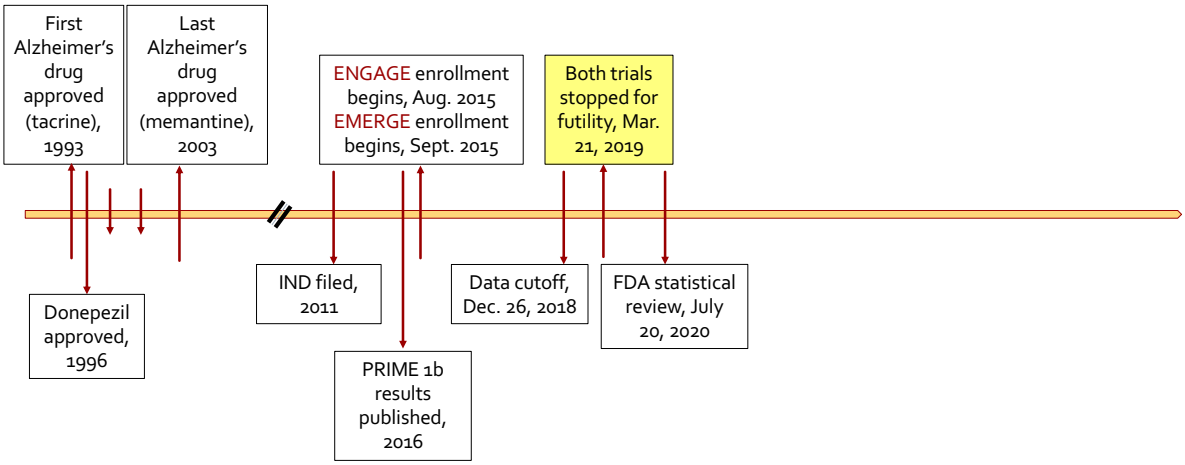
Very, very slightly worse

ADU: aducanumab, CDR-SB: Clinical Dementia Rating-Sum of Boxes, CI: confidence interval, ITT: intention-to-treat

*p<0.05.

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

Time line



FDA Statistical review

"In summary, the totality of the data does not seem to support the efficacy of the high dose [aducanumab].

....

For these reasons, substantial evidence has not been met in this application."

Center for Drug Evaluation and Research, Application number: 761178Orig1s000. STATISTICAL REVIEW(S), issued July 7, 2020.

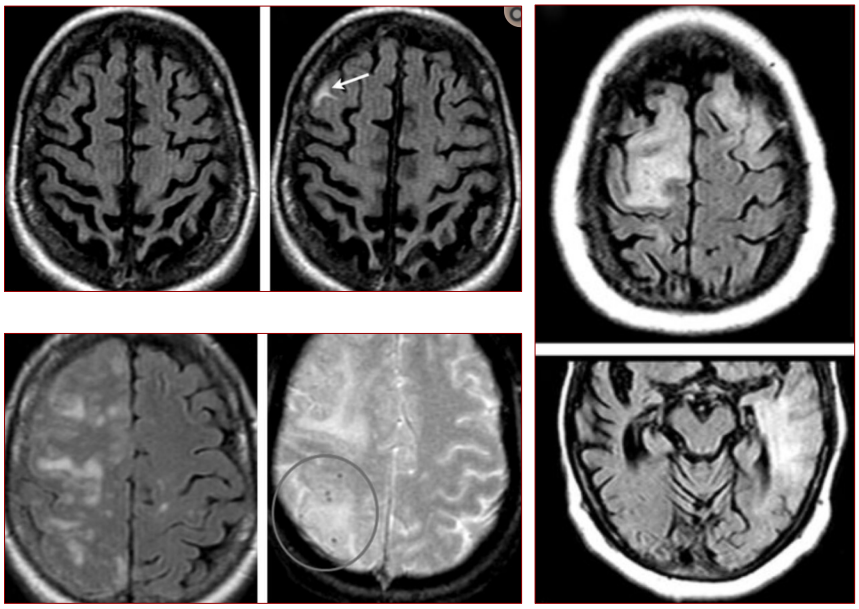
ARIA: An important side-effect

Barakos et al., *AJNR* 2013

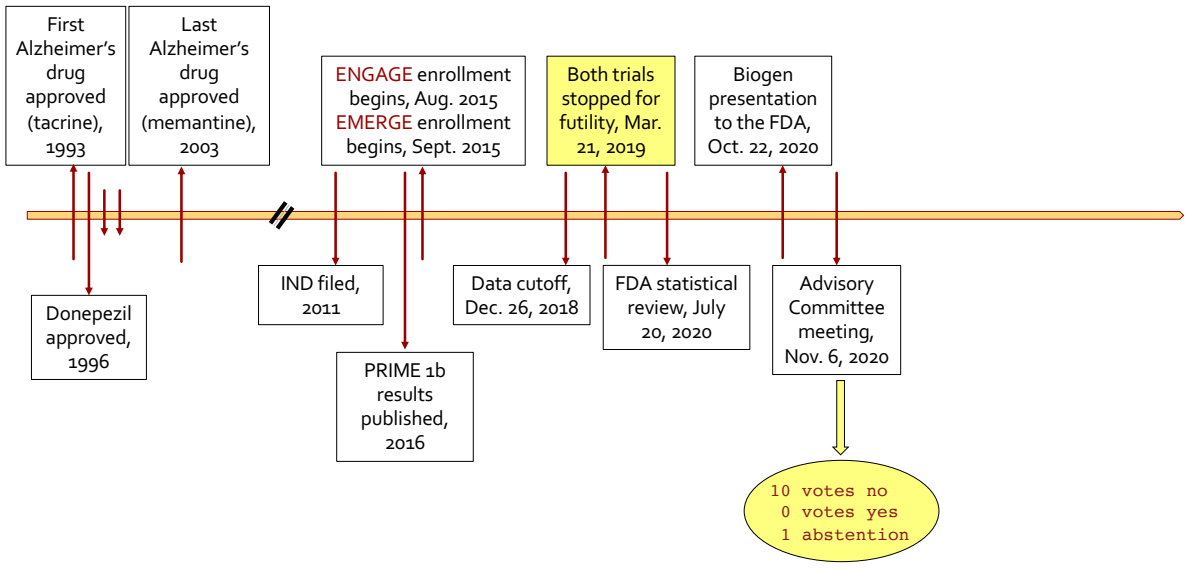
ARIA (amyloid related imaging abnormality) edema and hemorrhage

41% of people receiving high-dose aducanumab

10% of people receiving placebo



Time line



"Accelerated approval" based on amyloid

Fast Track

Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.
Fast Track

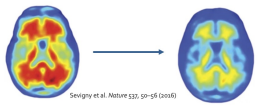
"In 2012, Congress passed the Food and Drug Administration Safety Innovations Act (FDASIA). Section 901 of FDASIA amends the Federal Food, Drug, and Cosmetic Act (FD&C Act) to allow the FDA to base accelerated approval for drugs for serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint.

Amyloid-PET scan

A surrogate endpoint used for accelerated approval is a marker - a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. Likewise, an intermediate clinical endpoint is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug...."

U.S. Food and Drug Administration

Time line



First Alzheimer's drug approved (tacrine), 1993

Last Alzheimer's drug approved (memantine), 2003

ENGAGE enrollment begins, Aug. 2015
EMERGE enrollment begins, Sept. 2015

Both trials stopped for futility, Mar. 21, 2019

Biogen presentation to the FDA, Oct. 22, 2020

Aducanumab approved, June 7, 2021

Phase-4 confirmatory trial required by Aug. 2029

Donepezil approved, 1996

IND filed, 2011

PRIME 1b results published, 2016

Data cutoff, Dec. 26, 2018

FDA statistical review, July 20, 2020

Advisory Committee meeting, Nov. 6, 2020

10 votes no
0 votes yes
1 abstention

Approved under the accelerated approval pathway

Take home messages

- ✓ Older FDA approved medications for Alzheimer's disease (like donepezil or memantine) improve cognitive skills compared to no treatment, but only to a modest degree.
- ✓ Aducanumab removes amyloid from the brain, but results from two very large Phase-3 trials did not show meaningful improvement in cognition or function after 18 months of drug infusion.
- ✓ Aducanumab has side effects (ARIA) that are common and sometimes serious.
- ✓ Aducanumab was approved by the FDA on the basis of its effects on brain amyloid, not because it is safe and effective ("accelerated approval").
- ✓ Some neurologists (and some hospital networks) will not prescribe aducanumab. Others will consider prescriptions for some patients.
- ✓ **We need treatments that make patients visibly better and prevent the disease from developing in the first place, and that requires research.**

Neurologists in the ADRC Clinical Core, in the Stanford Memory Disorders Clinic, or both


Dr. Michael Greicius

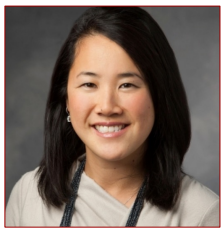

Dr. Victor Henderson


Dr. Frank Longo


Dr. Kathleen Poston


Dr. Sylvia Russo


Dr. Veronica Santini


Dr. Sharon Sha

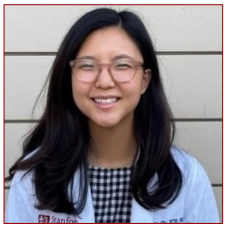

Dr. Irina Skylar-Scott


Dr. Kyan Younes

Clinical Core – ADRC & Udall Center – neuropsychologist, Memory Support Program manager, nurse coordinator, clinical research manager, and research associate coordinators


Dr. Maya Yutsis


Jennie Clark


Isabelle Yi


Veronica Ramirez


Nicole Caceres


Maria-Lucia Campos


Nicole Corso


James Kelbert


T'Lesa Meadowcroft

Aducanumab: Is there a new treatment for Alzheimer's disease?

Pacific Udall Center
Stanford MEDICINE

Thank You

To our patients, research volunteers, family members, caregivers