Alzheimer's disease and Aducanumab (Aduhelm™)

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Loma Linda University School of Medicine – C/o 2022

MANY STRENGTHS. ONE MISSION.
A Seventh-day Adventist Organization

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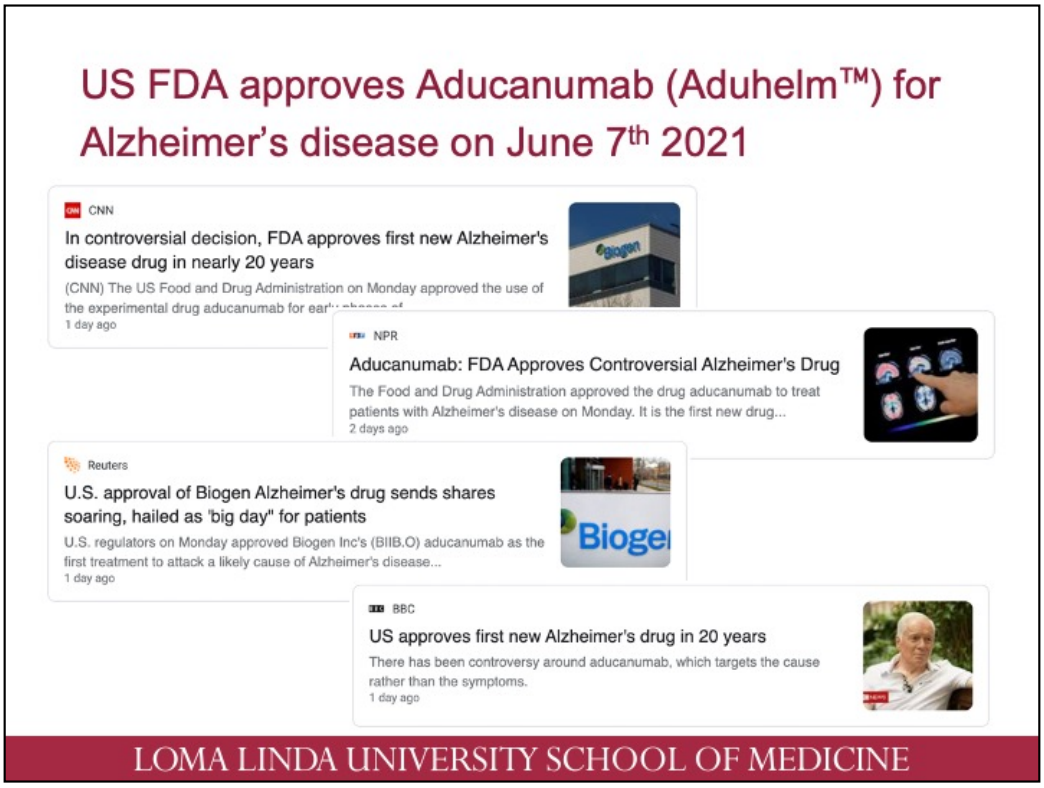
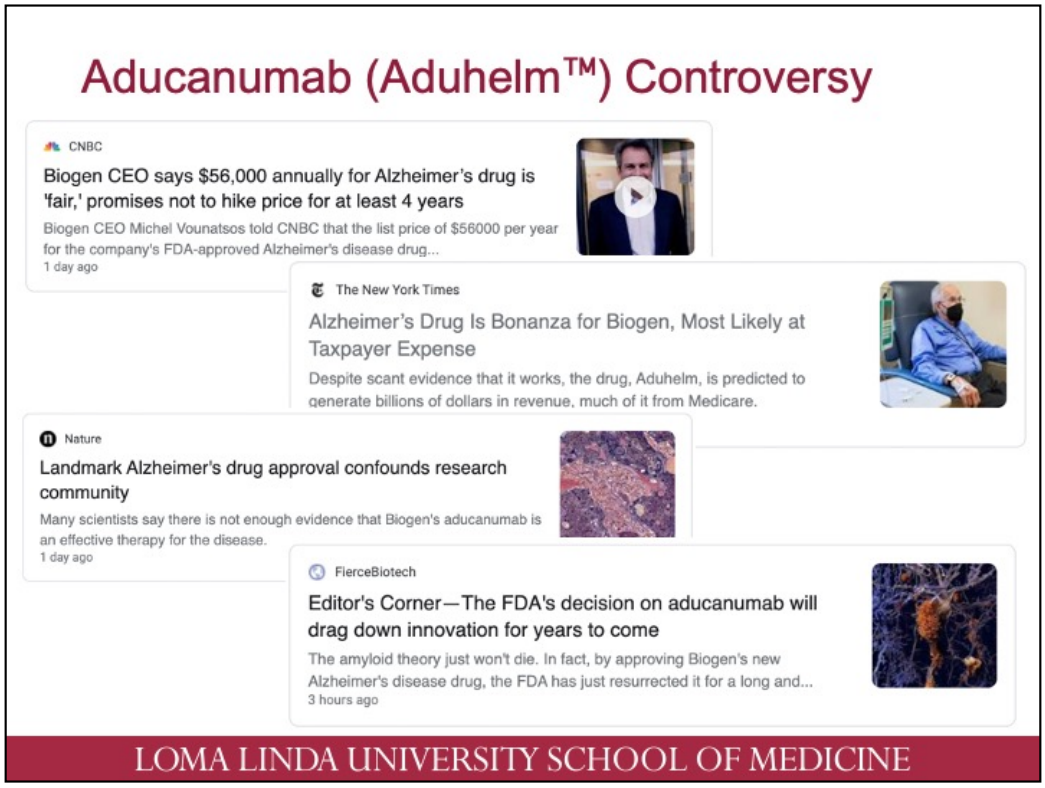


BIG deal, first AD therapy to be approved in nearly 20 years since memantine (Namenda) in 2003

Tacrine was approved by the US Food and Drug Administration (FDA) in 1993, now discontinued due to toxicity.

Then donepezil in 1996, rivastigmine in 1998, galantamine in 2001, and memantine in 2003 (made available in the United States in 2004).

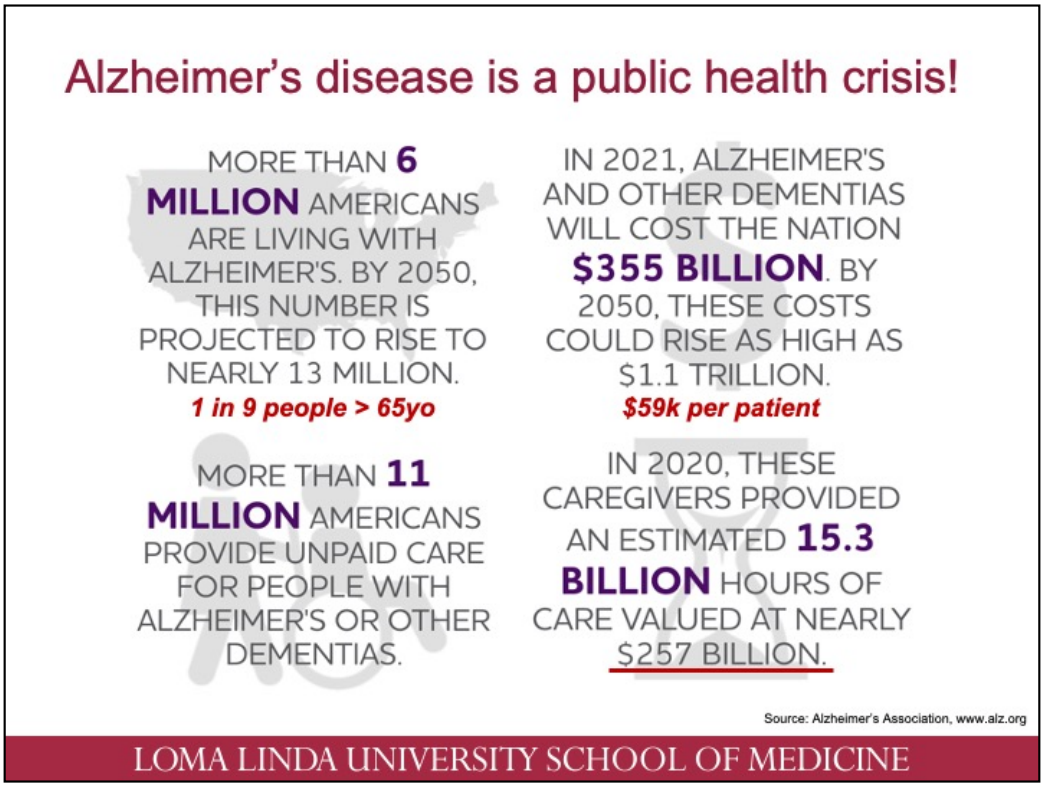


Controversy!!!

High Cost

Lack of Evidence poor Efficacy

Alzheimer's Disease and the Amyloid Hypothesis



National Health Expenditure 2019:

$3.8 trillion, $11.5k per person, 17.7% GDP

Medicare $799 billion

Medicaid $613 billion

Alzheimer's Disease

- Progressive neurodegenerative condition that is ultimately fatal
- Clinical diagnosis, confirmed by post-mortem autopsy
- Estimated to be responsible for ~60-80% of clinical dementia
- Classically associated with CNS pathology of ***beta-amyloid*** and ***tau-neurofibrillary tangles***
- ***NO CURE***
- Minimal clinical benefit with currently available pharmacotherapy, mainly in delaying further disease progression

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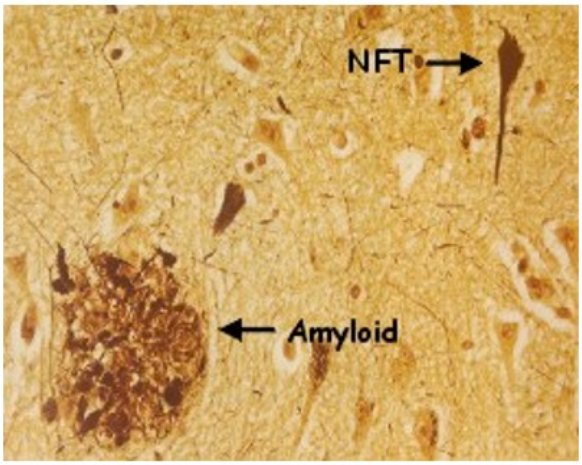
Etiology of Alzheimer's Disease

» In 1906, Alois Alzheimer report the first senile plaques and intracellular neuro-fibrillary tangles in the brain of 51 yo F who died from advanced dementia.



Alois Alzheimer, 1906

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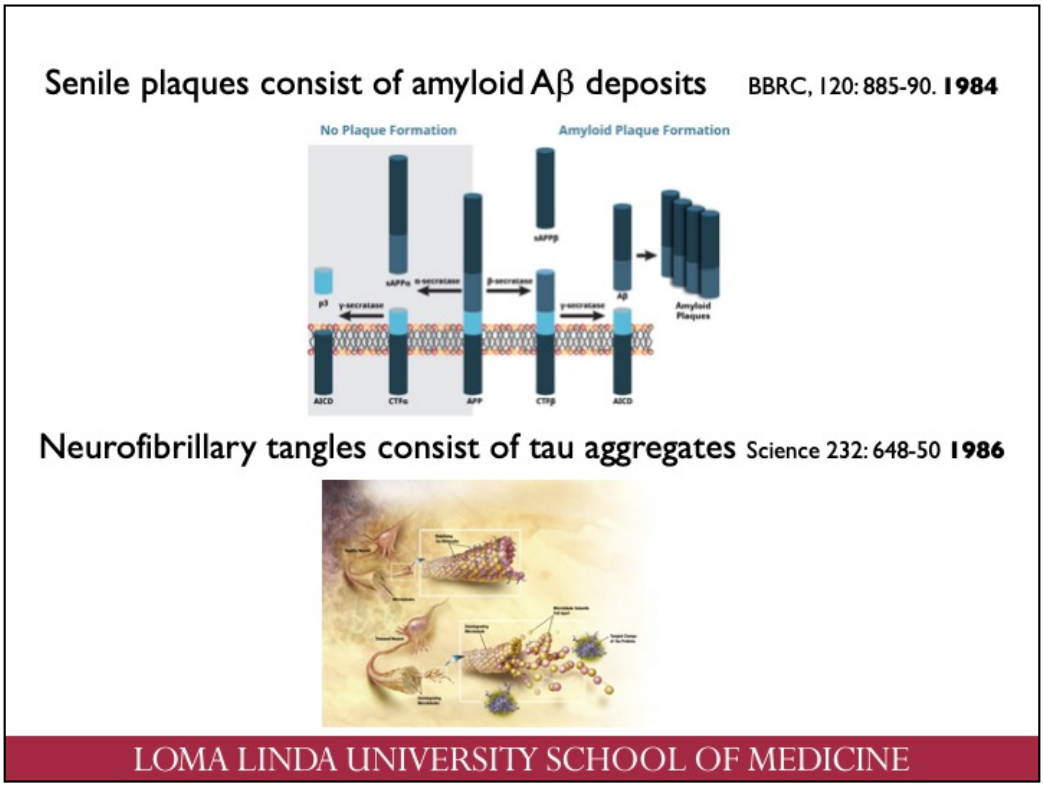
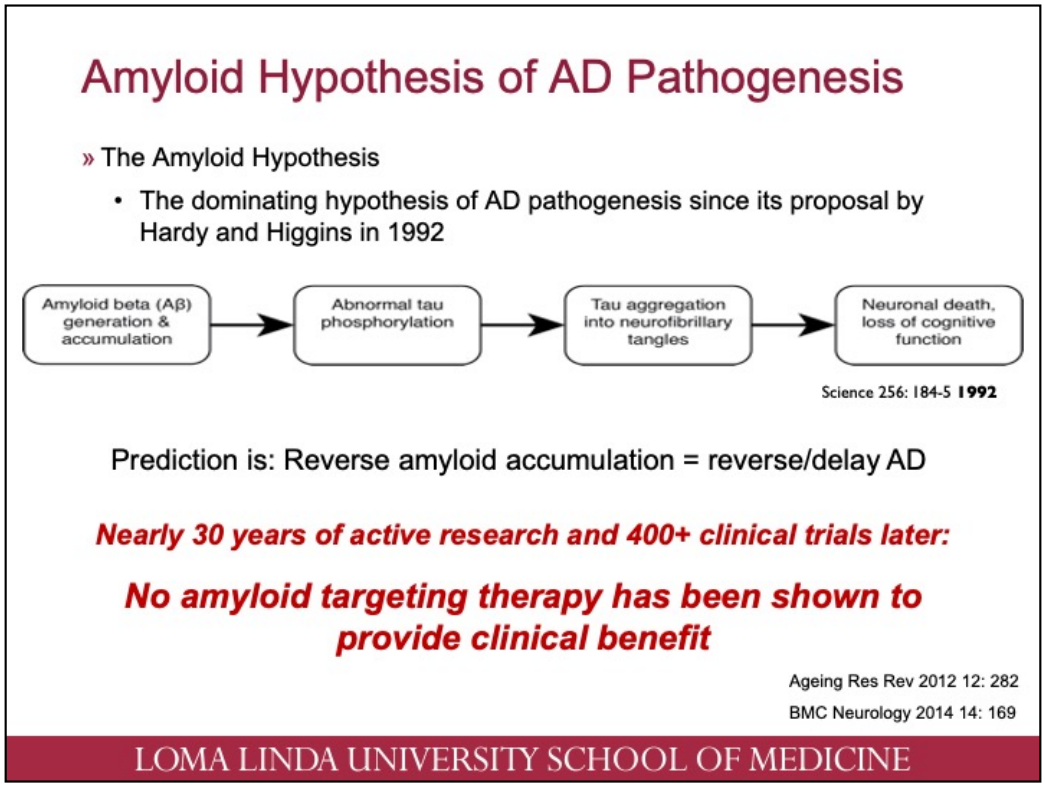
Then, no significant advances occurred until about 40 years ago, both plaques and tangles were biochemically and genetically characterized.



But it wasn't until 1984, with the availability of modern biochemistry and cell biology tools, that amyloid plaques and neurofibrillary tangles were analyzed and their main components described.

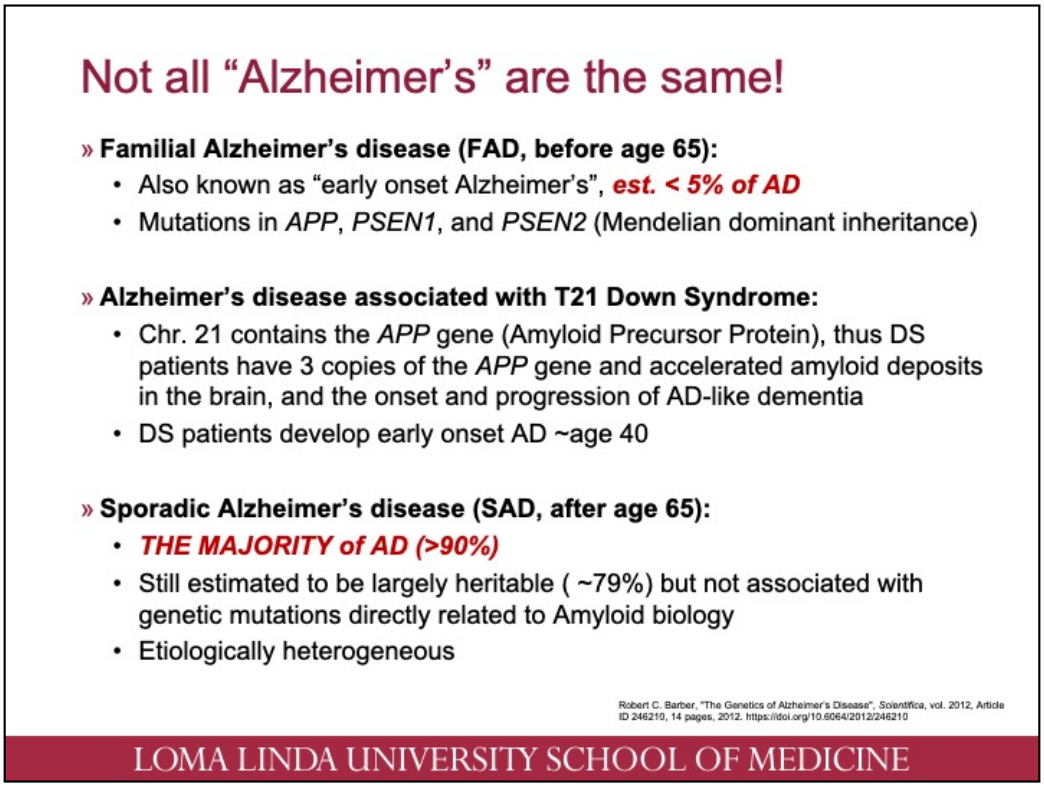
The first ones to fall were amyloid plaques, which were reported to consist mainly of amyloid ab deposits.

In 1986, the main component of NFTs was also identified. It was the microtubule binding protein tau. In a healthy neuron, tau regulates microtubule dynamics through its phosphorylation, thereby contributing to appropriate axonal transport. In an AD neuron, tau is abnormally phosphorylated, and this pattern of phosphorylation leads to its aggregation and to microtubule disruption. Because microtubules are central to axonal transport, and axonal transport is key to neuronal function, tau aggregation into NFTs lead eventually to cellular dysfunction and cell death



400+ trials between 2002-2012 alone (at the “peak” of AD research funding)

In 2021, there are 126 therapies in 152 treatments

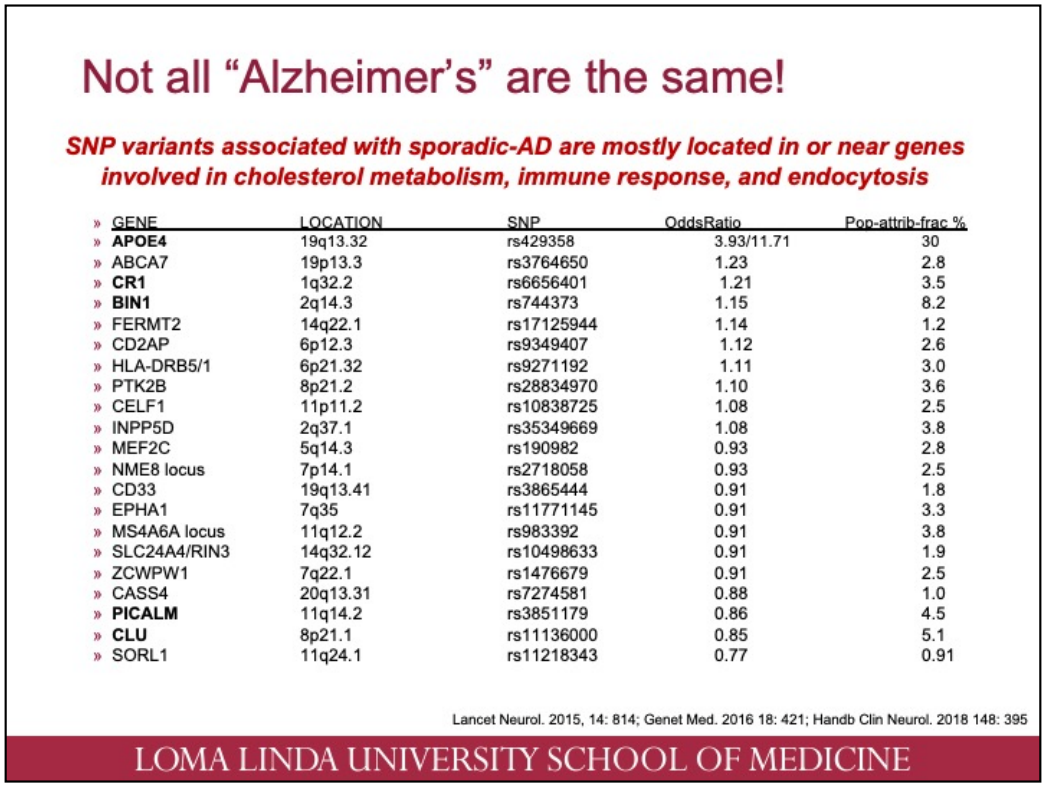


Maybe it is more intuitive for us clinicians

When there is a syndrome, a culmination of symptoms, it is very likely that there are different subtypes

In the case of AD, there is at least 3 distinct subtypes!

The reason I want to make these clinical distinctions is because in the realm of basic science research for AD, under the amyloid hypothesis, they clump all of these three into one AD and every therapeutic attempt has been geared towards.



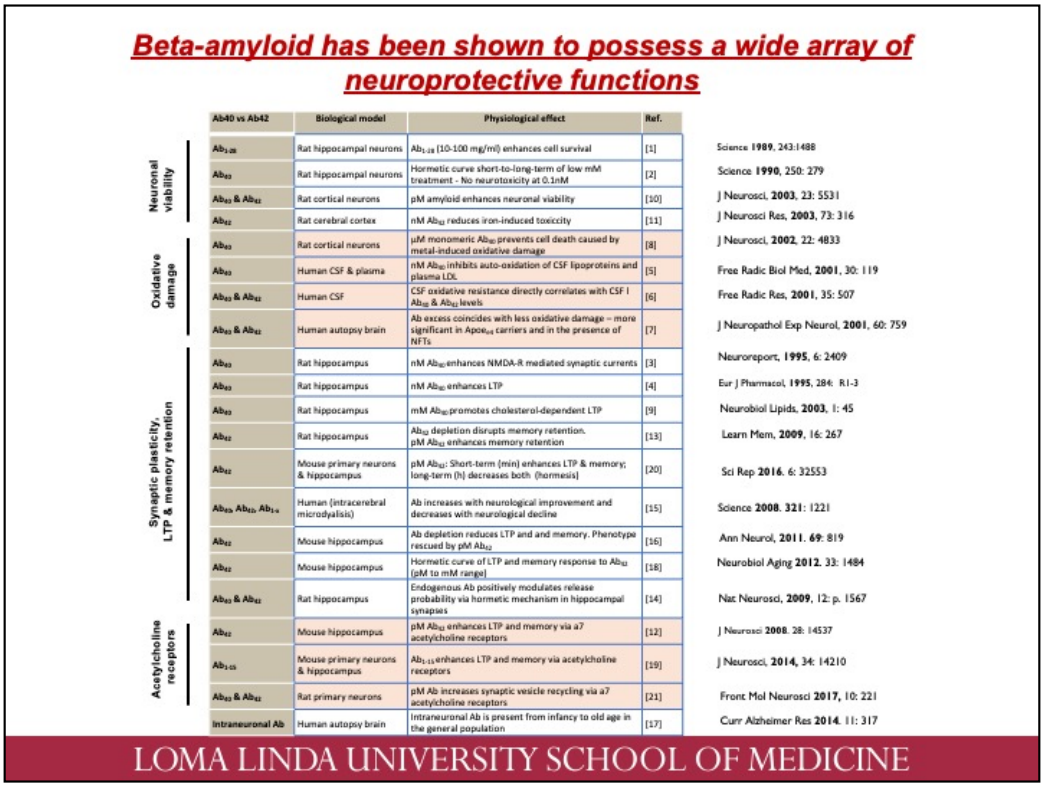
So the first problem is to identify early causative factors of AD. And what we know, in the absence of suitable animal models, comes from populations studies. And it looks as if cholesterol, inflammation and lifestyle outcomes are strongly linked to the risk of AD

*** additional genetic data in AD:

In these studies, which were published back to back in Nature Genetics [56, 57], Lambert et al. and Harold and colleagues described associations between late onset Alzheimer's disease and genetic markers in three genes in addition to *APOE*: clusterin (*CLU*), complement receptor 1 (*CR1*), and phosphatidylinositol binding clathrin assembly protein (*PICALM*).

J. C. Lambert, S. Heath, G. Even et al., "Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease," *Nature Genetics*, vol. 41, no. 10, pp. 1094–1099, 2009.

D. Harold, R. Abraham, P. Hollingworth et al., "Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease," *Nature Genetics*, vol. 41, no. 10, pp. 1088–1093, 2009.



So where do we fit amyloid in the pathogenic cascade of AD? The AH sees it as a toxic byproduct of the APP. But the reality is much more complex than that. Amyloid at low concentrations, between picomolar and low micromolar in in vitro systems, or at endogenous concentrations in the healthy brain, is in fact a physiological molecule, it plays a role in memory formation and initiates an adaptive protective responses against a variety of stress stimuli that are relevant to AD, such as cholesterol dysregulation, microbial infection and oxidative stress, and it does so through a hormetic mechanism.

Baruch-Suchodolsky R, Fischer B. Abeta40, either soluble or aggregated, is a remarkably potent antioxidant in cell-free oxidative systems. Biochemistry. 2009;48(20):4354-70.

Beta-amyloid peptide possesses potent anti-microbial activity

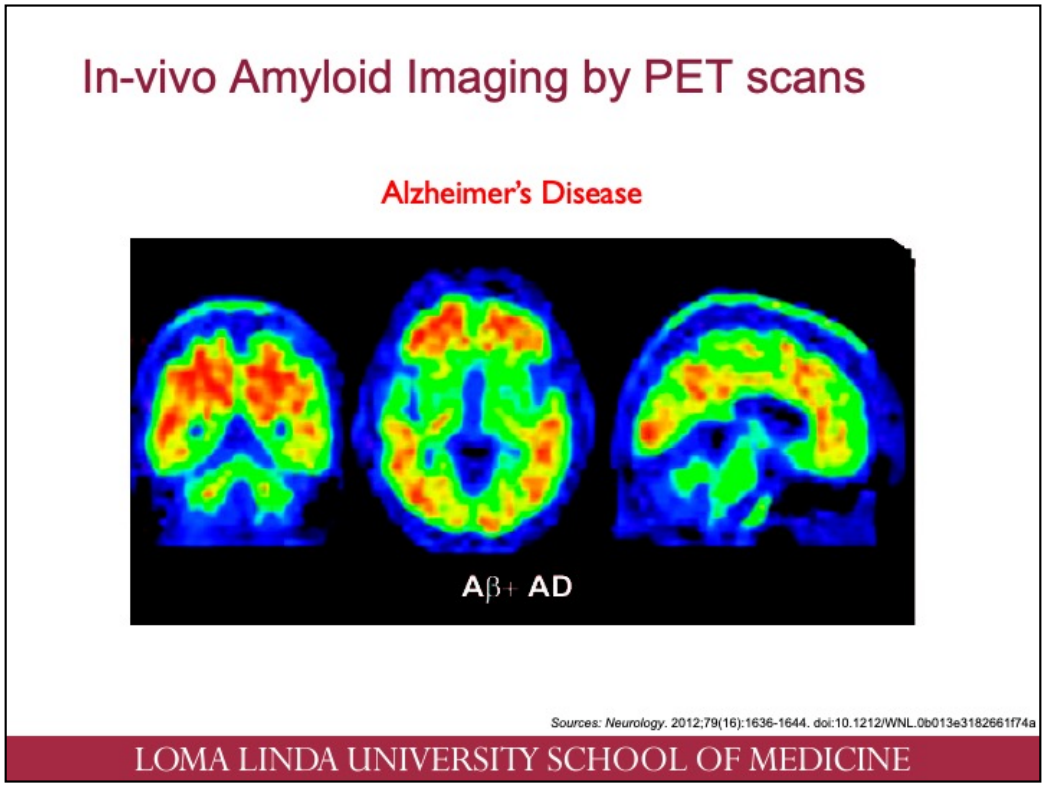
	MIC (μg/ml)					
Organism	**Aβ42**	**Aβ40**	**roAβ42**	**LL-37**	**reAβ42**	**scAβ42**
Candida albicans	0.78	0.78	0.78	6.25	>25	>50
Escherichia coli	1.56	1.56	3.13	1.56	>50	>50
Staphylococcus epidermidis	3.13	50	3.13	25	>50	>50
Streptococcus pneumoniae	6.25	12.5	6.25	1.56	50	>50
Staphylococcus aureus	6.25	25	12.5	6.25	>50	>50
Listeria monocytogenes	6.25	25	6.25	25	>50	50
Enterococcus faecalis	6.25	50	3.13	6.25	50	>50
Streptococcus agalactiae	12.5	50	>50	12.5	>50	>50
Pseudomonas aeruginosa	>50	>50	>50	6.25	>50	>50
Streptococcus pyogenes	>50	>50	>50	6.25	>50	>50
Streptococcus mitis	>50	50	>50	6.25	>50	>50
Streptococcus salivarius	>50	>50	>50	50	>50	>50

The antimicrobial activity of synthetic Aβ1-42 (**Aβ42**), Aβ1-40 (**Aβ40**), LL-37 (**LL-37**), reverse **Aβ42-1** (**rAβ42**), or scrambled Aβ42 (**scAβ42**) peptides were determined as minimal inhibitory concentrations (**MIC**) against 12 microorganisms. Antimicrobial activity was assayed by broth microdilution susceptibility test on 96-well plates with microbial growth in wells determined by visual inspection following an overnight incubation. Inhibition of growth in plate wells was confirmed by alamar blue cell viability assay and by surface plating of incubants on agar and counting CFU. Inoculums contained mid-logarithmic phase cells. Consistent with antimicrobial activity specific to the Aβ sequence, inhibition was not observed for reverse and scrambled peptides.
doi:10.1371/journal.pone.0009505.t001

PLoS One. 2010;5(3):e9505

If the normal function of Aβ is to function as an AMP, then an absence of the peptide may result in increased vulnerability to infection.

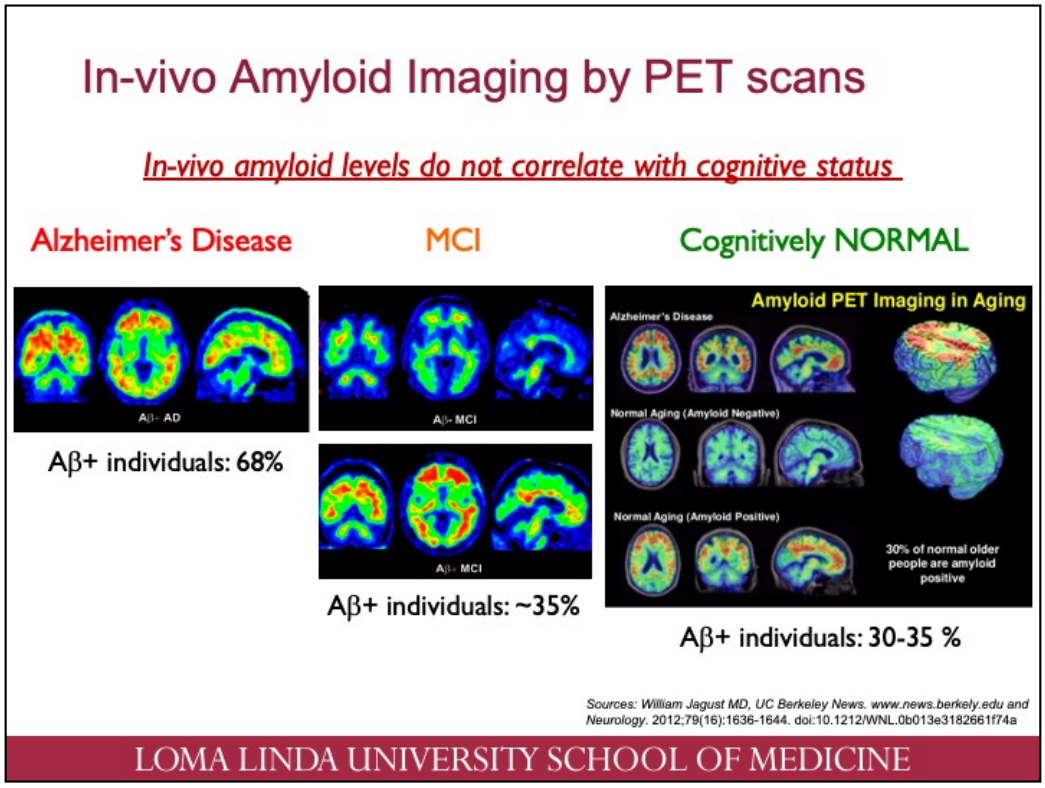
And it's also important to note that amyloid generation is only part of a broader mechanism, which is the processing of the amyloid precursor protein.



When in-vivo imaging for amyloid plaques became available in the early 2000s, it was a BIG deal. There was so much hope for this technology as an accurate diagnostic modality since we had to rely on post-mortem autopsy to confirm amyloid plaques in AD patients.

PET images using florbetapir dye to highlight beta-amyloid plaques show (A), a cognitively normal subject; (B) an amyloid-positive patient with Alzheimer's disease; (C) a patient with mild cognitive impairment; and (D) a patient with mild cognitive impairment who progressed to dementia during the study. Credit: Slide courtesy of the journal *Neurology.*

https://radiology.ucsf.edu/patient-care/services/specialty-imaging/alzheimer#:~:text=Since%202003%2C%20UCSF%20Imaging%20has,of%20plaques%20in%20living%20people.



However, when studies were carried out using this modality, we found that not all AD patients had amyloid plaques!!!

32% of AD patients did not have amyloid plaques

~65% of patients with mild cognitive decline did not have amyloid plaques

How do you explain this if amyloid accumulation is supposed to happen years, if not decades, before AD symptoms begin?

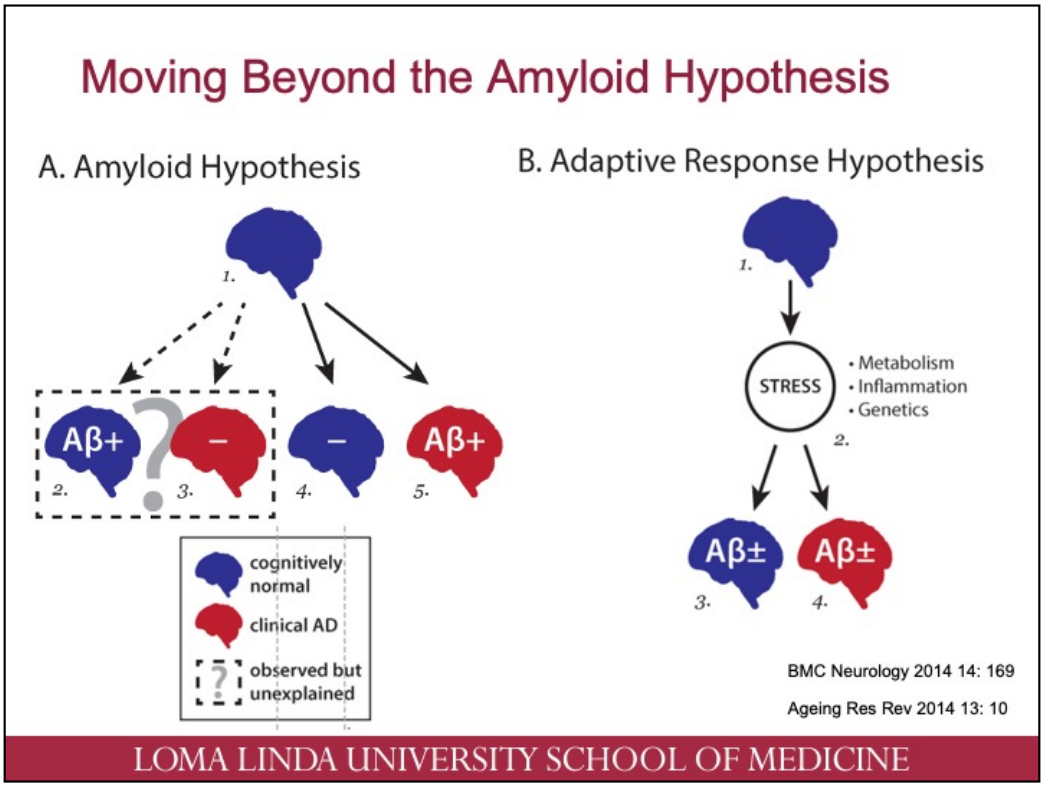
AND up to 35% of patients with normal cognitive function had significant amyloid plaques!!

--how are these individuals able to function cognitively if their brain is laden with amyloid?!!

BTW due to this clinical discrepancy, amyloid PET imaging was not adapted to regular clinical practice of AD care.

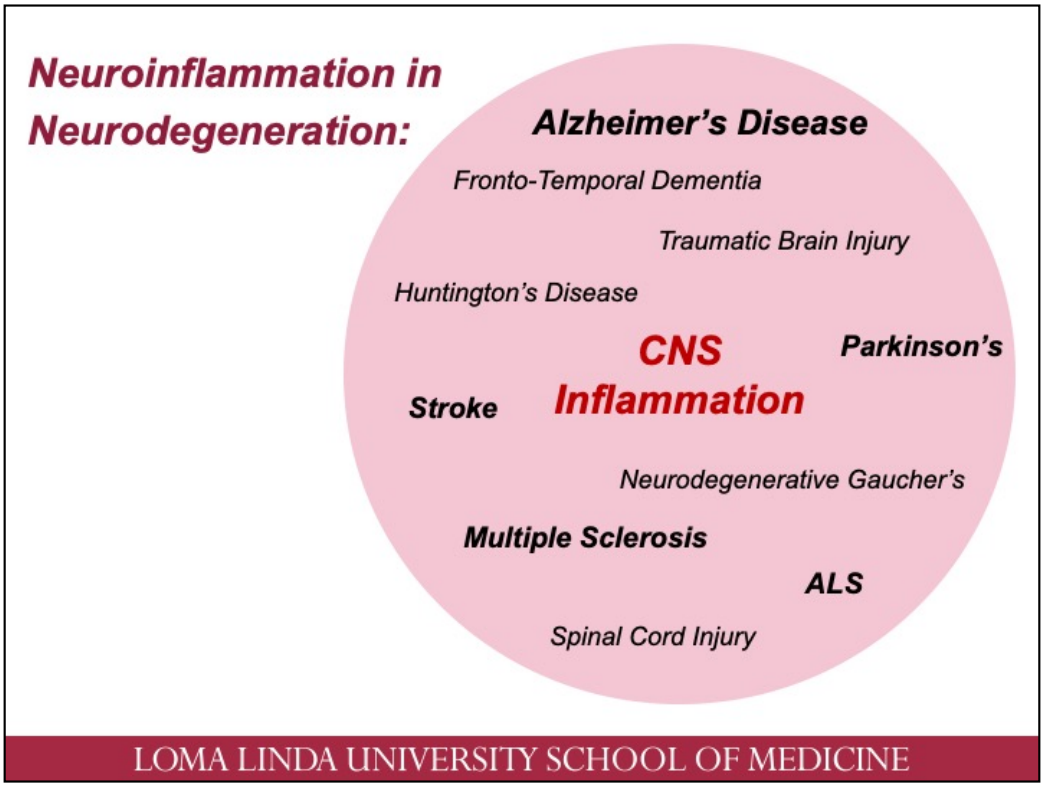
Instead, it is only used in research as a tool to assess a drug's ability to

clear amyloid from AD brains… (except full blown AD patients without positive amyloid PET have been excluded from studies!)



Amyloid hypothesis cannot explain the PET imaging findings of amyloid-free AD nor amyloid laden brains that are cognitively normal

Rather, a more nuanced and comprehensive approach will place amyloid as a downstream marker of stress that may or may not affect cognitive function based on individual patient's adaptive response to various sources of stress (including amyloid itself)

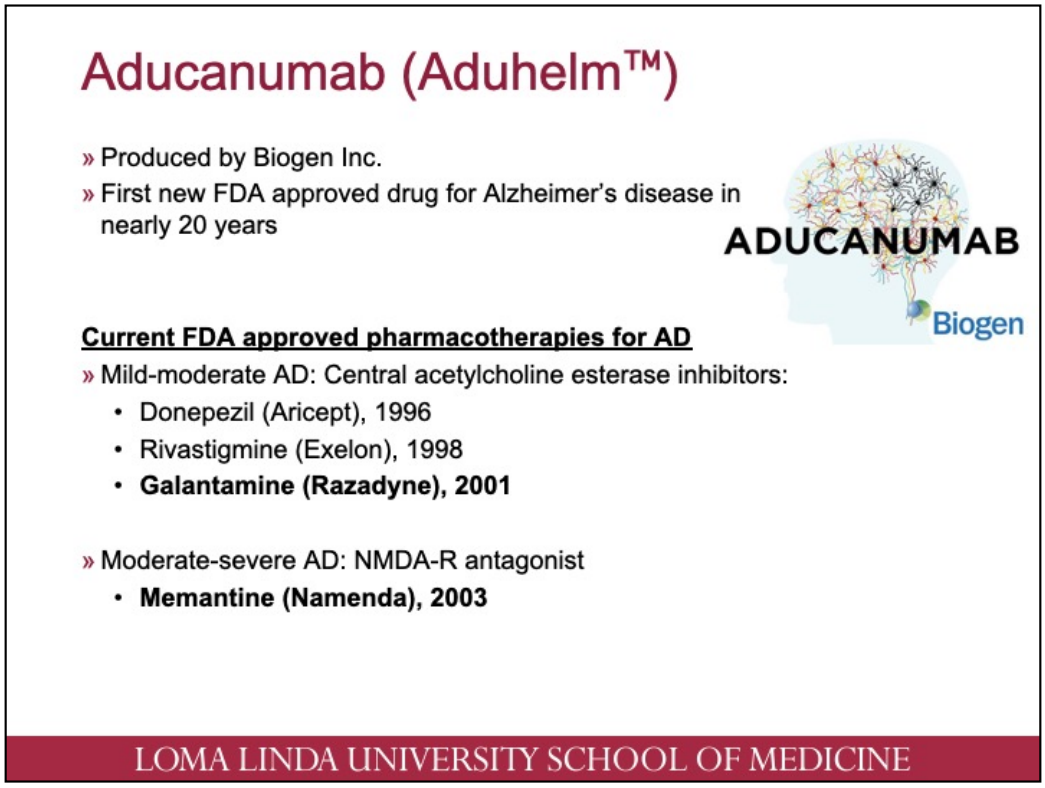


Uncontrolled inflammation is emerging as a common denominator of many neurodegenerative conditions, as well as many psychiatric conditions.

Aducanumab (Aduhelm™) for Alzheimer's Disease

Drug Facts
MOA
Indication
Route of Administration
Efficacy
Adverse Effects

Take home points for Patient Education

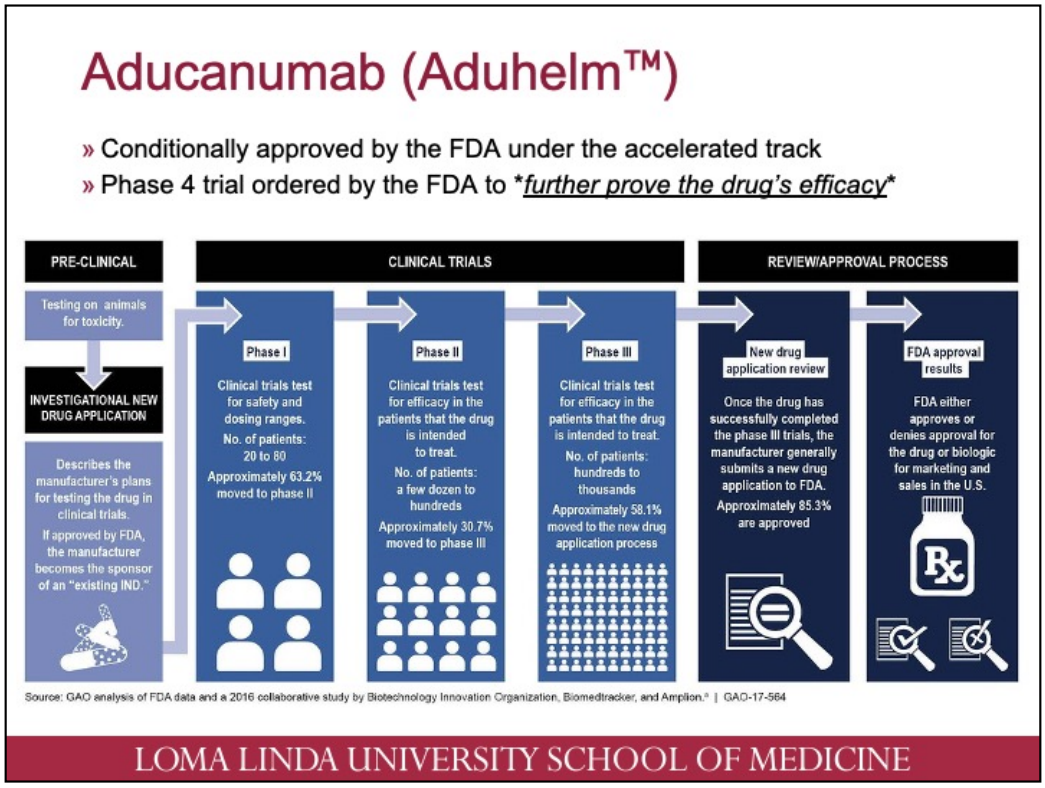


US Government Accountability Office

Memantine (Nmenda) 2003 – NMDA-R antagonist for mod-sev ALZD

BIG deal, first in nearly 20 years since memantine (Namenda) in 2003, Galatamine CNS-AchE inh 2001

Tacrine was approved by the US Food and Drug Administration (FDA) in 1993, donepezil in 1996, rivastigmine in 1998, galantamine in 2001, and memantine in 2003 (made available in the United States in 2004).



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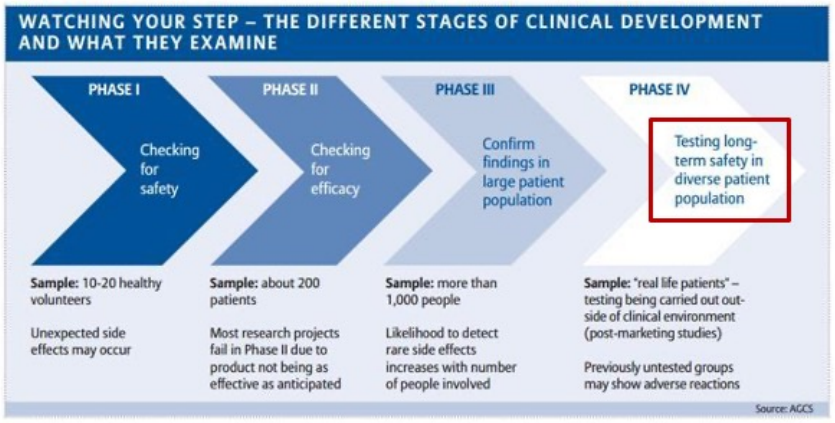
Aducanumab (Aduhelm™)



» FDA approved aducanumab against the FDA's own Peripheral and Central Nervous System Drug Advisory Committee.

- *0/11 voting members voted "yes" to whether the phase III trials of Aducanumab have proven sufficient clinical efficacy.*

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VOTE: In light of the understanding provided by the exploratory analyses of Study 301 and Study 302, along with the results of Study 103 and evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology, is it reasonable to consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease? YES/NO/UNCERTAIN

Vote Results: **Yes: 0 No: 10 Uncertain: 1**

Committee Discussion: *Almost all of the committee members voted "No", agreeing that it is not reasonable to consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease. These members were not persuaded by the analyses provided and expressed their reluctancy to suggest approval of aducanumab for the treatment of Alzheimer's disease due to the insubstantial evidence shown. In addition, these members expressed the difficulty for them to draw a conclusion on the information provided due to un-addressed criticisms provided by the statistical analysis of the studies. The one member who was uncertain on this question noted that Study 302 is positive, and Study 103 provided some additional evidence along with the evidence shown by the biomarkers. Please see the transcript for details of the Committee's discussion.*

FDA Advisory Committee

FDA U.S. FOOD & DRUG ADMINISTRATION

About Advisory Committees

The FDA uses committees and panels to obtain independent expert advice on scientific, technical, and policy matters. FDA seeks to include the views of women and men, members of all racial and ethnic groups, and individuals with and without disabilities on its advisory committees and, therefore, encourages nominations of appropriately qualified candidates from these groups.

The New York Times

Three F.D.A. Advisers Resign Over Approval of Alzheimer's Drug

He said the agency's approval of the drug, aducanumab, which is ... Alzheimer's experts — objected to two major aspects of the F.D.A.'s approval decision. ... In November, F.D.A. officials told the advisory committee members

16 hours ago

Sources: FDA; www.fda.gov, www.nytimes.com

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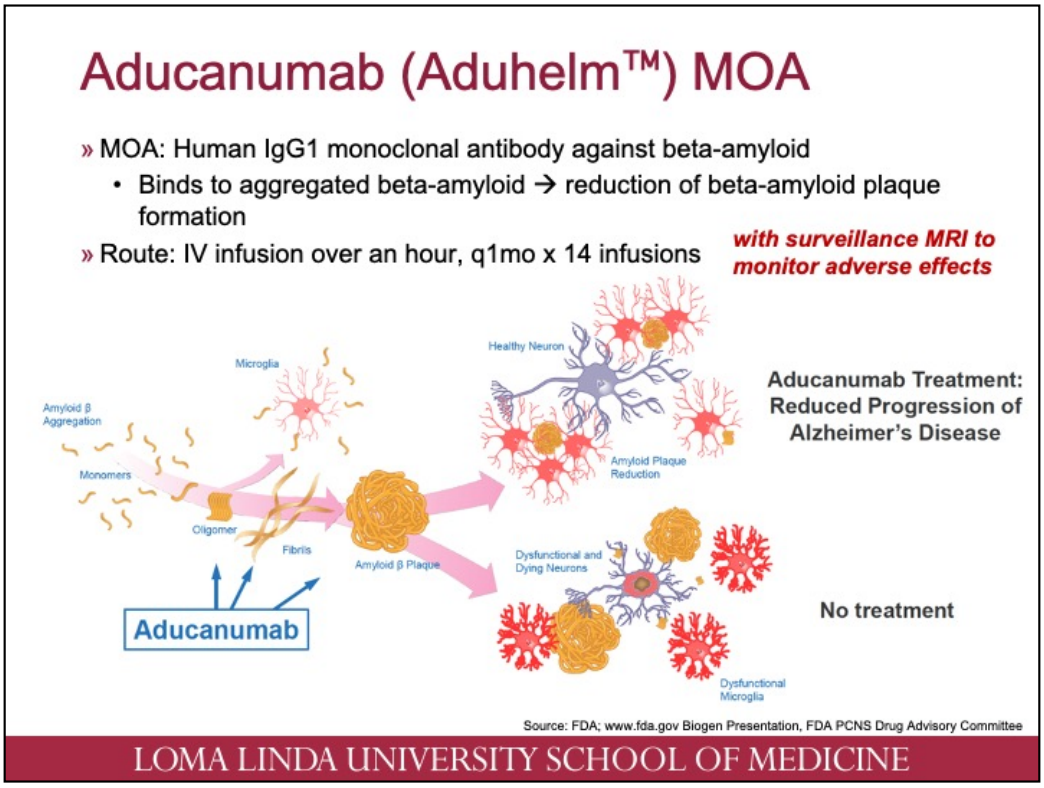
Aducanumab (Aduhelm™)

» Aducanumab was previously announced "futile" by Biogen's futility analysis of phase III trials.

» Biogen later "reanalyzed" the data, provided justification for poor outcomes and moved forward with Biologics License Application in 2020

Aducanumab US Regulatory History

Source: FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

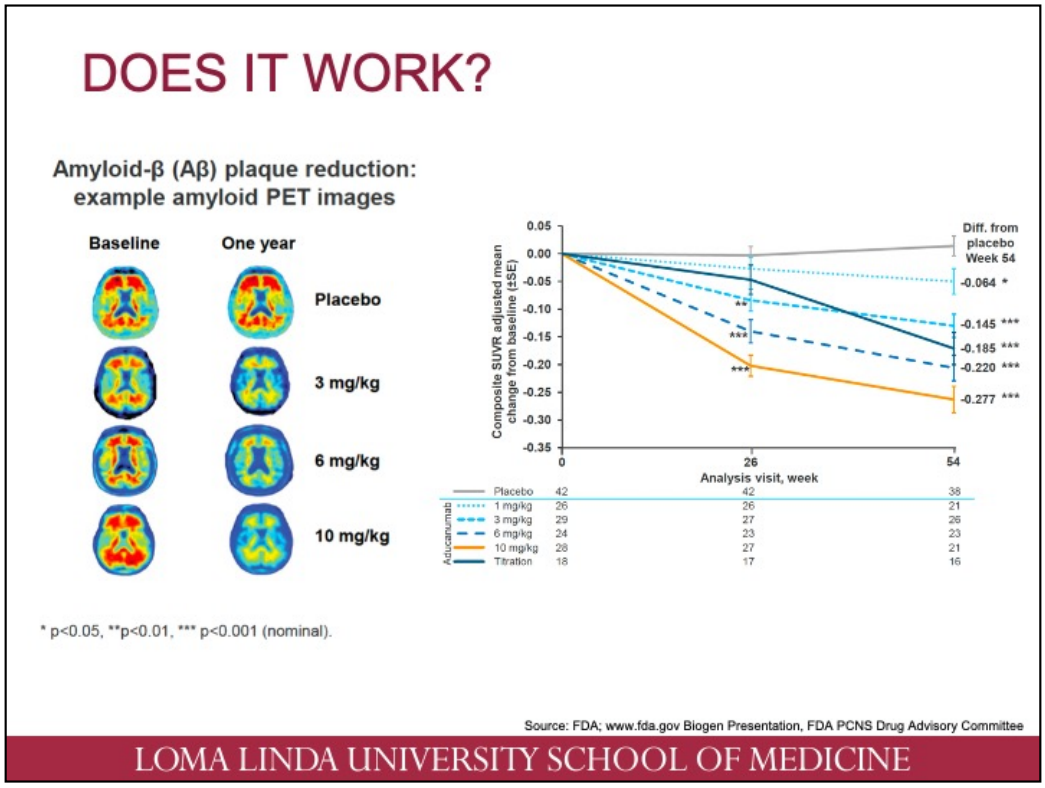


Other similar drugs:

Eli Lilly and Company: solanezumab, failed phase III trial 2015

Pfizer and J&J bapinezumab, failed in 2012 after 2,400 people

Roche – gantenerumab, halted after 3,000 pt



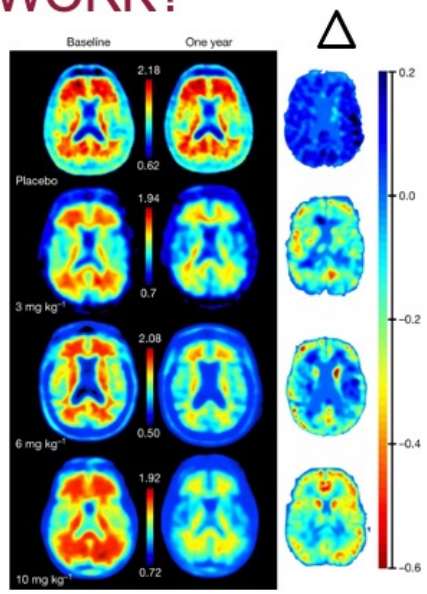
The answer is, it depends!

There is two parts to this

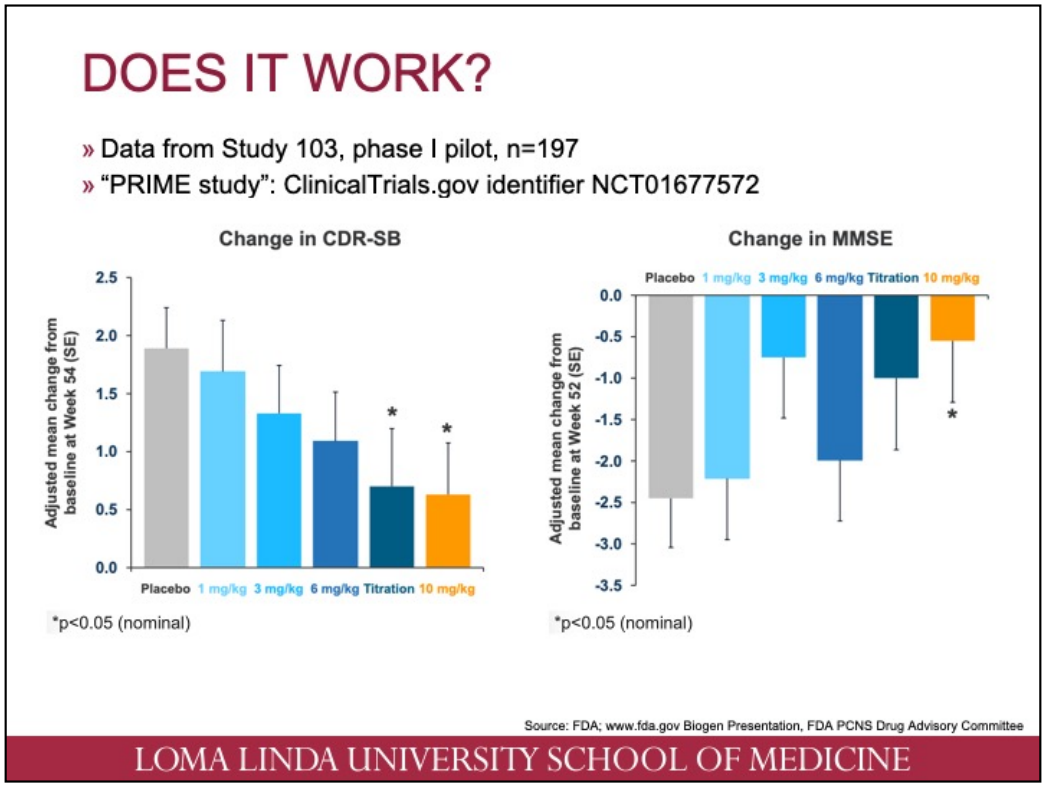
The first part is “does it remove amyloid” = YES

The second part is “does it improve function” = NOOOOO

DOES IT WORK?



Sevigny, J., Chiao, P., Bussière, T. *et al.* Addendum: The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature* **546,** 564 (2017). https://doi.org/10.1038/nature22809



The second part of the question in "does it work" is "does it provide clinical benefit?"

CDR-SB = decrease by ~1 pt on CDR-SB with large Ses (0-18, 0 is normal 18 is severe dementia)

MMSE = improvement by ~2 pts with large Ses (scored 0-30, >25 normal, <10 is severe dementia)

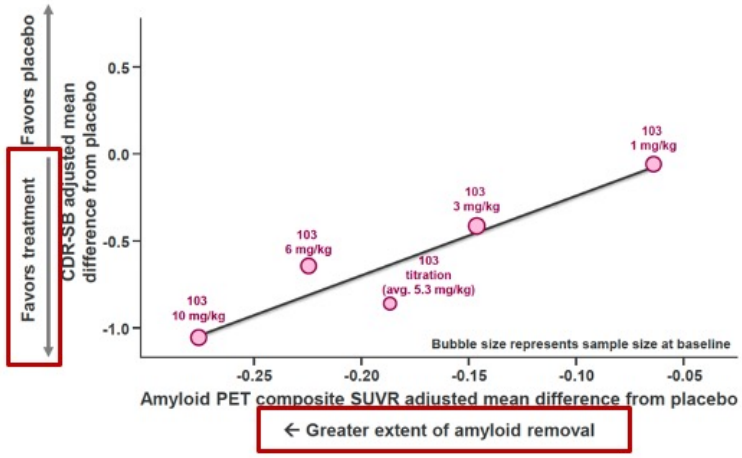
Clinical dementia rating – sum of boxes

Mini-mental status exam = created to trend clinical progression of AD symptoms

DOES IT WORK?

» Study 103, pilot proof of concept, n=197

» "PRIME": **Multiple Dose Study of Aducanumab (BIIB037),** ClinicalTrials.gov identifier ***NCT01677572***



FDA; www.fda.gov, Biogen Presentation, FDA PCNS Drug Advisory Committee,
Sevigny, J., Chiao, P., Bussière, T. *et al.* The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature* **537,** 50–56 (2016).

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DOES IT WORK?

» CDR-SB: Clinical Dementia Rating-Sum of Boxes
- Six areas: Memory, Orientation, Judgement and Problem Solving, Community Affairs, Home and Hobbies, Personal Care

No memory loss or slight inconsistent forgetfulness (0)	Fully oriented (0)	Solves everyday problems well; judgment good in relation to past performance (0)
Mild consistent forgetfulness; partial recollection of events; "benign" forgetfulness (0.5)	Fully oriented except for slight difficulty with time relationships (0.5)	Slight impairment in solving problems, similarities, and differences (0.5)
Moderate memory loss; more marked for recent events; interferes with everyday activities (1)	Moderate difficulty with time relationships; oriented for place and person at examination but may have geographic disorientation (1)	Moderate difficulty in handling complex problems; social judgment usually maintained (1)
Severe memory loss; only highly learned material retained; new material rapidly lost (2)	Severe difficulty with time relationships; usually disoriented to time, often to place (2)	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired (2)
Severe memory loss; only fragments remain (3)	Oriented to person only (3)	Unable to make judgments or solve problems (3)

Source: https://www.mdcalc.com/clinical-dementia-rating-cdr-scale

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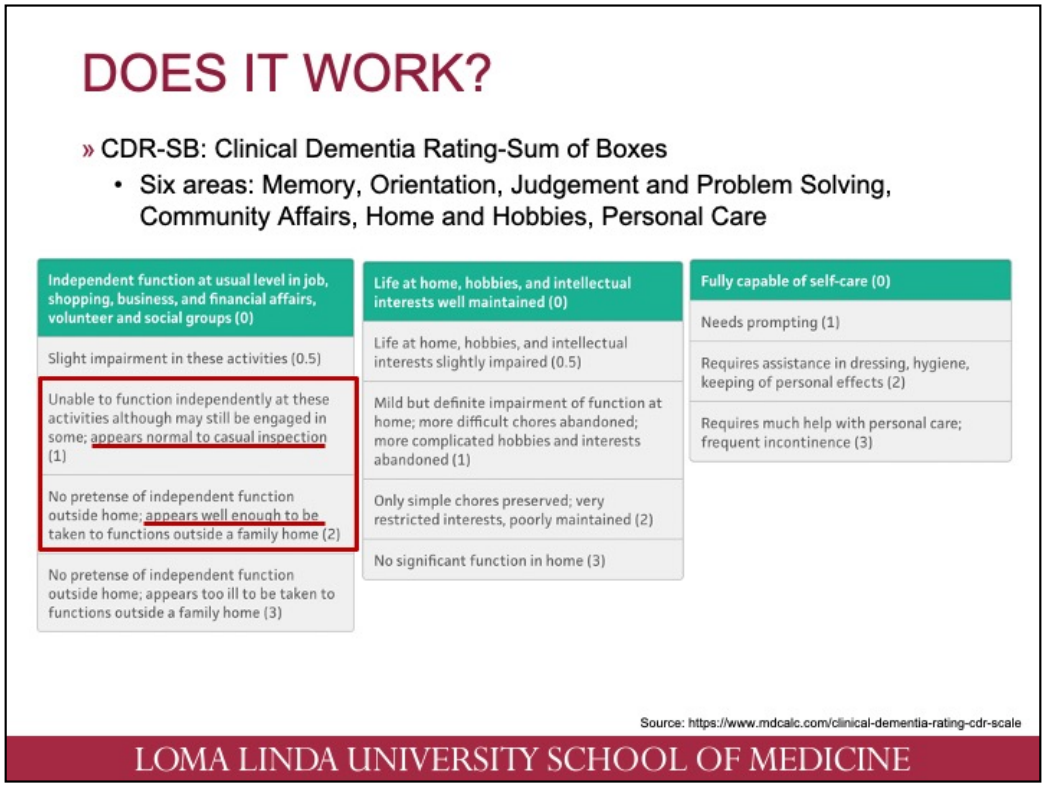
Biogen's aducanumab, AT BEST, improves CDR-SB by ~1 point in the successful group 302 EMERGE.

This was used as a "scientific evidence" to support its approval….

In reality, the 1 point improvement in CDR-SB is vague and minimal



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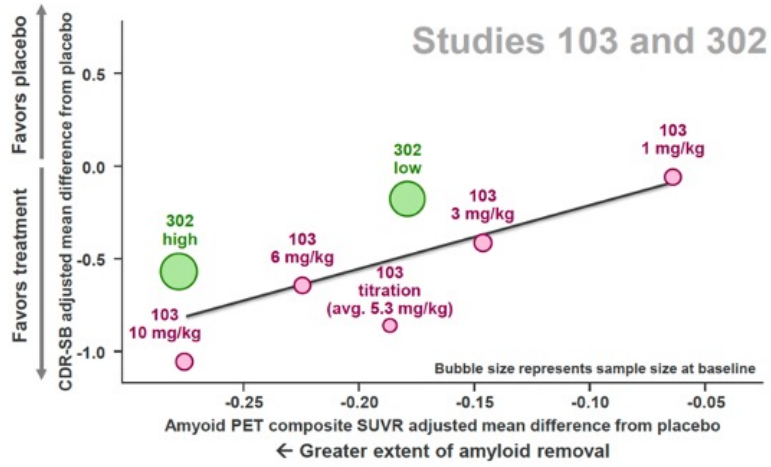
DOES IT WORK?

» Study 302, Phase III, n=1643, ~50% completed

» "EMERGE": **221AD302 (BIIB037),** ClinicalTrials.gov identifier ***NCT02484547***

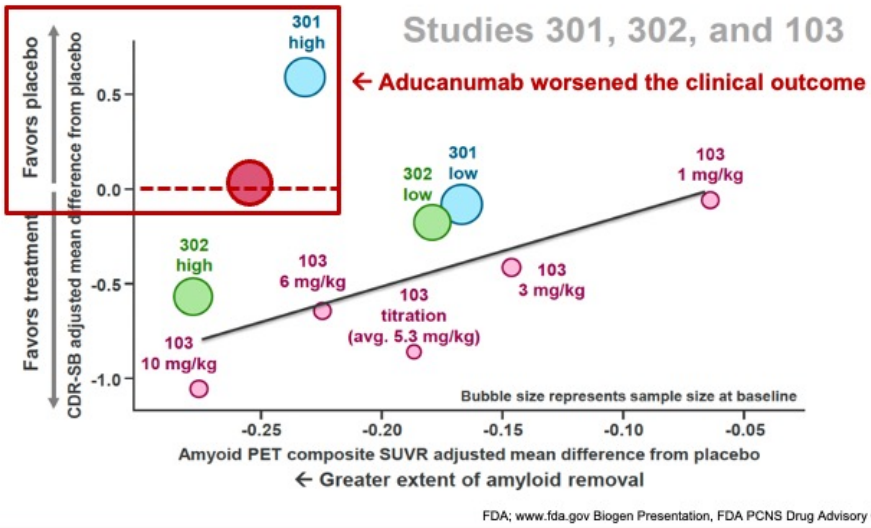


FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

DOES IT WORK?

» Study 301, Phase III, n=1653, ~60% completed

» "ENGAGE": **221AD301 (BIIB037),** ClinicalTrials.gov identifier ***NCT02477800***



FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

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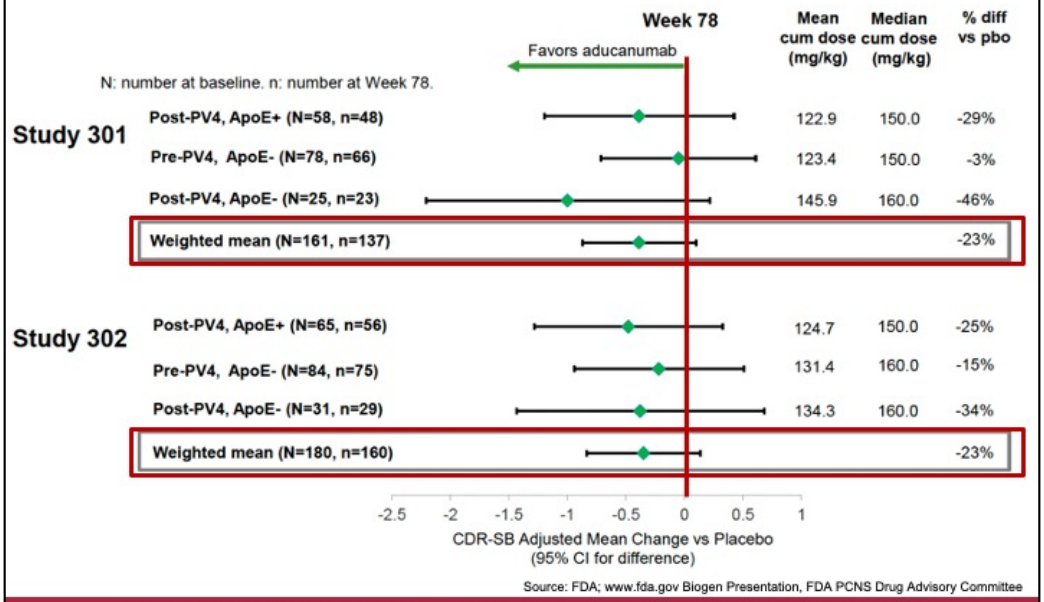
Biogen's Rationale for failed 301 high dose group



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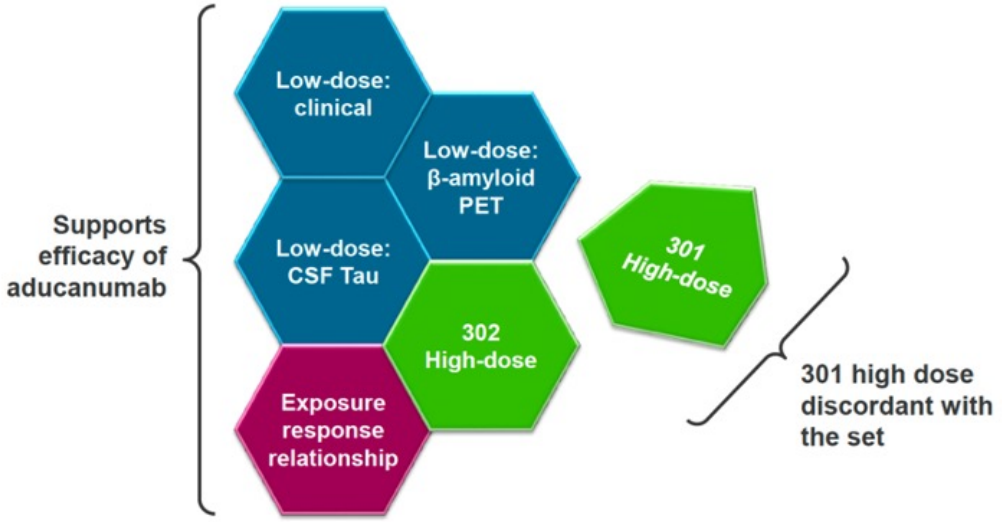
Biogen's Rationale for 301 high dose



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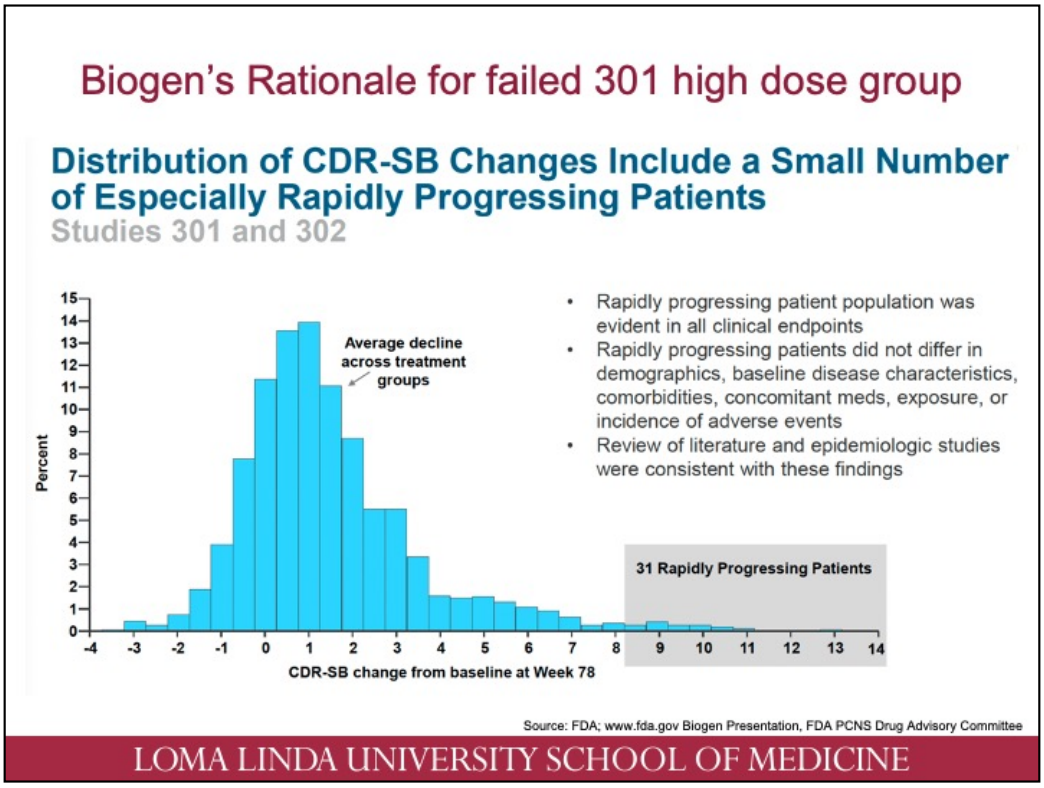
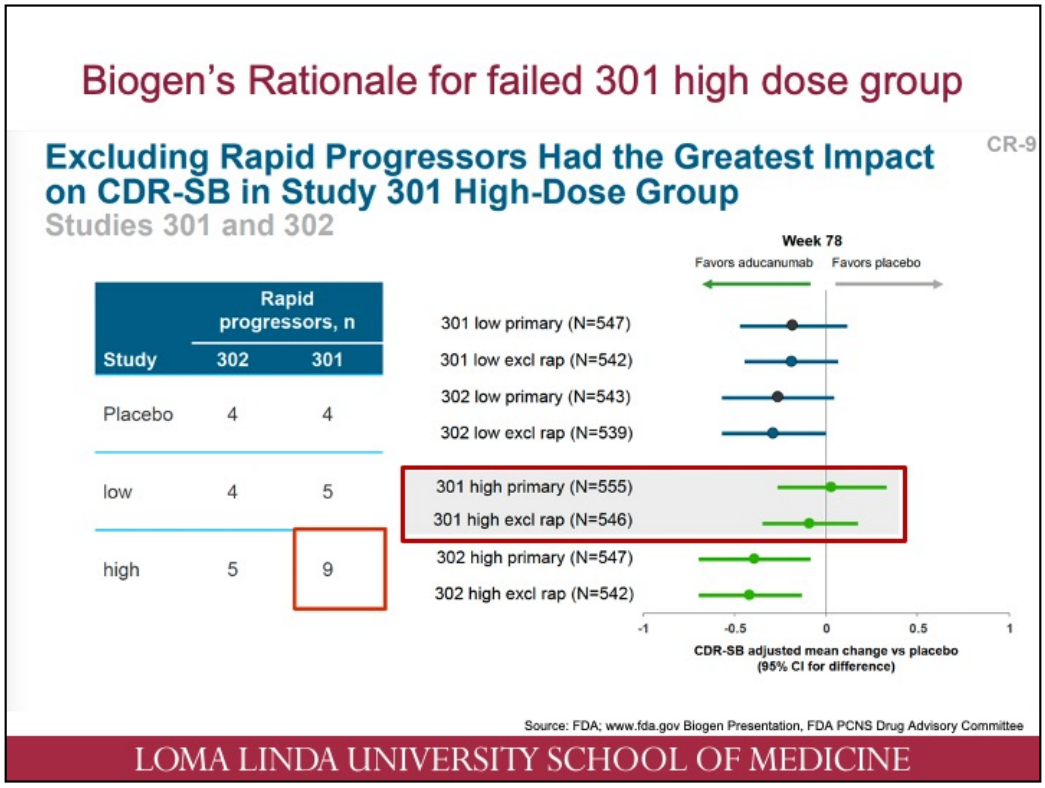


Basically claiming Sample Bias, claiming there were higher number of rapidly progressing outliers in the 301 high dose group which threw off the whole study



Basically claiming Sample Bias, claiming there were higher number of rapidly progressing outliers in the 301 high dose group which threw off the whole study

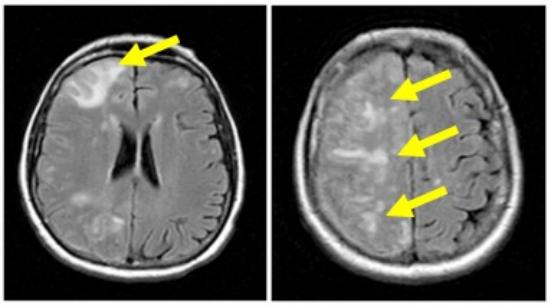
Adverse Effects: Aducanumab (Aduhelm™)

Amyloid-Related Imaging Abnormalities (ARIA)

Source: FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

ARIA refers to radiographic abnormalities observed with anti-Aβ antibodies

- ARIA-Edema (ARIA-E): vasogenic edema or sulcal effusion
- ARIA-Hemorrhage (ARIA-H): brain microhemorrhages or localized superficial siderosis
- May result from increased cerebrovascular permeability as a consequence of antibody binding to deposited amyloid-beta



ARIA-E detected on MR FLAIR
Vasogenic Edema appears white

Sperling, Reisa A et al. "Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup." *Alzheimer's & dementia : the journal of the Alzheimer's Association* vol. 7,4 (2011): 367-85. doi:10.1016/j.jalz.2011.05.2351

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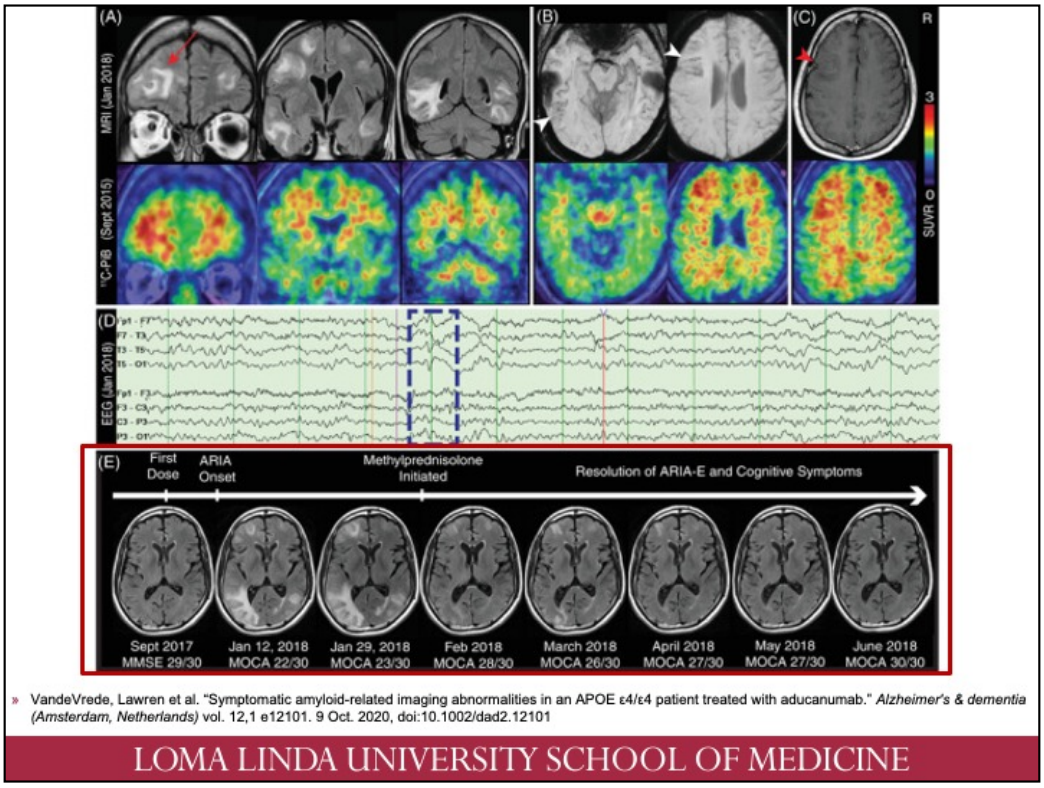

FIGURE 2 Amyloid-related imaging abnormalities (ARIA) after treatment with aducanumab. A, T2 fluid-attenuated inversion recovery (FLAIR) sequences (top) demonstrating ARIA-E after treatment with aducanumab, compared to 2015 ^{11}C-Pittsburgh Compound B (^{11}C-PiB) positron emission tomography (PET; bottom); red arrow highlights edema in area of high amyloid signal in left frontal pole. B, Susceptibility weighted imaging sequence demonstrating ARIA-H (top), compared to 2015 ^{11}C-PiB PET (bottom); white arrowheads indicate microhemorrhages in left frontal and temporal lobes. C, Post-contrast T1 sequence (top), compared to 2015 ^{11}C-PiB PET (bottom); red arrowhead indicates nodular enhancement in left frontal lobe. D, Electroencephalogram with left temporal sharps and after-going slow waves (dotted blue box), maximal electronegativity at T3 with field to T1, F7, T5, and O1. E, Sequential T2 FLAIR at the level of maximal edema, with subsequent resolution after treatment with intravenous steroids, with cognitive assessment showing resolution in parallel with ARIA-E

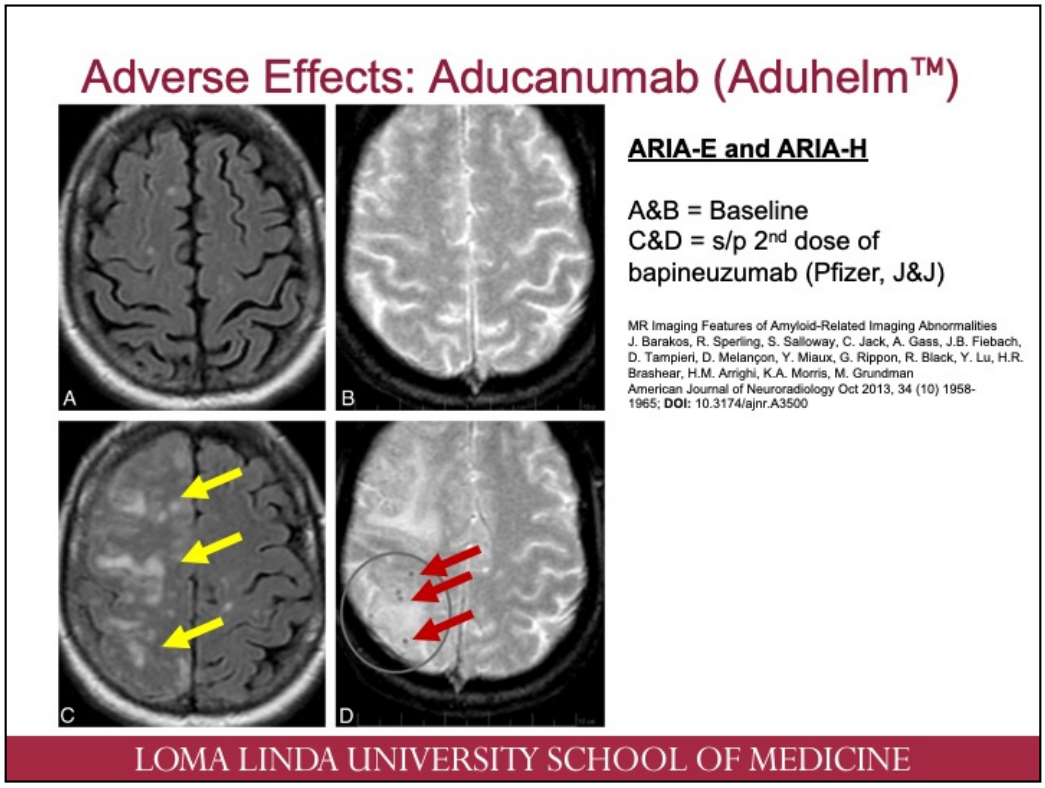

Fig 4.ARIA-E (edema) with incident ARIA-H (microhemorrhages). FLAIR and corresponding gradient recalled-echo/T2* sequences of the same patient, at baseline (*A* and *B*) and week 19 (*C* and *D*). By week 19 (6 weeks after the second dose of bapineuzumab), significant right-hemispheric edema has developed. As is characteristic of ARIA-E, despite the extensive parenchymal changes, DWI and ADC findings remained normal (not shown), confirming these findings as reflecting vasogenic as opposed to cytotoxic edema. On the corresponding gradient recalled-echo/T2* images, there is concomitant development of several punctate microhemorrhages in the right parietal region (*circle*). On subsequent imaging, the cerebral edema resolved while the microhemorrhages remained stable (not shown). In general, the severity of ARIA changes was associated with both *Apolipoprotein ε4* allele status and drug dosage. As such, this patient was an *Apolipoprotein ε4* homozygote and in the highest drug-dose arm.

Adverse Effects: Aducanumab (Aduhelm™)

	Patients, n (%)				
		Aducanumab			
	Placebo N=1087	3 mg/kg N=760	6 mg/kg N=405	10 mg/kg N=1033	Total (all doses combined) N=2198
Adverse events	945 (86.9)	700 (92.1)	347 (85.7)	946 (91.6)	1993 (90.7)
ARIA-E	29 (2.7)	223 (29.3)	83 (20.5)	362 (35.0)	668 (30.4)
Serious adverse events	151 (13.9)	105 (13.8)	54 (13.3)	141 (13.6)	300 (13.6)
Serious ARIA-E	1 (<0.1)	6 (0.8)	3 (0.7)	13 (1.3)	22 (1.0)
Fatal adverse events	5 (0.5)	3 (0.4)	0	8 (0.8)	11 (0.5)

Source: FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

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20-35% of patients experienced ARIA-E

~6% of patients across three doses had to stop the TX due to ARIA

Adverse Effects: Aducanumab (Aduhelm™)

ARIA-E Incidence

Studies 301 and 302 Placebo-Controlled Period

	Patients,[a] n (%)	
	Placebo N=1076	Aducanumab 10 mg/kg N=1029
ARIA-E	29 (2.7)	362 (35.2)
ApoE ε4 carriers	16/742 (2.2)	290/674 (43.0)
ApoE ε4 non-carriers	13/334 (3.9)	72/355 (20.3)

Source: FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

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ApoE e4 carriers have significantly higher risk of AD… and this most genetically vulnerable AD patients are the ones who suffer the most adverse effects!

Adverse Effects: Aducanumab (Aduhelm™)

	Patients, n (%)	
	Placebo N=1087	Aducanumab 10 mg/kg N=1033
Adverse events	**945 (86.9)**	**946 (91.6)**
ARIA-E	29 (2.7)	362 (35.0)
Headache	165 (15.2)	212 (20.5)
ARIA-H Brain microhemorrhage	71 (6.5)	197 (19.1)
Fall	128 (11.8)	155 (15.0)
ARIA-H Superficial siderosis	24 (2.2)	151 (14.6)
Diarrhea	74 (6.8)	92 (8.9)

Source: FDA; www.fda.gov Biogen Presentation, FDA PCNS Drug Advisory Committee

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Take Home Points for Patient Education

» Aducanumab is a biologic, a human IgG1 antibody against CNS beta-amyloid plaques
» Aducanumab is administered intravenously at an infusion center q1mo.

» Aducanumab was approved by the FDA against FDA's independent expert panel
  • *None of the 11 voting members voted "yes" to the drug's efficacy*
» Aducanumab's clinical efficacy is questionable with two conflicting phase III trials that were abruptly stopped due to futility analysis
  • Under the best scenario, Aducanumab appears to improve CDR-SB by ~1 pt s/p 1+ year of therapy

» Aducanumab is associated with significant adverse effects of ARIA-E and ARIA-H which can be fatal
  • ~35% patients will develop ARIA-E, ~45% if ApoE e4 carrier
  • ******Pt with amyloid-plaques (Cerebral Amyloid Angiopathy) are already at increased risk of hemorrhage, Aducanumab appears to increase this risk******
  • Therefore, aducanumab requires surveillance MRIs to monitor adverse effects.

» Aducanumab costs $56,000 per year + infusion cost + surveillance MRI cost + radiology + ARIA treatment

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Question: Would you prescribe Aducanumab for AD?

Any questions?