FDA-Approved Treatments for Alzheimer's Disease: The Good, The Bad, and the Ugly

Pierre N. Tariot, M.D.

Banner Alzheimer's Institute
Co-Director, Alzheimer's Prevention Initiative
Research Professor of Psychiatry
University of Arizona College of Medicine
Phoenix, Arizona

Tariot Disclosures

I have an interest in relation to several organizations that could be perceived as a possible conflict of interest in the context of this presentation, as summarized below:

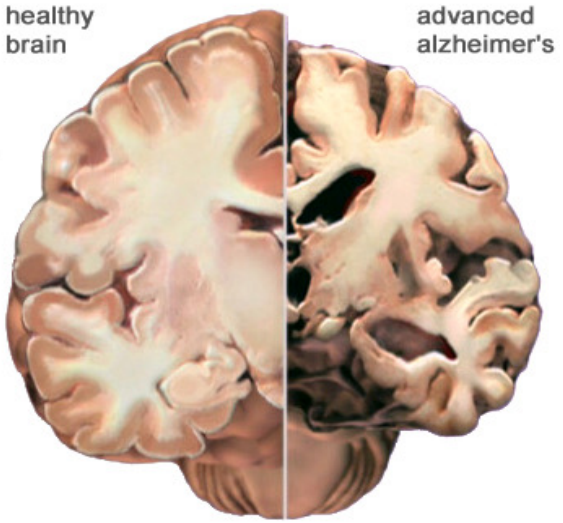
Interest	Name of organization
Grants	National Institute on Aging (RF1 AG041705, 1UF1AG046150, R01 AG031581, R01 AG055444, P30 AG19610)
Advisory board	Abbvie, AC Immune, Acadia, Athira, Corium, Cortexyme, Eisai, Genentech, ImmunoBrain, Merck, Novo Nordisk,
Consulting fees	Acadia, Lundbeck, Merck, Otsuka & Astex, T3D Therapeutics

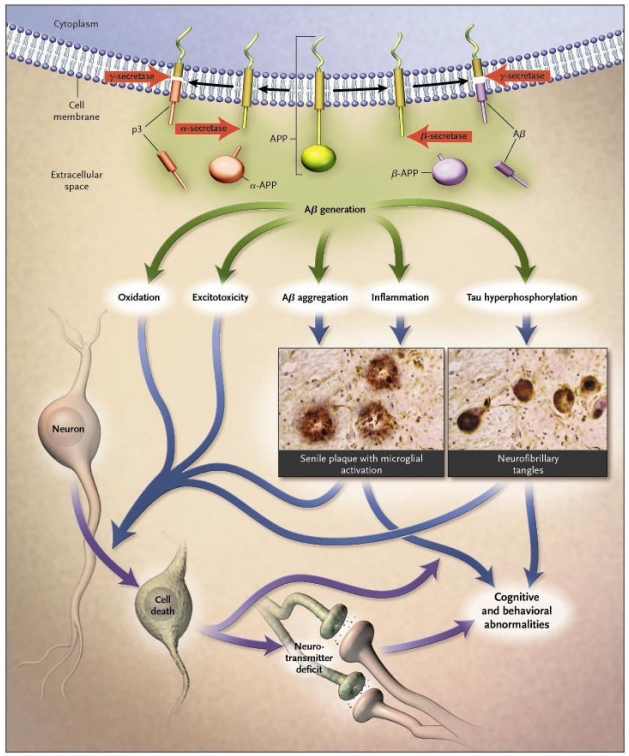
The Main Changes in the Brain in Alzheimer's Disease

- Amyloid plaques
- Neurofibrillary tangles (tau)
- Inflammation
- Change in biochemicals and neurotransmitters
- Shrinkage of the brain (atrophy)

Disease Modifying Rx

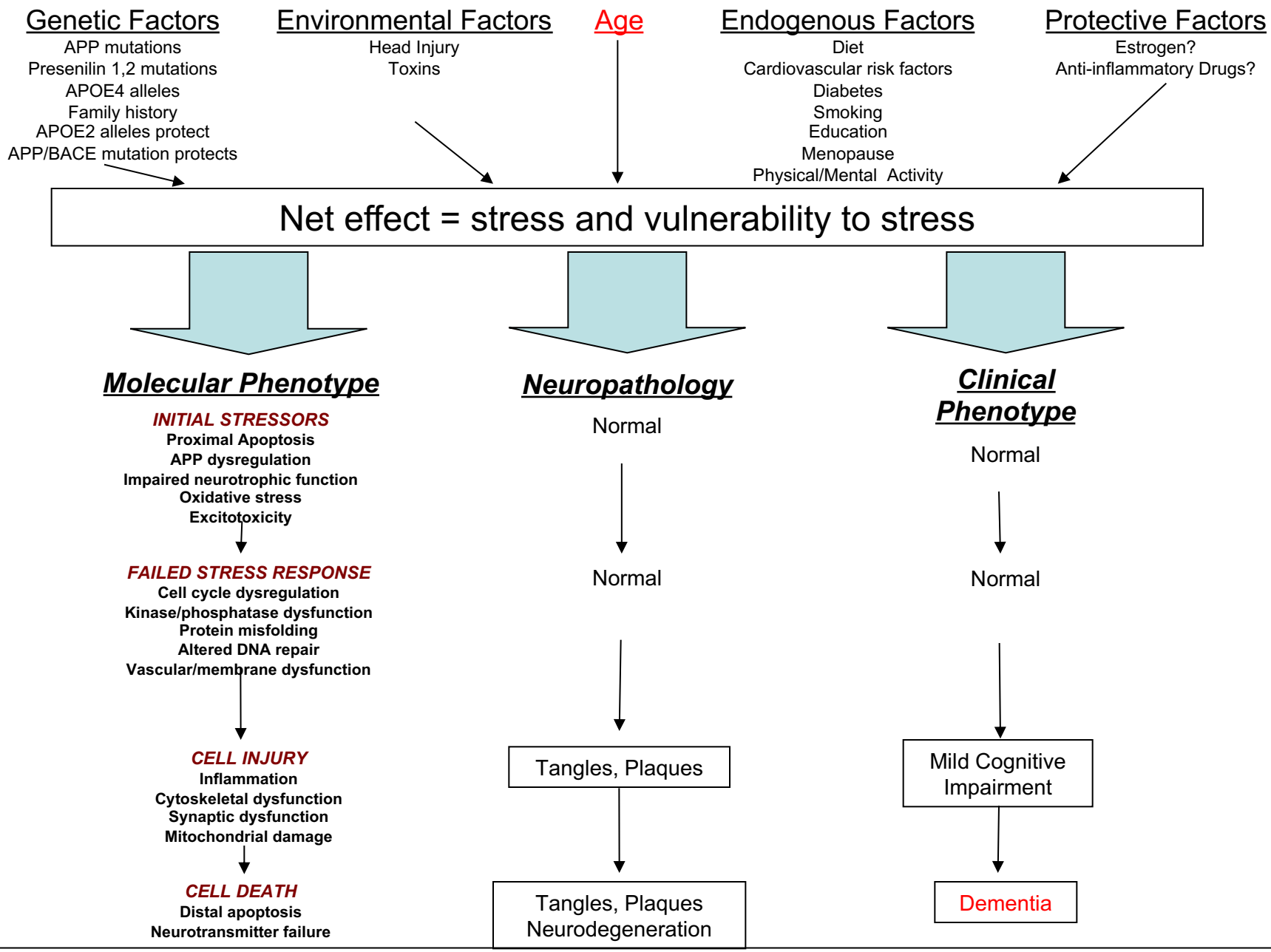
Symptomatic treatment





Cummings, NEJM, 2004

A Proposed Temporal Progression of Alzheimer's Disease(s)



The figure depicts apparently continuous processes, though they are likely to be asynchronous. Yaari R, Kumar S, Tariot PN. Expert Opinion 3(7):745-760, 2008.

Types of Interventions

- "Symptomatic" therapy:
  - Interventions that improve cognition, defer functional decline, or ameliorate behavioral symptoms without altering the underlying disease processes that comprise AD pathogenesis and without producing enduring changes that persist when the treatment is withdrawn.
- Disease modifying therapy:
  - Interventions that produce an enduring change in the clinical progression of AD by interfering in the underlying pathophysiological mechanisms of the disease process that lead to cell death as demonstrated by biomarkers

Cummings, NEJM, 2004

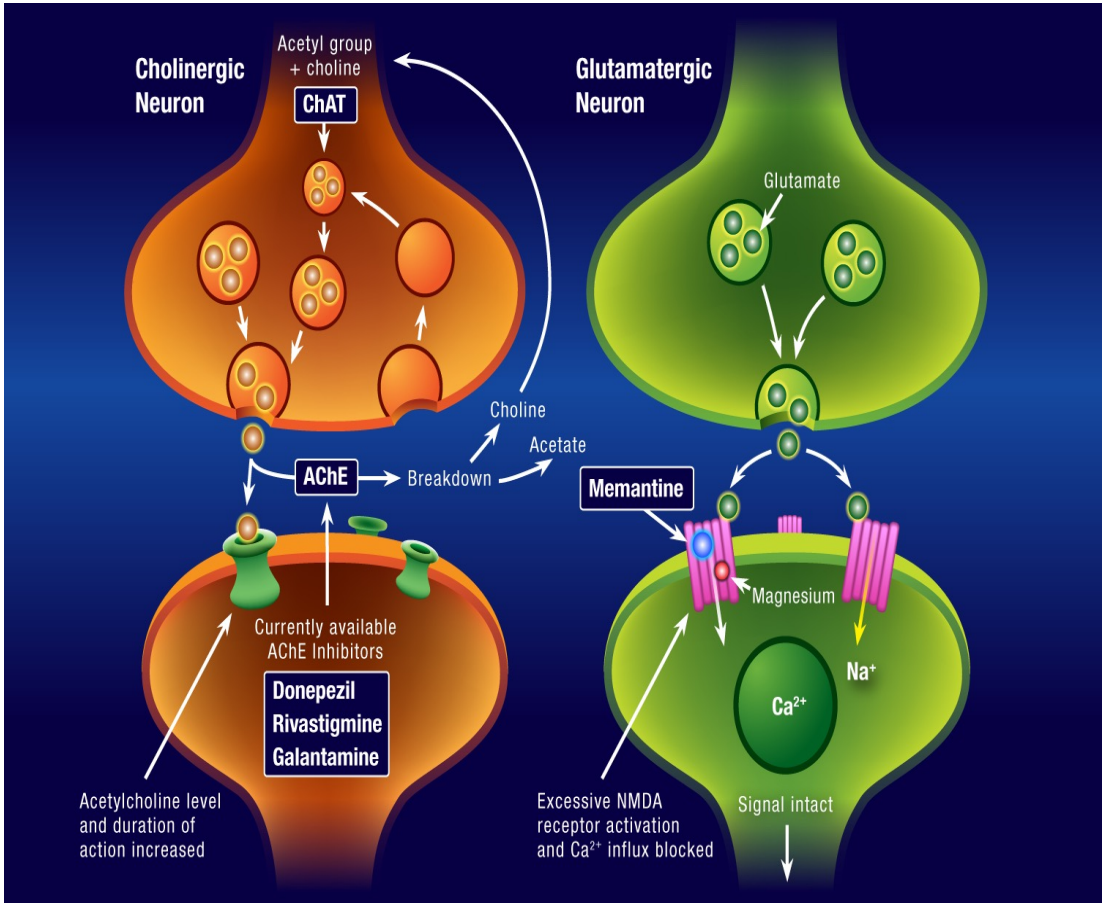
Initial FDA-Approved Medications for Alzheimer's Disease Dementia

- Cholinesterase-inhibitors: donepezil, rivastigmine, galantamine, tacrine*
  - All FDA approved for treatment of *mild to moderate* AD dementia
  - Donepezil is FDA approved for treatment of *severe* AD dementia (2006)
  - 1/week donepezil patch approved by FDA 3/22
  - Galantamine available as a generic since 2009; donepezil & rivastigmine since 2010
  - Rivastigmine available as 1/day patch
- NMDA (glutamate) receptor antagonist: memantine
  - FDA approved for treatment of moderate to severe AD dementia (generic 2015)
    - Alone or in combination with a cholinesterase inhibitor

*No longer used clinically

Pharmacology of Acetylcholinesterase Inhibitors

- Block the action of the enzyme responsible for the breakdown of the neurotransmitter acetylcholine
- Enhance cholinergic neurotransmission in the brain



Cholinesterase Inhibitor Therapy in AD

MCI

- Benefits cognition?

Early-Stage Dementia

- Benefits cognition

Moderate Dementia

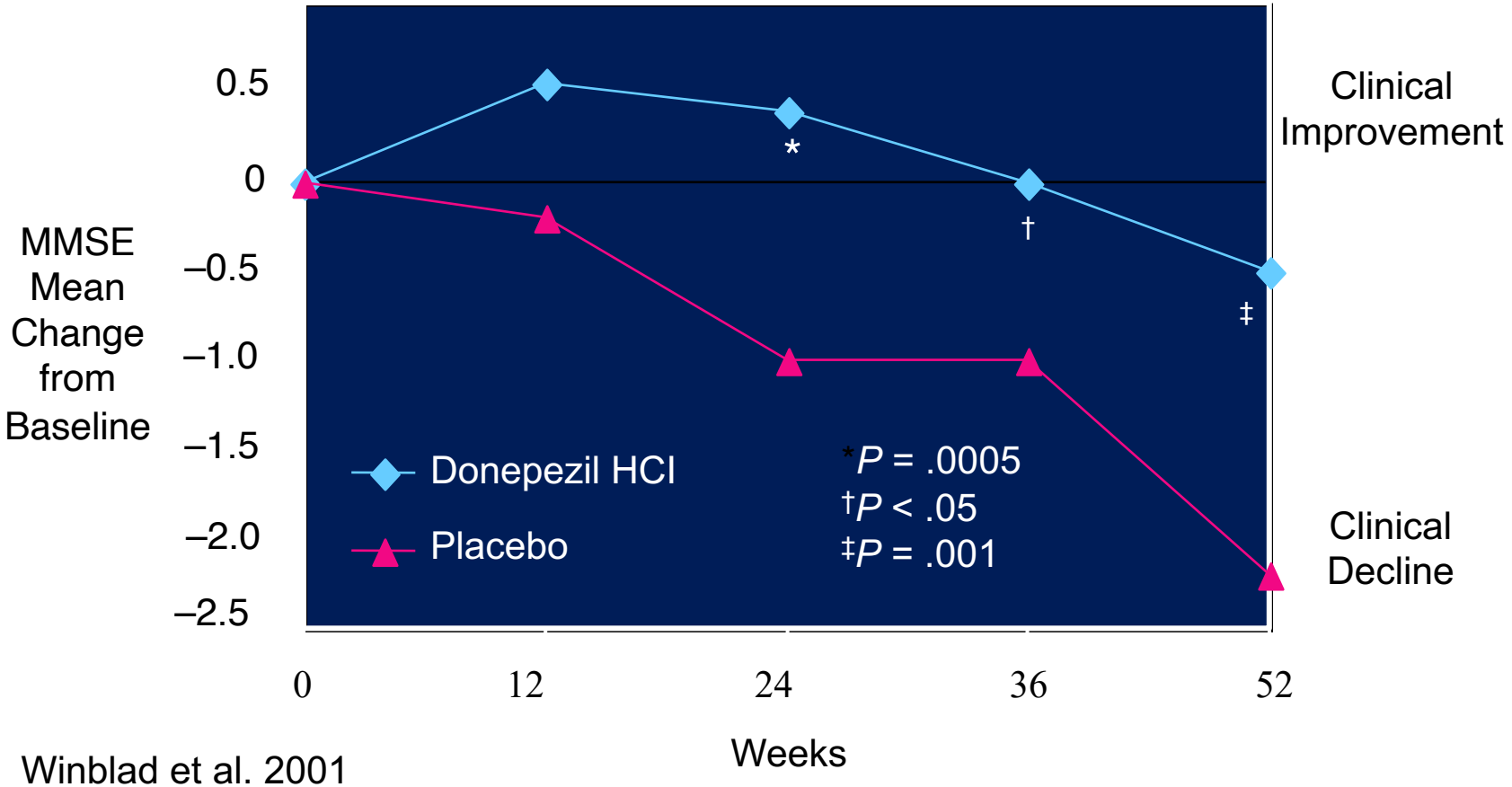
- Benefits cognition
- Preserves global status
- Preserves ADLs
- Benefits behavior?

Severe Dementia

- Benefits cognition
- Preserves global status
- Preserves ADLs
- Benefits behavior?

Class approved for mild-moderate AD
Donepezil and rivastigmine also approved for severe AD

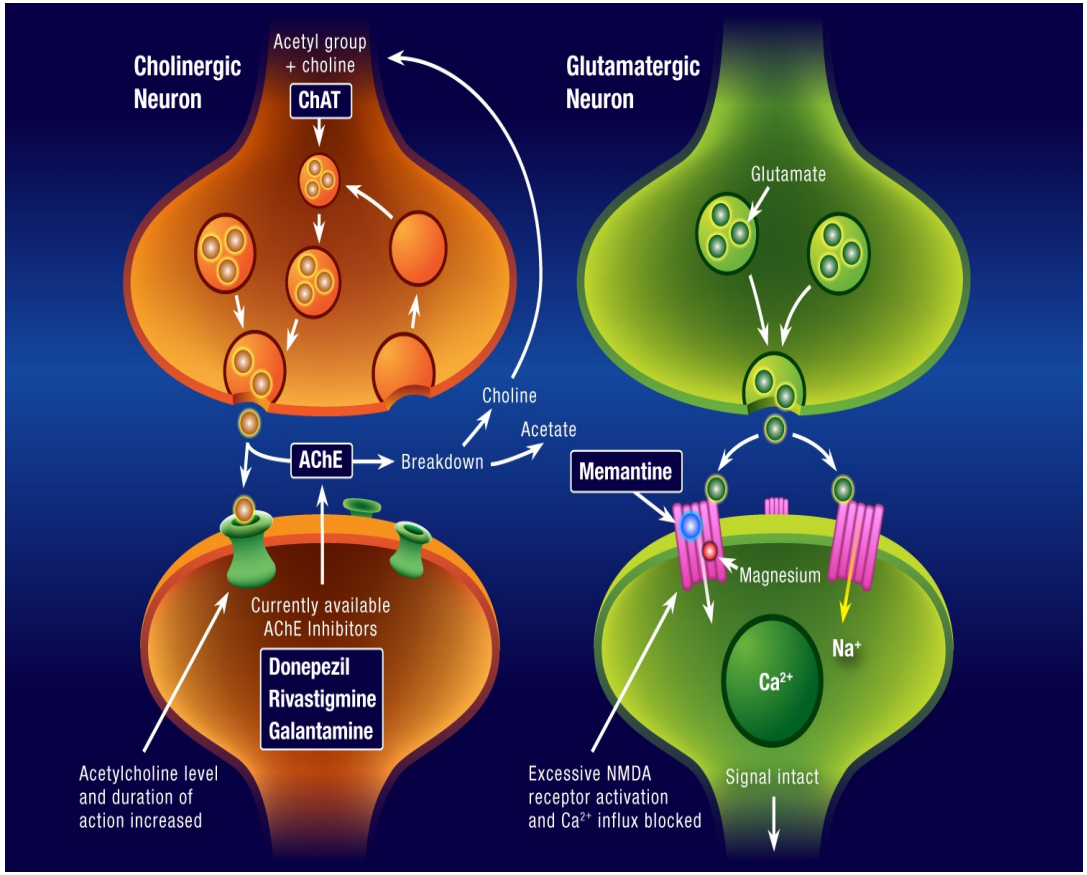
1-Year, Placebo- Controlled Trial of Donepezil: Slowing of Cognitive Decline in Mild-Moderate AD Dementia



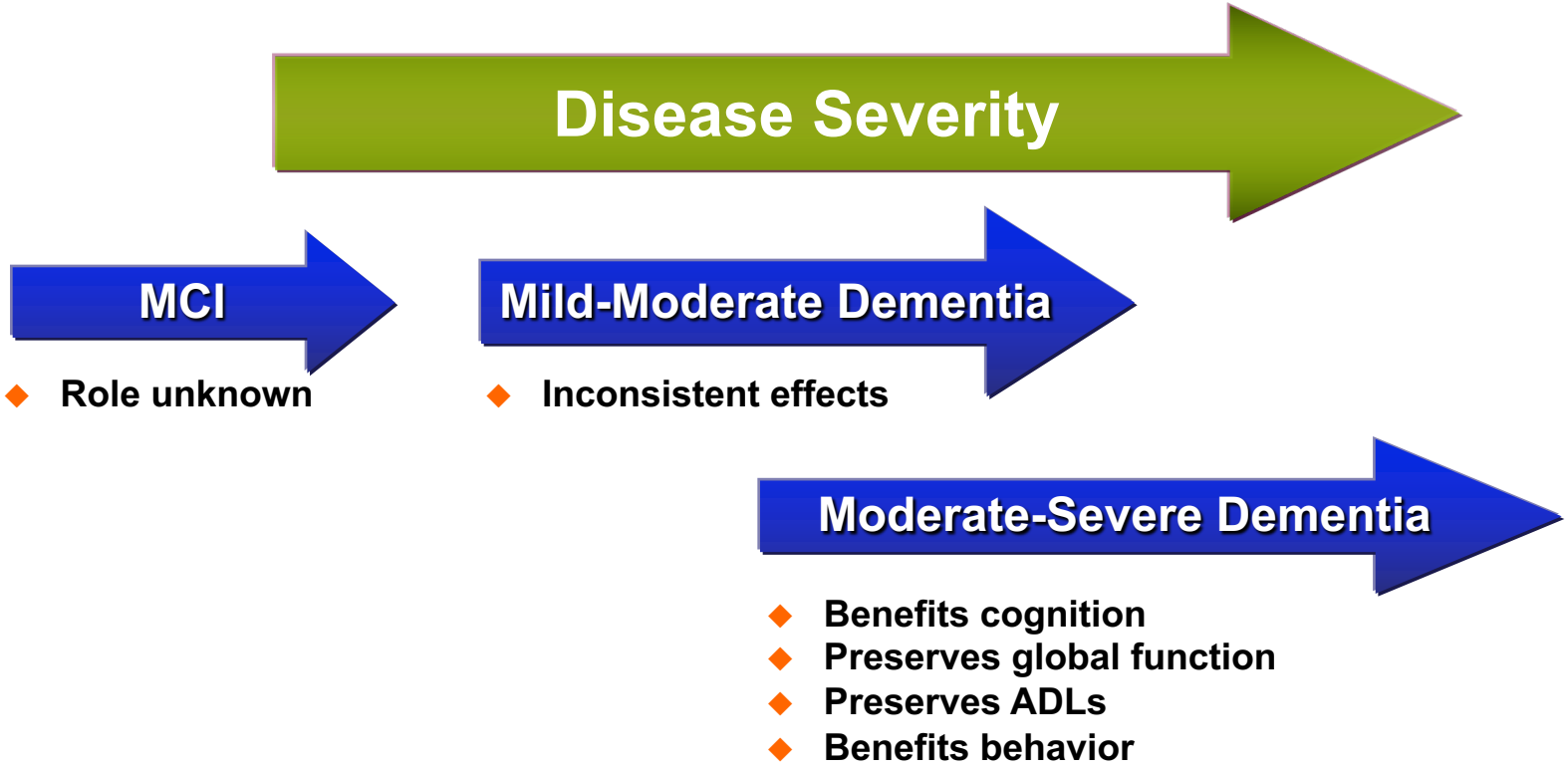
Winblad et al. 2001

Pharmacology of Memantine

- Moderate affinity, reversible uncompetitive NMDA antagonist (glutamatergic neurons)
- Renal dosing required for severe renal impairment



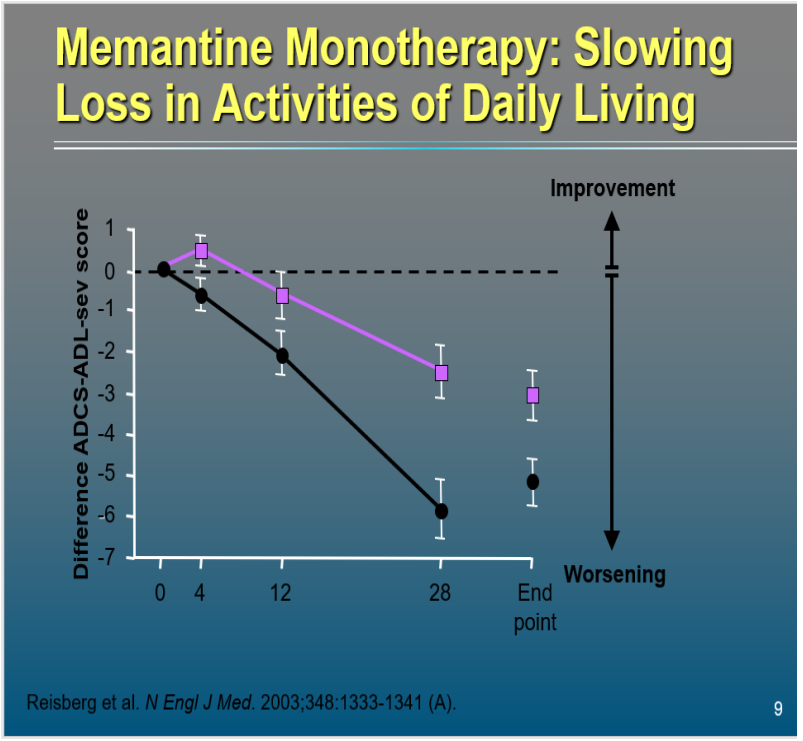
Memantine Therapy for AD*



*Approved for moderate-severe AD, alone or in combination with cholinesterase inhibitors

Memantine Monotherapy in Severe AD Dementia

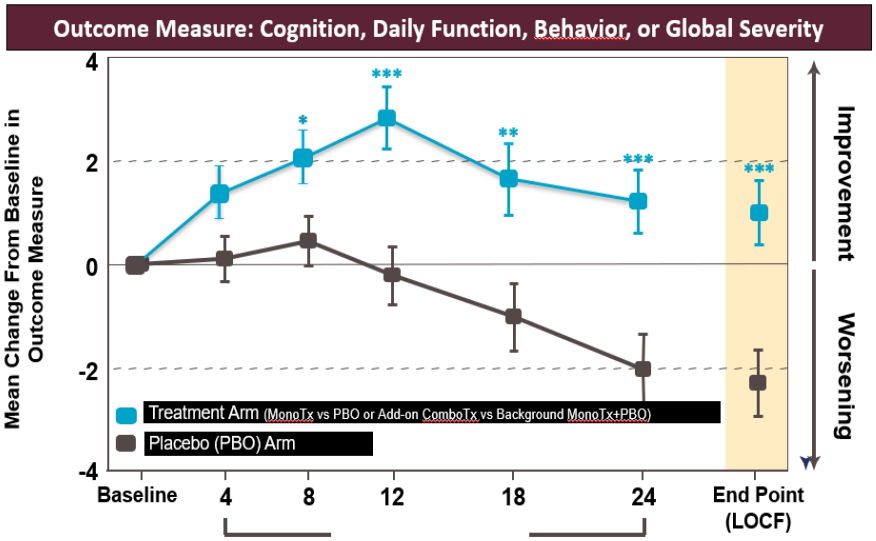
- Clinical benefit for moderate to severe AD
  - Cognition
  - Performance on ADLs
  - Behavior and mood
- Irrespective of taking a cholinesterase inhibitor
- No benefit in people with mild AD
- Moderate-certainty evidence suggesting no benefit for agitation



McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, Maayan N, Ware J, Debarros J. Memantine for dementia. Cochrane Database Syst Rev. 2019 Mar 20;3(3):CD003154. doi: 10.1002/14651858.CD003154.pub6. PMID: 30891742; PMCID: PMC6425228.
*Kishi T, Matsunaga S, Oya K, Nomura I, Ikuta T, Iwata N. Memantine for Alzheimer's Disease: An Updated Systematic Review and Meta-analysis. J Alzheimers Dis. 2017;60(2):401-425. doi: 10.3233/JAD-170424. PMID: 28922160.

Memantine/Cholinesterase Inhibitor (AChEI) Add-On Therapy

- One clearly positive trial (see graph)
  - Primary outcome was a cognitive measure
- Meta-analysis suggested that, compared with AChEIs alone, M+AChEIs showed a greater reduction in behavioral disturbances and a trend toward cognitive improvement



Tariot PN et al; Memantine Study Group. *JAMA*. 2004;291(3):317-324.

Kishi T, Matsunaga S, Oya K, Nomura I, Ikuta T, Iwata N. Memantine for Alzheimer's Disease: An Updated Systematic Review and Meta-analysis. J Alzheimers Dis. 2017;60(2):401-425. doi: 10.3233/JAD-170424. PMID: 28922160.

Dosing for AChEIs and Memantine (from Prescribing Information for each drug)

MEDICATION	STARTING DOSE	DOSING RANGE
Donepezil	5 mg/d for 4–6 weeks	5–15 mg/d After 3 months, can consider 23-mg dose formulation, approved for mod-severe only Note: new 1/week TD formulation available late 2022
Rivastigmine	1.5 mg BID, increasing by 1.5 mg every 2 weeks	6–12 mg/d
Rivastigmine Patch	4.6 mg/d for 4 weeks	9.5 mg/d; if worsening, consider 13.3-mg maximum dose
Galantamine	4 mg BID (8 mg once daily for XR) for 4 weeks	8–24 mg/d
Memantine (immediate release)	5 mg/d, increasing by 5 mg every week	10–20 mg/d
Memantine XR($$)	7 mg/d, increasing by 7 mg every week	14–28 mg/d
Donepezil/Memantine ($$)	7mg/10 mg memantine HCl XR/donepezil HCl daily	7 mg/10 mg; 14 mg /10mg ; 21 mg/10 mg; 28mg/10 mg daily

Pharmacologic Treatments for AD: Common Side Effects

Cholinesterase Inhibitors	Memantine
• Nausea • Vomiting • Diarrhea • Weight loss • Loss of appetite • Muscle weakness	• Dizziness • Headache • Constipation • Confusion

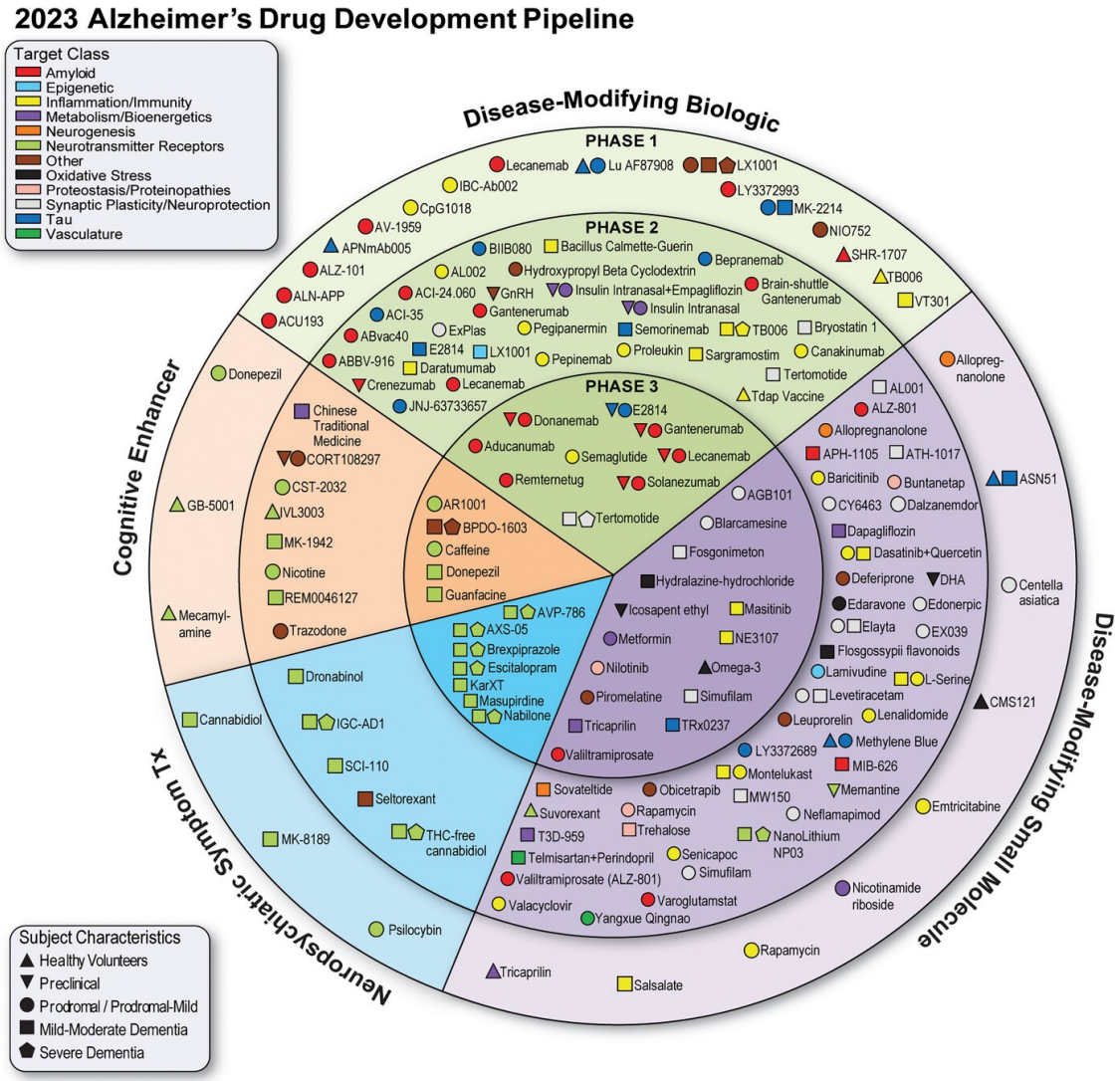
National Institute on Aging. Alzheimer's disease medications. November 2008. NIH Publication. No. 08-3431. Available at: http://www.nia.nih.gov/Alzheimers/Publications/medicationsfs.htm. Accessed July 24, 2009.

One Clinical Practice Guideline for Symptomatic Drugs*

- Newly diagnosed patients with mild AD should be treated with AChEI
- Addition of memantine:
  - Newly diagnosed patients with moderate AD
  - Patients who progress from mild to moderate AD
- Newly diagnosed patients with severe AD should be treated with memantine (an AChEI can be added)
- In mild AD:
  - Memantine monotherapy may be used when AChEI is not tolerated
  - Combination with AChEI should be considered when the disease is progressing rapidly
- Patients with mixed dementia may be treated according to AD guidelines
- Treatment may be discontinued in patients who advance to “profound” disease and who have lost all cognitive and functional abilities
- AD therapy should be continued during acute illness / hospitalization unless contraindicated

*Fillit HM, et al. The American Journal of Geriatric Pharmacotherapy. 2006;4 (suppl A):S9-S24.

2023 Alzheimer's Drug Development Pipeline



Cummings J et al 2023. DOI: 10.1002/trc2.12385

Why Amyloid Matters

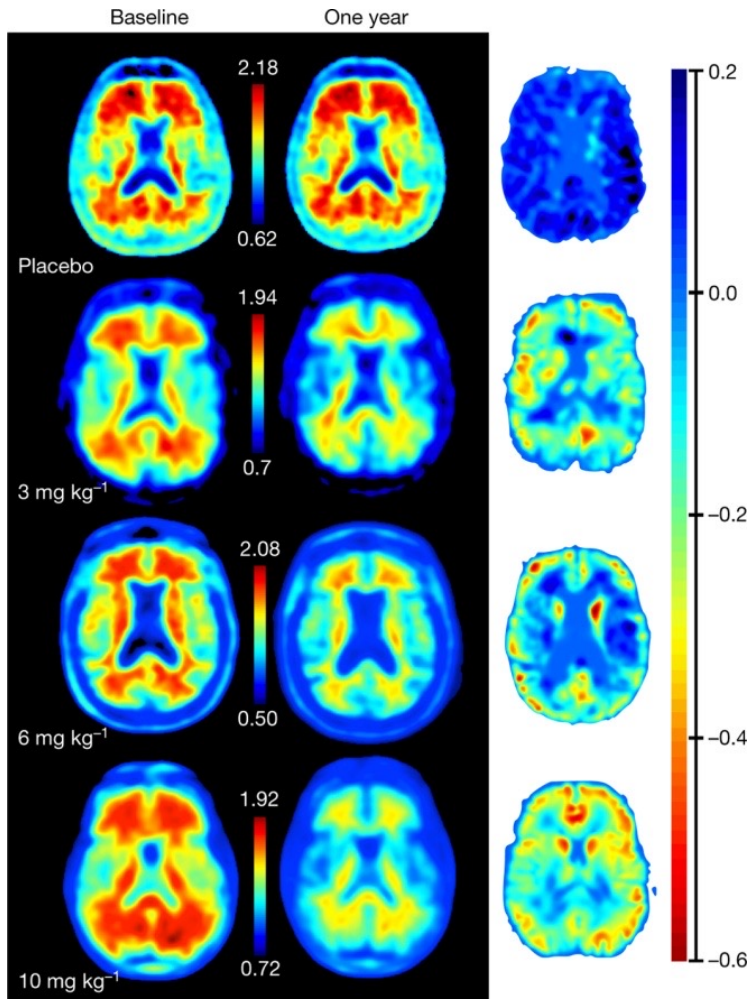
- Amyloid plaques are a pathological hallmark of Alzheimer's disease
- Amyloid fragments are toxic in many animal models
- Amyloid buildup predicts future dementia
- The rare causes of familial Alzheimer's all involve abnormal processing of amyloid
- A rare mutation blocks the pathological amyloid cascade and prevents AD (Icelandic mutation: Jonsson 2012)
- Can we block this cascade with drugs/ biologics?
- When is the right time to intervene?

- Note: most early anti-amyloid agents failed

Current Monoclonal Antibodies (MAB) in AD - Overview

Drug	Route of Administration, Frequency	Phase	Status	Prevention Trial?	ARIA Rates %
Aducanumab	Intravenous, every 4 weeks	Phase 4	Accelerated Approval	No	25-35
Lecanemab	Intravenous, biweekly	**It worked!**	**Traditional Approval**	Phase 3, AHEAD 3-45 enrolling, also in DIAN	13
Gantenerumab	Subcutaneous, every 4 weeks	Phase 3, active, not enrolling	Breakthrough Designation	Phase 3, GRADUATE, enrolling, also in DIAN	29
Donanemab	Intravenous, every 4 weeks*	Phase 3, active, not enrolling	Breakthrough Designation	Phase 3, TRAILBLAZER-ALZ3, enrolling	30

Aducanumab Phase Ib: Reduced brain amyloid after 1 year



nature

J Sevigny *et al*. *Nature* **546**, 564 (2017) doi:10.1038/nature22089

Aducanumab

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

S. Budd Haeberlein[1], P.S. Aisen[2], F. Barkhof[3,4], S. Chalkias[1,], T. Chen[1], S. Cohen[5], G. Dent[1], O. Hansson[6,7], K. Harrison[1], C. von Hehn[1,*], T. Iwatsubo[8], C. Mallinckrodt[1,*], C.J. Mummery[9], K.K. Muralidharan[1], I. Nestorov[1], L. Nisenbaum[1,*], R. Rajagovindan[1,*], L. Skordos[1,*], Y. Tian[1], C.H. van Dyck[10], B. Vellas[11], S. Wu[1], Y. Zhu[1], A. Sandrock[1,*]*

- Two parallel trials – EMERGE (Europe) and ENGAGE (USA)
  - Primary outcome of Clinical Dementia Rating – Sum of Boxes (CDR-SB)
- Futility Analysis
  - "50% of the participants (whose data were used) had the opportunity to complete week 78"
  - Assumption violations per authors:
    - 1) treatment effect similar in both studies
    - 2) treatment effect would not substantially change during the study

Aducanumab, cont'd

Table 2. Primary and secondary endpoints at week 78

Endpoint	EMERGE			ENGAGE		
	Placebo decline ± SE (n=548)	Difference vs placebo (%)‖ 95% CI P		Placebo decline ± SE (n=545)	Difference vs placebo (%)‖ 95% CI P	
		Low dose (n=543)	High dose (n=547)		Low dose (n=547)	High dose (n=555)
Primary						
CDR-SB*	1.74±0.11	−0.26 (−15%)	−0.39 (−22%)	1.56±0.11	−0.18 (−12%)	0.03 (2%)
		−0.57, 0.04	−0.69, −0.09		−0.47, 0.11	−0.26, 0.33
		.090	.012		.225	.833

Table 3. Summary of adverse events

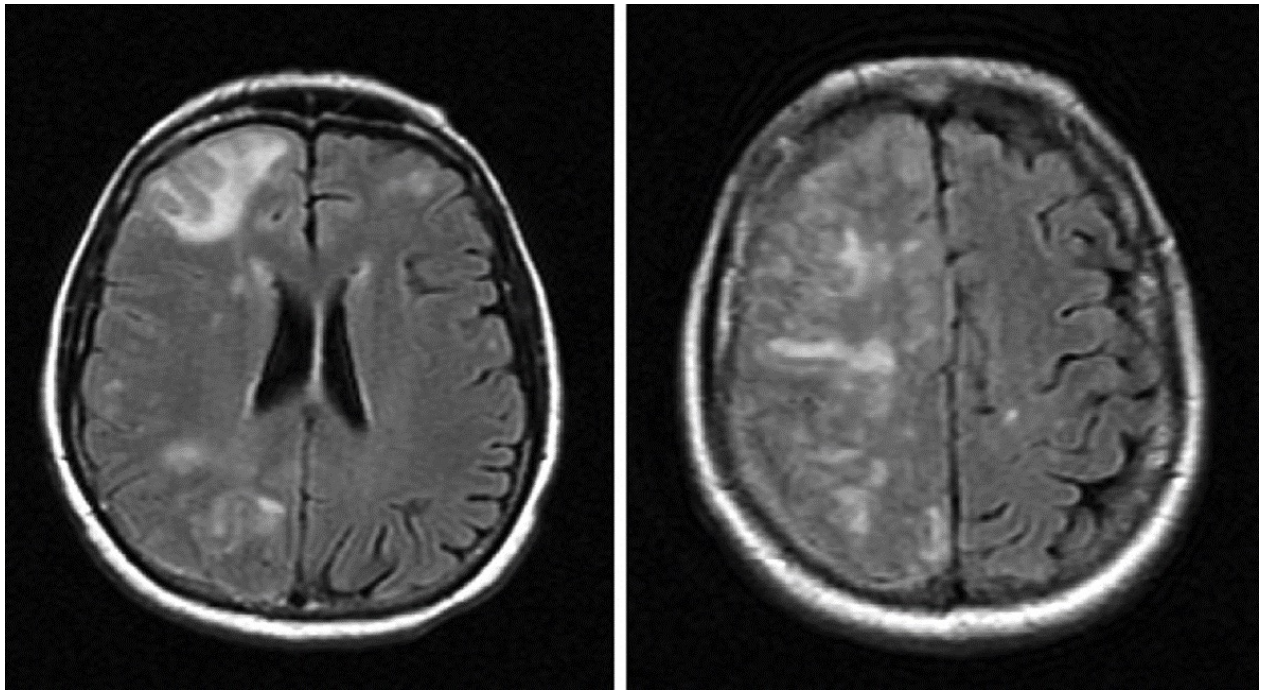
	Event, n (%)					
	EMERGE			ENGAGE		
	Placebo	Low dose	High dose	Placebo	Low dose	High dose
Safety MRI population	n=544	n=537	n=541	n=532	n=545	n=554
ARIA-E	13 (2)	140 (26)	188 (35)	16 (3)	141 (26)	199 (36)
ApoE ε4 carriers	7/371 (2)	109/366 (30)	156/362 (43)	9/371 (2)	114/390 (29)	159/378 (42)
ApoE ε4 noncarriers	6/173 (4)	31/171 (18)	32/179 (18)	7/161 (4)	27/155 (17)	40/176 (23)
Brain microhemorrhage	37 (7)	87 (16)	108 (20)	34 (6)	89 (16)	104 (19)
Brain microhemorrhage in participants without ARIA-E	35 (7)	30 (8)	32 (9)	32 (6)	24 (6)	21 (6)
Localized superficial siderosis	14 (3)	52 (10)	73 (13)	10 (2)	51 (9)	89 (16)
Localized superficial siderosis in participants without ARIA-E	9 (2)	9 (2)	7 (2)	6 (1)	7 (2)	5 (1)

Haeberlein et al., 2022

Aducanumab, cont'd

- Monthly infusions
- Titration required
- May slow down cognitive/functional decline by about **22%**
- About **35%** of patients on high dose experienced reactions in the brain, called "Amyloid-Related Imaging Abnormalities" or ARIA
  - Most were asymptomatic
  - Dose- and ApoE4-genotype related
- Frequent MRI is required during titration to monitor for ARIAs
- Not covered by insurance company Medicare, VA, etc.
  - Uptake has been very low
- Placebo-controlled efficacy trial still required for traditional FDA approval

ARIA-E: Vasogenic Edema



- Reprinted from Alzheimer's & Dementia, 7/4, Sperling RA, Jack CR Jr, Black SE, Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup, 367-385, copyright 2011, with permission from Elsevier

Lecanemab

- Key Inclusion Criteria
  - 50-90 years old
  - MCI or mild dementia
  - Amyloid+ by PET or CSF
  - Episodic memory impairment
    - 1 SD below age-adjusted mean on Wechsler Memory Scale IV-Logical Memory

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2023 VOL. 388 NO. 1

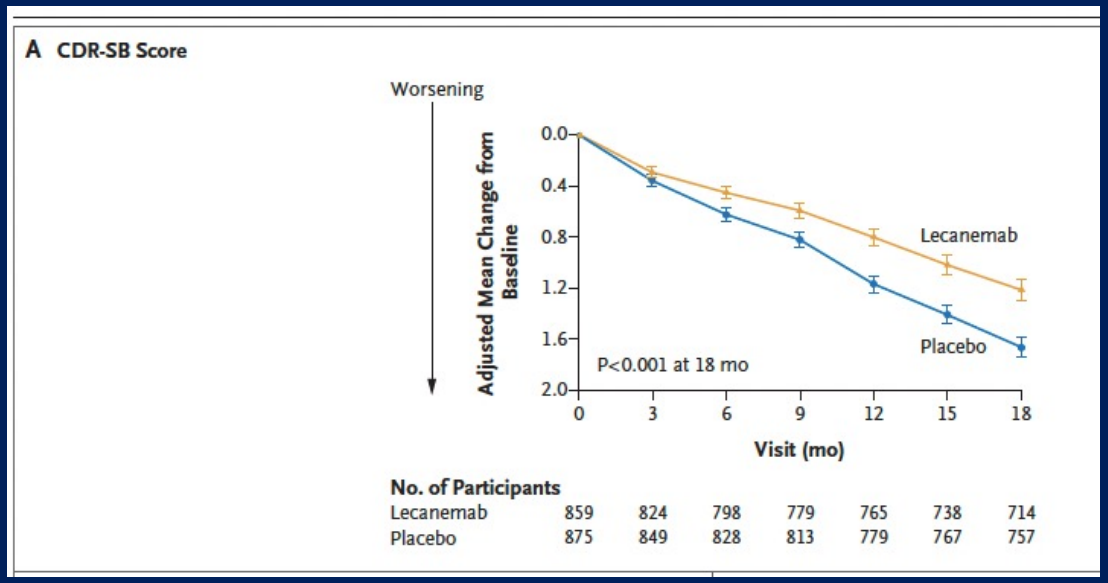
Lecanemab in Early Alzheimer's Disease

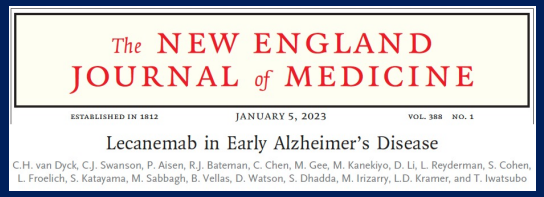
C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

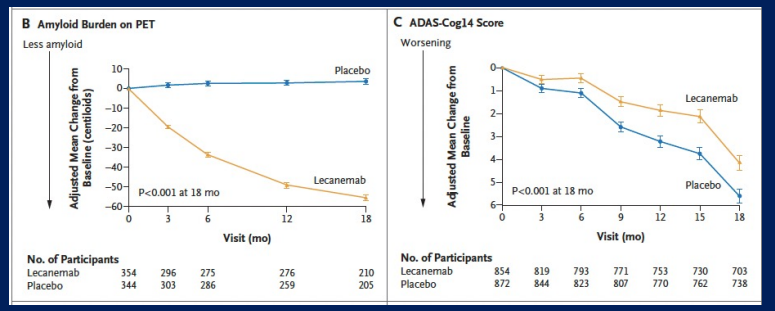
Table 1. Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population).*

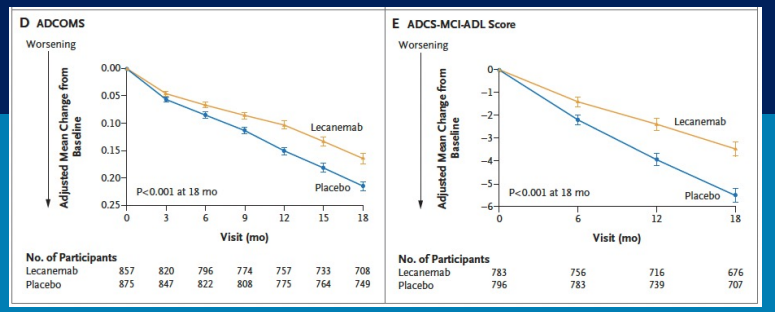
Characteristic	Lecanemab (N=859)	Placebo (N=875)
Age — yr	71.4±7.9	71.0±7.8
Sex — no. (%)		
Female	443 (51.6)	464 (53.0)
Male	416 (48.4)	411 (47.0)
Race — no. (%)†		
White	655 (76.3)	677 (77.4)
Black	20 (2.3)	24 (2.7)
Asian	147 (17.1)	148 (16.9)
Other or missing	37 (4.3)	26 (3.0)
Hispanic ethnic group — no. (%)†	107 (12.5)	108 (12.3)
Time since diagnosis — yr	1.41±1.51	1.34±1.54
Time since onset of symptoms — yr	4.13±2.35	4.15±2.53
Global CDR score — no. (%)‡		
0.5	694 (80.8)	706 (80.7)
1	165 (19.2)	169 (19.3)
Clinical subgroup — no. (%)		
Mild dementia due to Alzheimer's disease	331 (38.5)	331 (37.8)
Mild cognitive impairment due to Alzheimer's disease	528 (61.5)	544 (62.2)

Lecanemab









- 27% Slowing of decline on the CDR-SB
  - 1.66 decrease in placebo
  - 1.21 decrease in treatment group
- FDA granted full approval 2023

Lecanemab

Table 3. Adverse Events.*

Event	Lecanemab (N=898)	Placebo (N=897)
Overall — no. (%)		
Any adverse event	798 (88.9)	735 (81.9)
Adverse event related to lecanemab or placebo†	401 (44.7)	197 (22.0)
Serious adverse event	126 (14.0)	101 (11.3)
Death	6 (0.7)	7 (0.8)
Adverse event leading to discontinuation of the trial agent	62 (6.9)	26 (2.9)
ARIA‡		
ARIA-E — no. (%)	113 (12.6)	15 (1.7)
Symptomatic ARIA-E — no. (%)§	25 (2.8)	0
ApoE ε4 noncarrier — no./total no. (%)	4/278 (1.4)	0/286
ApoE ε4 carrier — no./total no. (%)	21/620 (3.4)	0/611
ApoE ε4 heterozygote	8/479 (1.7)	0/478
ApoE ε4 homozygote	13/141 (9.2)	0/133
ARIA-E according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	15/278 (5.4)	1/286 (0.3)
ApoE ε4 carrier	98/620 (15.8)	14/611 (2.3)
ApoE ε4 heterozygote	52/479 (10.9)	9/478 (1.9)
ApoE ε4 homozygote	46/141 (32.6)	5/133 (3.8)
ARIA-H — no. (%)	155 (17.3)	81 (9.0)
Microhemorrhage	126 (14.0)	68 (7.6)
Superficial siderosis	50 (5.6)	21 (2.3)
Macrohemorrhage	5 (0.6)	1 (0.1)
Symptomatic ARIA-H§	6 (0.7)	2 (0.2)
Isolated ARIA-H: no concurrent ARIA-E	80 (8.9)	70 (7.8)

ARIA

- ARIA-E 12.6%
  - Symptomatic ARIA-E 2.8%
- ARIA-H 17.3%
  - Symptomatic ARIA-H 2.8%
- Higher risk in APOE4 carriers
  - Highest in homozygotes

Clinical Use Guidelines for Lecanemab

Cummings et al, Meaningful use guidelines for lecanemab. J Prev Alz Dis 2023; Published online March 27, 2023, http://dx.doi.org/10.14283/jpad.2023.30

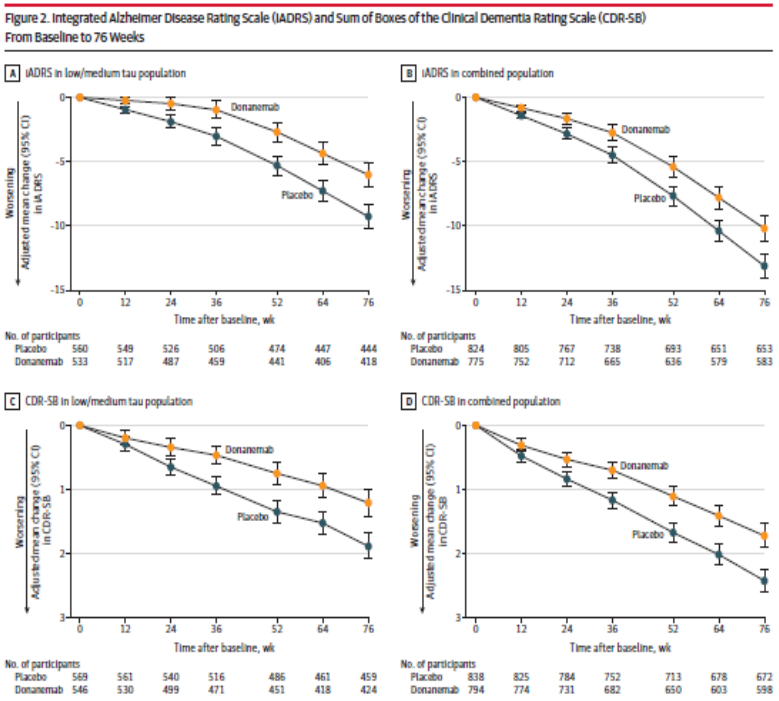
Phase 3 Trial of Donanemab in Early Alzheimer's Disease

JAMA | Original Investigation

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

John R. Sims, MD; Jennifer A. Zimmer, MD; Cynthia D. Evans, PhD; Ming Lu, MD, MS, MPH; Paul Ardayfio, PhD; JonDavid Sparks, PhD; Alette M. Wessels, PhD; Sergey Shcherbinin, PhD; Hong Wang, PhD; Emel Serap Monkul Nery, MD; Emily C. Collins, PhD; Paul Solomon, PhD; Stephen Salloway, MD; Liana G. Apostolova, MD; Oskar Hansson, MD, PhD; Craig Ritchie, MD, PhD; Dawn A. Brooks, PhD; Mark Mintun, MD; Daniel M. Skovronsky, MD, PhD; for the TRAILBLAZER-ALZ 2 Investigators

- Different anti-amyloid antibody
- Earlier Phase 2 trial was 1st to show a disease modifying effect
  - Selected patients with medium level of tau tangles ("sweet spot")
- Primary focus was patients with low-medium tangle burden
- Rapid reduction of brain amyloid

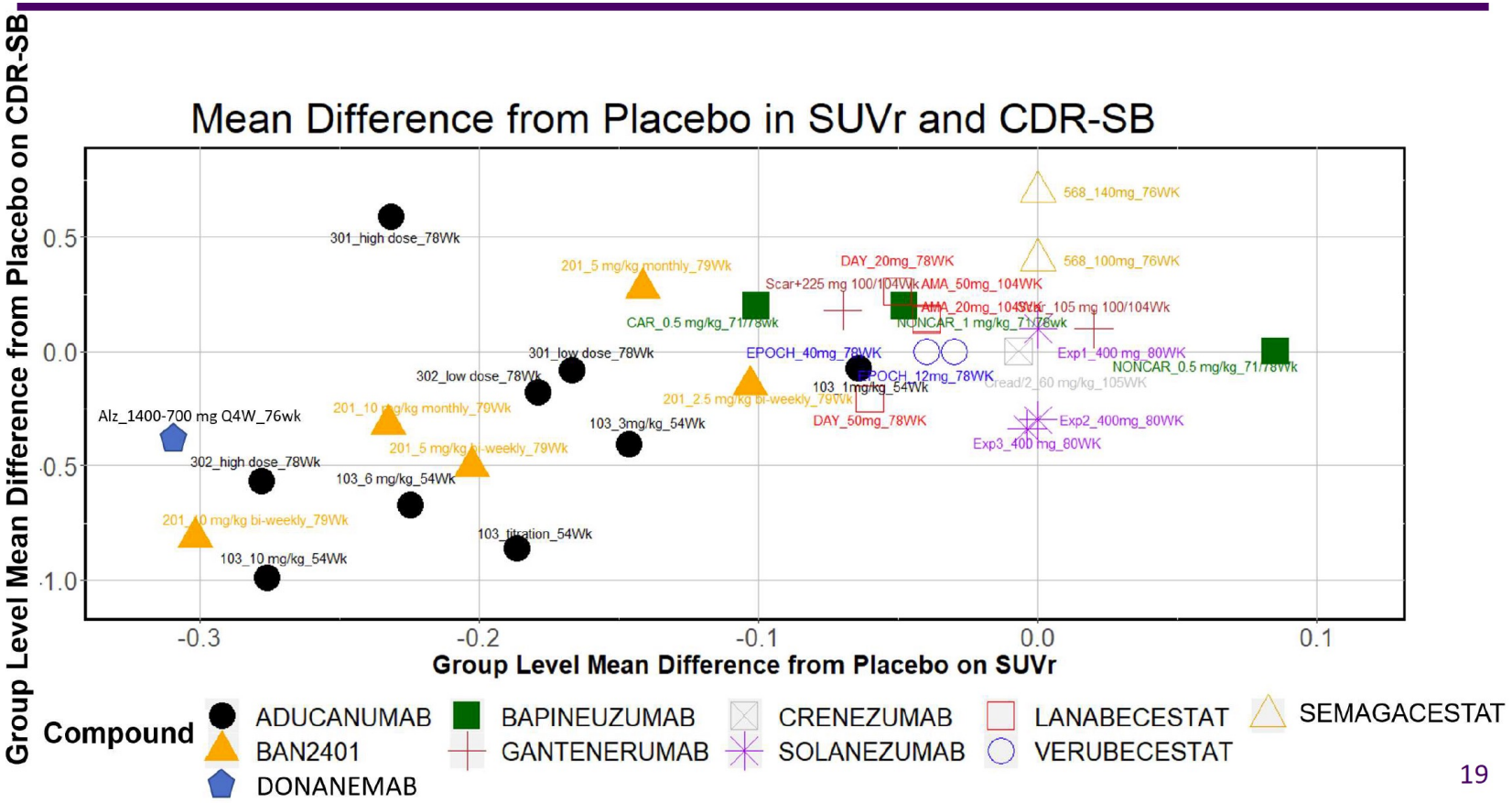


Donanemab in Early Alzheimer's Disease – Phase 3 Topline Results

Population	Intermediate Tau		Combined Intermediate & high Tau	
	Relative % Slowing	P-value	Relative % Slowing	P-value
iADRS	35%	p<0.000004	22%	p<0.00006
CDR-SB	**37%**	p<0.000005	**29%**	p<0.00000007
ADCS-iADL	40%	p<0.0001	28%	p<0.0002
ADAS-Cog13	32%	p<0.00005	20%	p<0.0007

In the overall donanemab treatment group, ARIA-E occurred in **24.0%** of treated participants, with 6.1% experiencing symptomatic ARIA-E.

Data Suggest that Amyloid mAbs that Do Not Clear Plaques Do Not Work Clinically (Even When Given Pre-symptomatically)



Blood Tests for soluble forms of Tau and Amyloid in Alzheimer's Disease: Not quite ready for the clinic (but CSF tests are)

Where do we go from here?

- Refining currently available monoclonal antibodies such as **subcutaneous administration**
  - Lecanemab subcutaneous in ongoing trials.
  - Aducanumab considering subcutaneous study.
  - Donanemab follow-on compound in ongoing trials.
- Development of next generation of antibodies with less adverse events and ?more efficacy
  - Remternetug: “2nd generation” donanemab
- Start treatment before symptoms onset in participants who already have amyloid plaque → **Secondary prevention**
  - Lecanemab (AHEAD), donanemab (TRAILBLAZER 3)

Backup

Mild Cognitive Impairment – Treatment

- *None of the neurotransmitter-based drugs are FDA-approved*
  - Clinical trials results bottom line: “the glass is half-full”
  - NIH-funded Petersen trial of donepezil is considered most informative
    - Primary outcome was negative: delayed progression to dementia at year 3
    - Secondary: Delayed progression to dementia at 1 year, better cognitive performance for 2+ years
  - Best practice per AAN is to discuss pro’s/con’s of cholinesterase inhibitors (but not memantine)
    file:///C:/Users/PTariot/Downloads/Practice%20Guideline%20Update%20Summary_%20Mild%20Cognitive%20Impairment.pdf accessed 10/16/2020
- New disease modifiers ARE FDA-approved for MCI
- Consider clinical research/trial referral
  - Explosion in number of therapeutic targets being tested
  - Most are putative disease modifiers

Where do we go from here?, cont'd

- Lifestyle interventions trials (e.g., BP, sleep, metabolic syndrome, exercise, etc.)
  - **U.S. POINTER** (The Alzheimer's Association U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk): physical activity, nutritional guidance, cognitive training, social activities and management of heart-health risk factors
  - **Middle Path:** Hypertension intervention in mid-life (Jeremy Pruzin et al)
  - Further prevention trials in Colombia
- Anti-tau monoclonal antibody therapies have not panned out yet
  - **BIIB080** first antisense oligonucleotide (ASO) targeting tau expression in Phase 2 trial
- Other mechanisms: too soon to say (microbiome-directed, inflammation, neuroprotection, membrane stabilization, etc.)
- **Combination treatments?**
  - Different anti-amyloid mechanisms: e.g., immunotherapy followed by oral agent
  - Anti-amyloid and anti-tau
  - Other: Lifestyle intervention/risk factor reductions plus amyloid &/or tau-directed therapies