

# Alzheimer's Disease

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## Presenter Disclosure

- › Faculty/Presenter:  
**Tina Korownyk**
- › Relationships with commercial interests:
  - **Grants/Research Support:** CIHR, PRIHS
  - **Speakers Bureau/Honoraria:** ACFP, CFPC, other provincial colleges
  - **Consulting Fees:** N/A
  - **Other:** Member of Canadian Taskforce on Preventive Healthcare



## Objectives

- Discuss theories, recent trials for Alzheimer's Management
- Review current evidence for pharmacologic treatment of Alzheimer's
- Review observational data, limitations and associated recommendations

11 THINGS WE'D REALLY LIKE TO KNOW

### Will We Ever Cure Alzheimer's?

Few drugs have been approved for treatment of this dementia, and none works very well. It has become one of the most intractable problems in medicine.

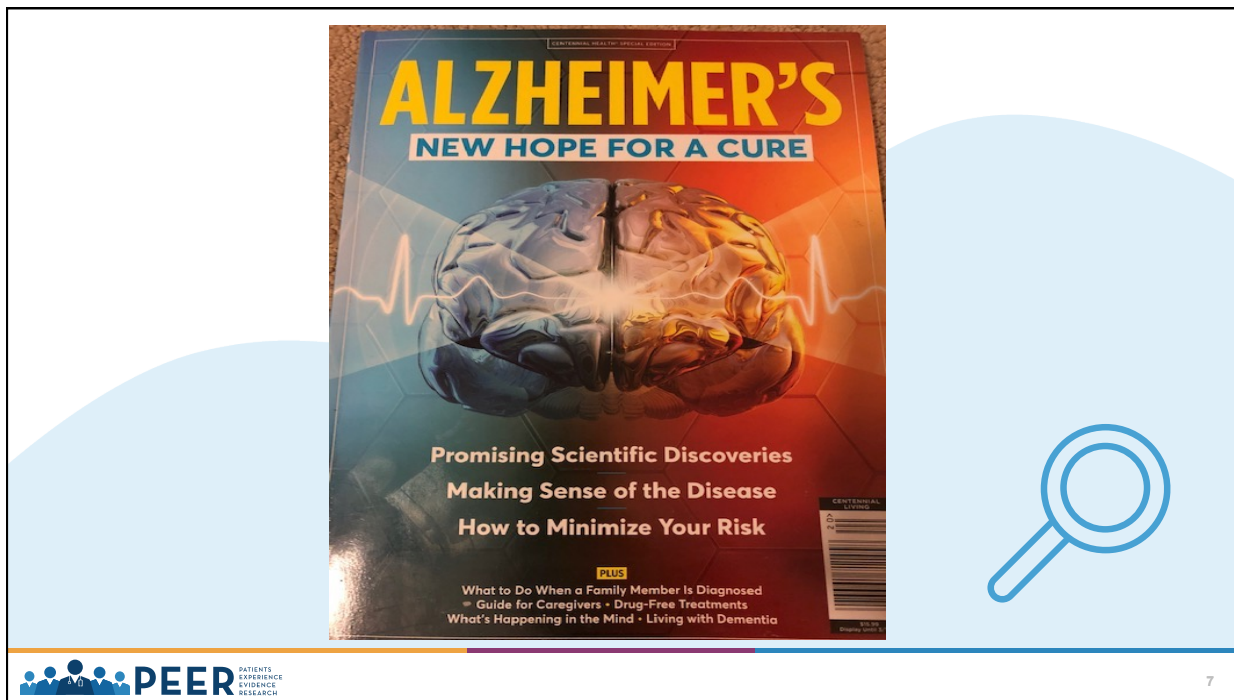
*The Futurist*

**The Outlook for Alzheimer's Disease: No Cure Is Yet in Sight,**

Jens Mortensen for The New York Times

I was thinking about our conversation yesterday. I think dad is willing to go to the ends of the earth for mom bc he knows that at the very least it will make her feel like even though the rest of the world has given up in her...he hasn't.

hope. I think if she feels like we've given up on her....that's when she's going to start really deteriorating quickly. So let them search and travel in the mean time even if the only thing that they end up with is hope. I think Hope will be enough to sustain her and keep her from deteriorating rapidly.



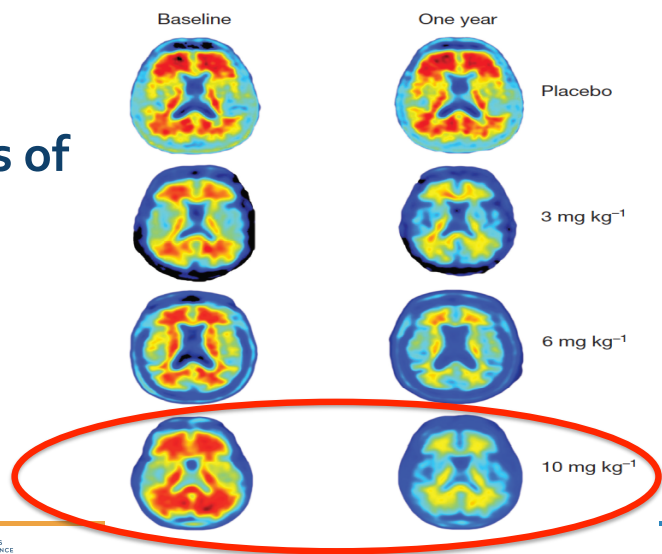
## A New Hope: Aducanumab

- RCT 165 pts, age 73, MMSE ~24, positive Aβ PET scan, monthly IV 1,3,6,10 mg/kg dosing versus placebo
- At one year...

Measure	Scale	Worse	Baseline	Placebo vs 10	Main Types of AE
MSE	0-30	low	24	2.7 vs 0.5 MCID = 1 - 3	Edema (NNH 3), Headache (NNH 5), superficial iron deposition in CNS (8)
CDR-SoB	0-18	high	3.2	1.8 vs 0.7 MCID = 1 - 2	
FCSRT	0-48	lower	14	No diff	
Discontinue due to AE				10% vs 31% (ss)	

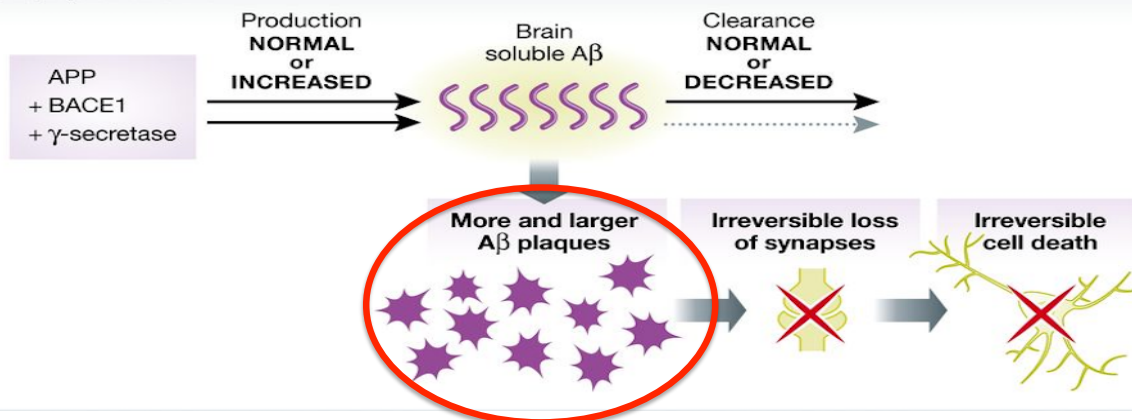
## A New Hope: Aducanumab

PET Scans of Amyloid Deposits.



## Amyloid changes in AD

### C Symptomatic AD



**The New York Times**

## An Alzheimer's Drug Trial Gave Me Hope, and Then It Ended

I was a small piece in the search to find a cure. Now I feel as if I'm getting erased, and medical science doesn't have any answers.

**Aducanumab**  
Biogen Mar 2019

**Crenezumab**  
Roche Jan 2019

**Solanezumab**  
Lilly Nov 2016

**Bapineuzumab**  
Pfizer, Johnson & Johnson 2012

**PEER** PATIENTS EXPERIENCE EVIDENCE RESEARCH

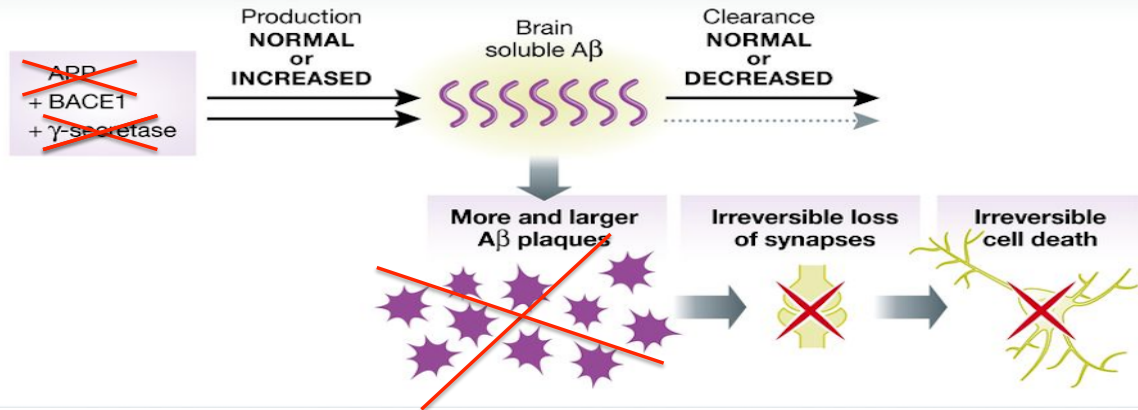
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## 2018

- Eli Lilly, AstraZeneca, Pfizer and Merck canceled research on dementia therapies.
- Pfizer pulled out of the market entirely
- Three **BACE<sub>1</sub> inhibitor** trials ended due to futility or adverse events
  - Merck (**Verubecestat**) – a/es, no benefit mild to moderate or prodromal AD
  - AstraZeneca/Eli Lilly (**Lanabecestat**) – no benefit mild cognitive impairment or mild AD
  - Janssen (**Atabecestat**) - liver toxicity

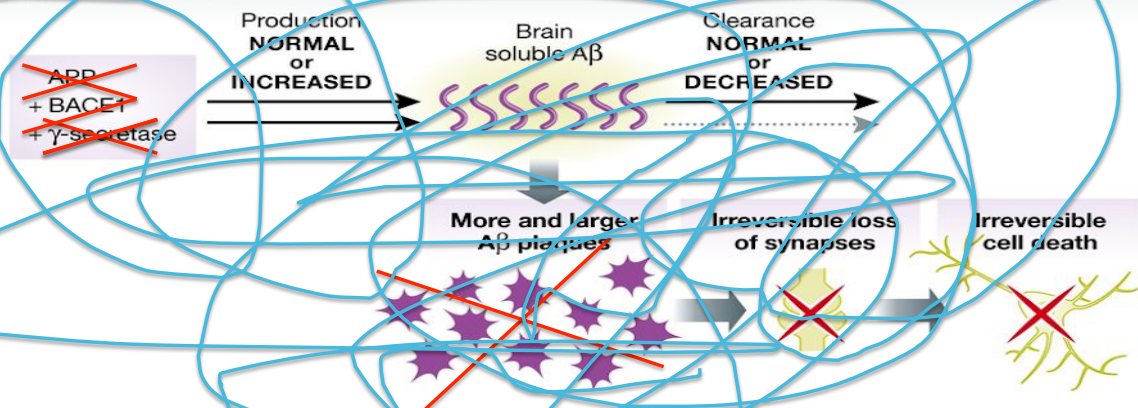
# Amyloid changes in AD

## C Symptomatic AD



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# Amyloid changes in AD

**C Symptomatic AD**

The diagram illustrates the amyloid hypothesis in symptomatic AD. It shows a flow from left to right: **Production** (NORMAL or INCREASED), **Brain soluble Aβ**, and **Clearance** (NORMAL or DECREASED). On the left, a box lists ~~APP~~, ~~+ BACE1~~, and ~~+ γ-secretase~~. On the right, a box lists ~~cross~~ and ~~s~~, and **Irreversible cell death**. A yellow box highlights a review article: "The amyloid hypothesis of Alzheimer's disease at 25 years" by Dennis J Selkoe<sup>1\*</sup> & John Hardy<sup>2,1\*</sup>. The diagram is overlaid with blue scribbles and a red 'X' over a neuron.

**Review**

**The amyloid hypothesis of Alzheimer's disease at 25 years**

Dennis J Selkoe<sup>1\*</sup> & John Hardy<sup>2,1\*</sup>

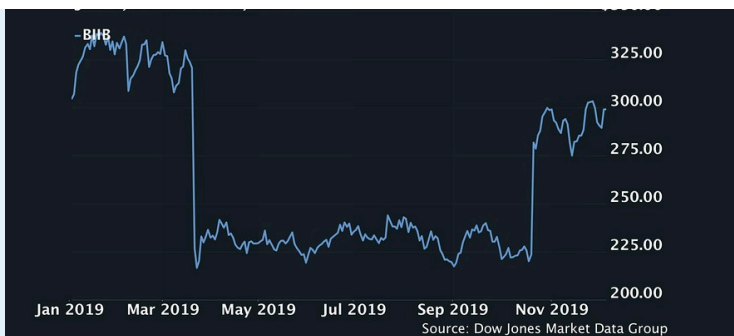
EMBO Molecular Medicine

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EMBO Mol Med (2018) e9717

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## Biogen scraps two Alzheimer drug trials, wipes \$18 billion from market value

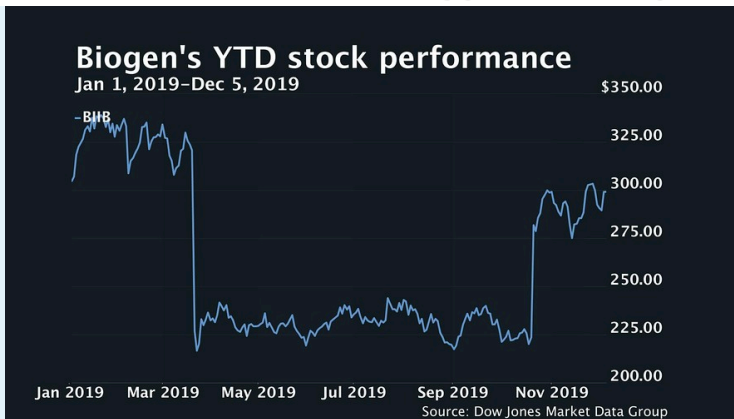


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## 'Reports of My Death Are Greatly Exaggerated.' Signed, Aducanumab



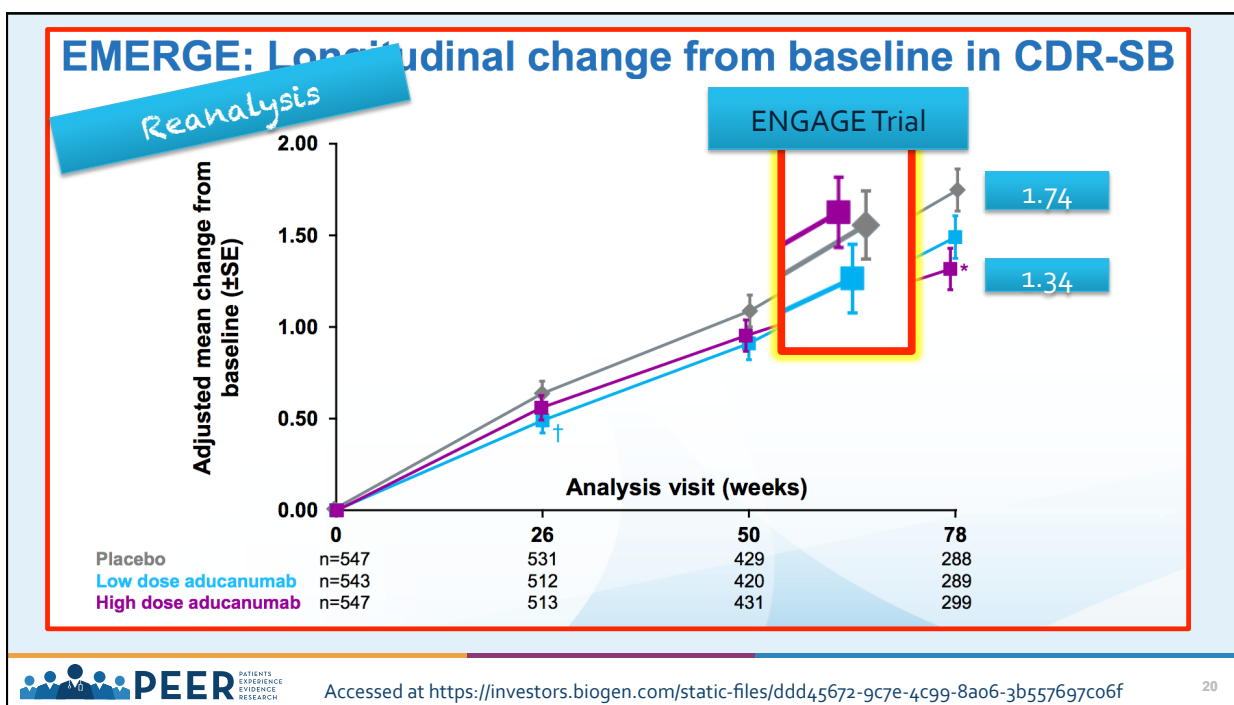
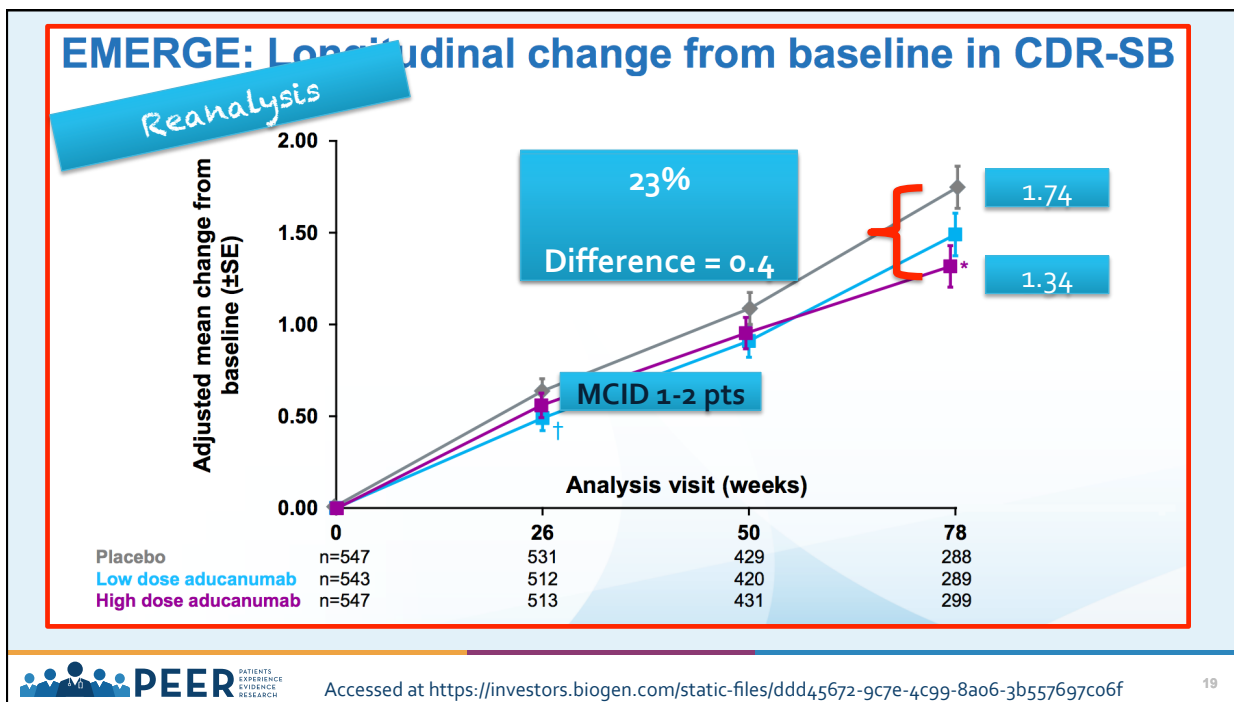
## Emerge & Engage: A tale of 2 RCTs

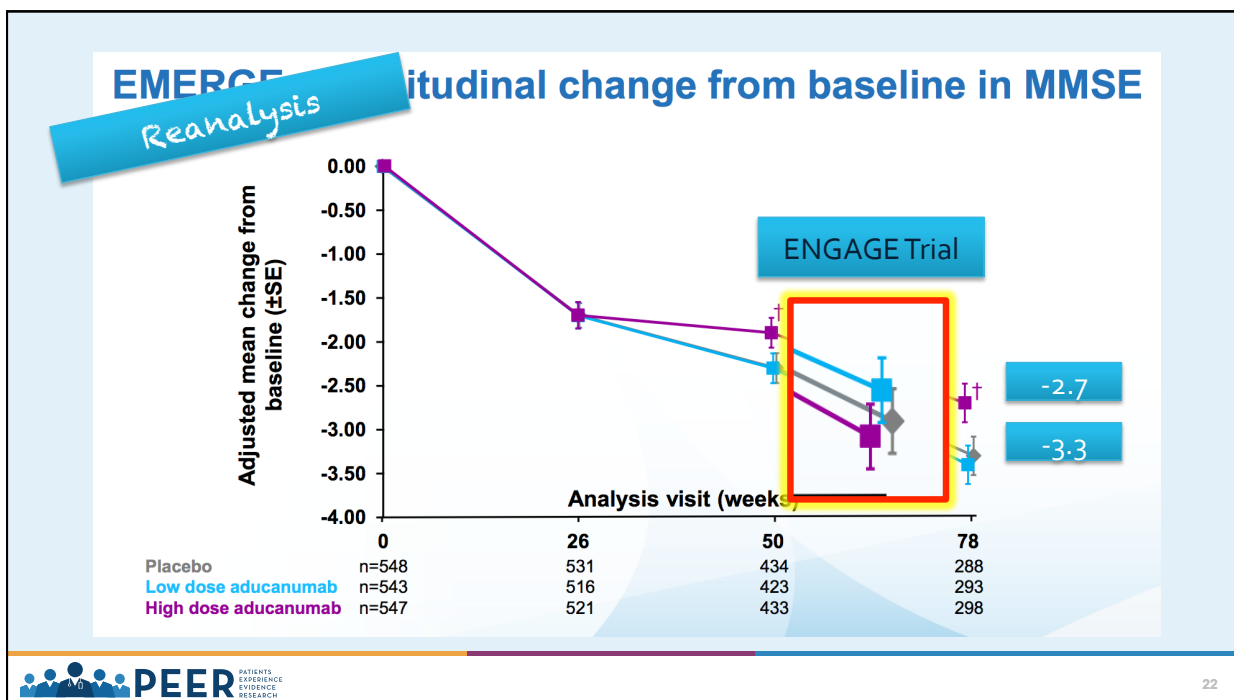
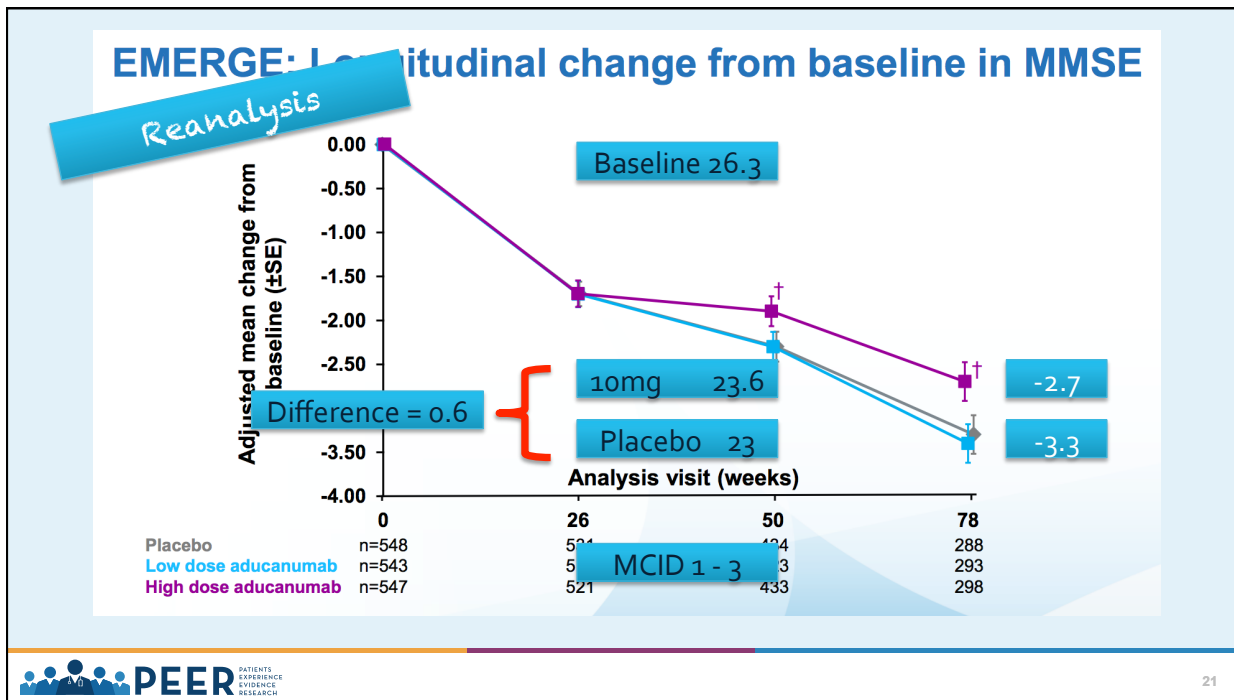


**Emerge: Positive**      **23% benefit!**  
1350 patients

**Engage: Negative**      **2% worse**  
1350 patients

**Total 3285 pts, 348 sites in multiple countries**





**EMERGE Reanalysis** Longitudinal change from baseline in MMSE

**ENGAGE Trial**

**Considerations:** Full data set not yet released, Post hoc, Multiple analysis, Protocol amendments, A/Es: Edema 34% vs 2% NNH = 4, superficial iron deposition in CNS 13% vs 3% NNH = 10, Headache 19% vs 15% NNH = 25. Biggest effect seen in high dose, edema most common in high dose, required additional imaging = likely unblinding

Placebo  
Low dose aduc  
High dose aduc

**Current Excitement Scale: 0.6**

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PREV ARTICLE | THIS ISSUE | NEXT ARTICLE

**DETERMINANTS OF SUCCESSFUL AGING: DEVELOPING AN INTEGRATED RESEARCH AGENDA FOR THE 21ST CENTURY** | 2 SEPTEMBER 2003

**Healthy Aging and Dementia: Findings from the Nun Study**

David A. Snowdon, PhD  
Article, Author, and Disclosure Information

*Figure 1. Sister Matthia, a model of healthy aging in the Nun Study, at 104 years of age, 3 months before she died.*

Braak and Braak Staging of Alzheimer Disease Pathology	Participants with Memory Impairment, %
0 Sparse	0
1 + 2 Mild	42
3 + 4 Moderate	68
5 + 6 Severe	92

**PEER** PATIENTS EXPERIENCE EVIDENCE RESEARCH

Bennett et al. J Alzheimers Dis. 2018;64(s1):S161-S189.

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## Religious Orders Study and Rush Memory Aging Project

Longitudinal study, started 1994, 78 years, no dementia

3414 persons

Ongoing clinical evaluations

36% 1,232 cases mild cognitive impairment (MCI)

22% 764 cases dementia

1,506/1717 brain autopsies following death  
(mean age 89 years)



Bennett et al. J Alzheimers Dis. 2018;64(s1):S161-S189.<sup>25</sup>

## Religious Orders Study and Rush Memory Aging Project

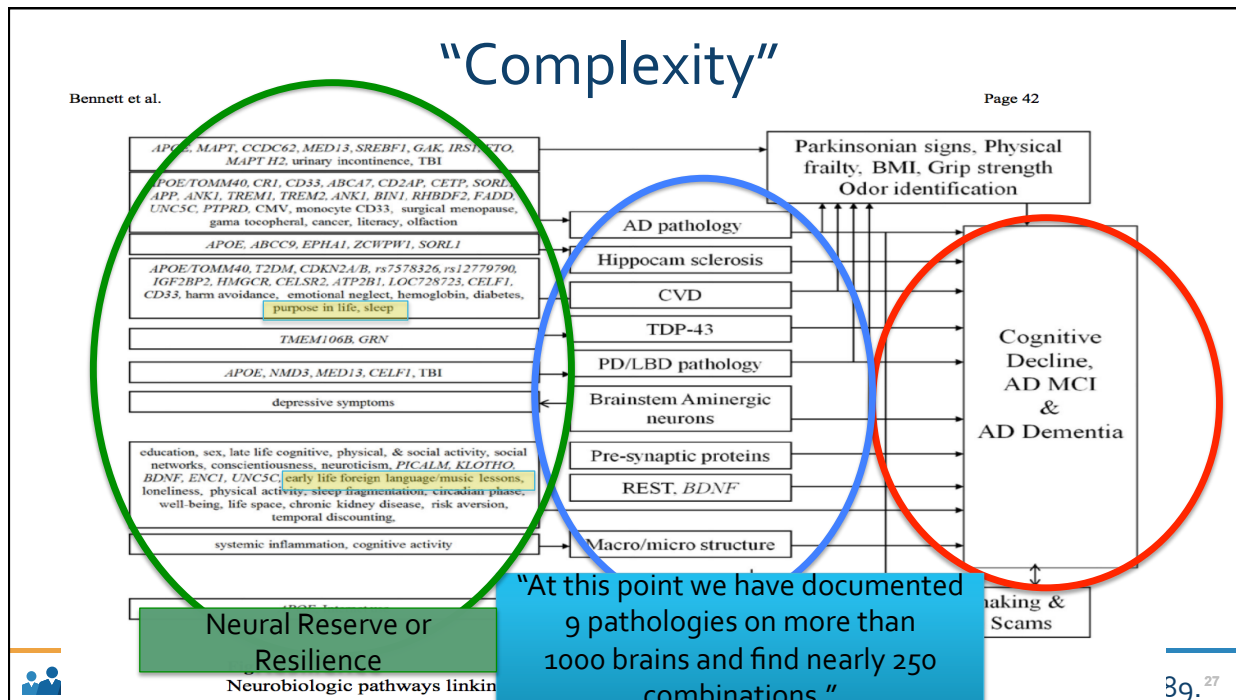
> 400 publications

“Perhaps the over-arching theme running through the work is ***complexity.***”

- 1) continuum of AD
- 2) mixed and newly recognized pathologies
- 3) neural reserve or resilience



Bennett et al. J Alzheimers Dis. 2018;64(s1):S161-S189.<sup>26</sup>



## Success in AD Research

- Reviewed 244 compounds in 413 clinical trials of Alzheimer’s Disease between 2002 and 2012
  - Of 244 compounds, only 1 approved (memantine)
  - Highest failure rate of any disease: 99.6%
    - (Cancer 81%)

## Success in AD Research

Drug	Year FDA Approved
Tacrine	1993 Removed 2013
Donepezil (Aricept)	1996
Rivastigmine (Exelon)	1998
Galantamine (Reminyl)	2001
Memantine	2003
Donepezil + Memantine	2014

No "new" treatments approved by FDA since 2003

## Cholinesterase Inhibitors

- Cholinesterase trials vs Placebo: MSE 10-26\*
  - Quality of Life scores unchanged

	Donepezil <sup>1</sup> 2019	Galantamine <sup>2</sup> 2006	Rivastigmine <sup>3</sup> 2018	All <sup>4</sup>
MMSE	1.1	?	0.74	1.37
ADAS - Cog	2.67	3.38	1.79	2.73
ADAS - Cog of 4	?	NNT 6	NNT 18*	?
Glob Clin State	NNT 9	NNT 7	NNT 13	NNT 14
Adverse Events	NNH 15	?	NNH 8	NNH 10



## Cholinesterase Inhibitors

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Glob Clin State	NNT 9	NNT 7	NNT 13	NNT 14
Adverse Events	NNH 15	?	NNH 8	NNH 10

Reminder:EMERGE trial Aducanumab MMSE improvement 0.6 over placebo



\* Health Technol Assess 2012;16(21). 1) Cochrane 2018 Jun 18;6:CD001190 (10mg x 6 months). 2) Cochrane 2006; 1: CD001747. 3) Cochrane 2015; 9: CD001191. (\*2009) 4) Cochrane 2006; Issue 1: CD005593.

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## Patient Outcomes: Cholinesterase Inhibitors

- RCT 565 patients, mild-moderate AD, 3 years.
- No significant benefit:
  - institutionalization (42% vs 44%)
  - Disability progression (58% vs 59%)
  - behavioural symptoms
  - carer psychopathology
- Conclusion: Donepezil is not cost effective. (Other reviews have concluded the opposite)



Lancet. 2004 Jun 26;363(9427):2105-15. Health Technol Assess 2012;16(21)

# Memantine

	Improvement	Added to ChEi	On Scale of	% Improvement
Clinical Global Rating	0.21	0.21	7	3
Cognitive Function	3.11	2.48	100	3
Functional Performance in ADLs	1.09	0.95	54	2
Behavioral Disturbance	1.84	2.20	144	1

## Bottom-Line: Effects are small & inconsistent

- Not approved for mild-moderate dementia.
- NICE 2018 recommends consideration in mod-severe dementia on ChEIs.
- Adverse events similar overall RR 1.03
  - Dizziness 6.1% versus 3.9%, NNH = 46

## Controversial

### OUTLOOK

**Towards better patient care:  
drugs to avoid in 2020**

Donepezil

Rivastigmine

Galantamine

Memantine



## The Lancet Commissions

## Dementia prevention, intervention, and care: 2020 report of the Lancet Commission



Gill Livingston, Jonathan Huntley, Andrew Sommerlad, David Ames, Clive Ballard, Sube Banerjee, Carol Brayne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Sergi G Costafreda, Amit Dias, Nick Fox, Laura N Gitlin, Robert Howard, Helen CKales, Mika Kivimäki, Eric B Larson, Adesola Ogunniyi, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

**12 Risk factors - interventions could potentially modify outcomes**

**Limits: Largely observational, confounders, reverse causation?**

### Relative risk for dementia (95% CI)

Early life (<45 years)	
Less education	1.6 (1.3-2.0)
Midlife (age 45-65 years)	
Hearing loss	1.9 (1.4-2.7)
TBI	1.8 (1.5-2.2)
Hypertension	1.6 (1.2-2.2)
Alcohol (>21 units/week)	1.2 (1.1-1.3)
Obesity (body-mass index $\geq 30$ )	1.6 (1.3-1.9)
Later life (age >65 years)	
Smoking	1.6 (1.2-2.2)
Depression	1.9 (1.6-2.3)
Social isolation	1.6 (1.3-1.9)
Physical inactivity	1.4 (1.2-1.7)
Diabetes	1.5 (1.3-1.8)
Air pollution	1.1 (1.1-1.1)



## In Summary...How can we offer Hope?

### Prevention:

- Systolic BP  $\leq$  130 from ~ age 40 \*
- Encourage hearing aids
- Avoid smoking, encourage smoking cessation
- Limit Etoh (>21 units/week increases risk)
- Minimize Obesity
- Prevent head injury
- Reduce second hand smoke & air pollution exposure
- Children need education

### Treatment:

- Cholinesterase inhibitors
  - May Improve dementia ~ 1 in 10 (over placebo)
  - Adverse events severe enough to stop taking for 1 in 10 (over placebo)
- Memantine
  - Combination may have limited benefit in mod-severe dementia
- Don't forget caregivers!
- Consider referral to First Link Alzheimer's Society

