



- The Aging and Memory Clinic Speakers Series
  - Saint Louis University
- “Dementia Medications and their Alternatives”





***“Memory is a passion  
no less powerful or pervasive  
than love.”***

***Elie Wiesel***

***“All Rivers Run to the Sea”***



From: **A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012**

JAMA Intern Med. 2017;177(1):51-58. doi:10.1001/jamainternmed.2016.6807

**Table 3. Cognitive Function, by Age Range, 2000 and 2012 Cohorts**

Cognitive Function	No. (%) [95% CI] <sup>a</sup>							
	65-74 y		75-84 y		≥85 y		Total (Age >65 y)	
	2000 (n = 5566)	2012 (n = 4983)	2000 (n = 3668)	2012 (n = 3991)	2000 (n = 1312)	2012 (n = 1537)	2000 (n = 10 546)	2012 (n = 10 511)
Normal	4320 (78.1) [76.5-79.7]	3931 (82.8) [81.1-84.4]	2231 (62.0) [60.1-64.0]	2603 (67.5) [65.6-69.3]	415 (32.8) [30.3-35.4]	580 (40.8) [38.0-43.6]	6966 (67.2) [65.8-68.6]	7114 (72.4) [71.1-73.6]
CIND	942 (16.5) [15.2-17.8]	837 (14.0) [12.7-15.4]	924 (24.4) [23.0-25.9]	936 (22.6) [20.9-24.3]	427 (32.9) [29.5-36.5]	451 (29.9) [27.4-32.6]	2293 (21.2) [20.1-22.3]	2224 (18.8) [17.8-19.9]
Dementia	304 (5.4) [4.7-6.3]	215 (3.2) [2.7-3.8]	513 (13.6) [12.1-15.1]	452 (9.9) [9.0-10.9]	470 (34.4) [31.2-37.6]	506 (29.3) [26.9-31.8]	1287 (11.6) [10.7-12.7]	1173 (8.8) [8.2-9.4]
<b>Age- and Sex-Standardized to 2000 Population</b>								
Normal	4320 (78.1) [76.5-79.7]	3931 ( <b>82.9</b> ) [81.1-84.4]	2231 (62.0) [60.1-64.0]	2603 ( <b>67.6</b> ) [65.6-69.3]	415 (32.8) [30.3-35.4]	580 ( <b>40.7</b> ) [38.0-43.6]	6966 (67.2) [65.8-68.6]	7114 ( <b>72.6</b> ) [71.2-73.7]
CIND	942 (16.5) [15.2-17.8]	837 (14.0) [12.7-15.4]	924 (24.4) [23.0-25.9]	936 ( <b>22.5</b> ) [20.9-24.3]	427 (32.9) [29.5-36.5]	451 ( <b>29.7</b> ) [27.4-32.6]	2293 (21.2) [20.1-22.3]	2224 (18.8) [17.8-19.9]
Dementia	304 (5.4) [4.7-6.3]	215 (3.2) [2.7-3.8]	513 ( <b>13.5</b> ) [12.1-15.1]	452 (9.9) [9.0-10.9]	470 ( <b>34.3</b> ) [31.2-37.6]	506 ( <b>29.6</b> ) [26.9-31.8]	1287 (11.6) [10.7-12.7]	1173 ( <b>8.6</b> ) [8.1-9.3]

Abbreviations: CIND, cognitive impairment—no dementia; HRS, Health and Retirement Study.<sup>16</sup>

<sup>a</sup> Values in parentheses are weighted percentages (95% CIs) derived using the HRS sampling weights to adjust for the complex design of the HRS survey.

Values for 2012 weighted percentages in the lower half of the table are age- and sex-standardized to the 2000 population using direct standardization. Boldface values differ from those in the non-age- and sex-standardized data.

# DEMENTIA is DECREASING in the United States

# Seattle-based Adult Changes in Thought study

- Alzheimer's disease..... 45%
- Vascular based lesions..... 33%
- Lewy Body Dementia..... 10%

# Reversible Causes of MCI/Dementia

**D**rugs (digoxin, theophylline, cimetidine, anticholinergic)

**E**motional (depression)

**M**etabolic (hypothyroidism, B12)

**E**yes and ears (sensory isolation)

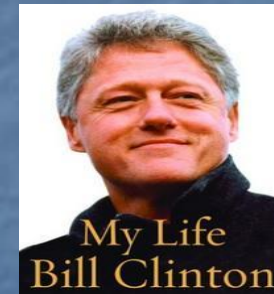
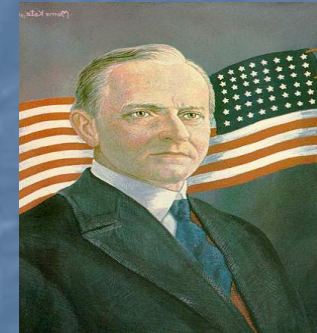
**N**ormal Pressure Hydrocephalus (ataxia, incontinence, and dementia)

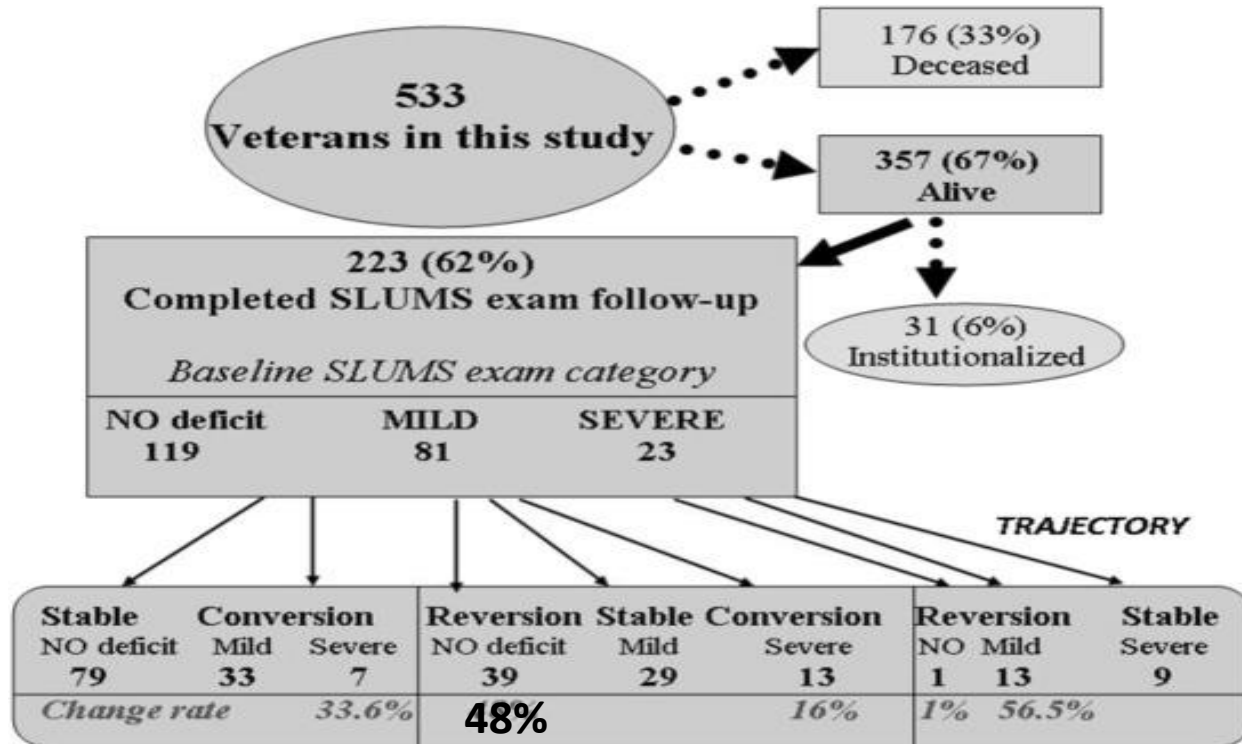
**T**umor or other space-occupying lesion

**I**nfection (syphilis, chronic infections)

**A**trial fibrillation (vitamin B12 deficiency)/Alcoholism

**S**leep Apnea



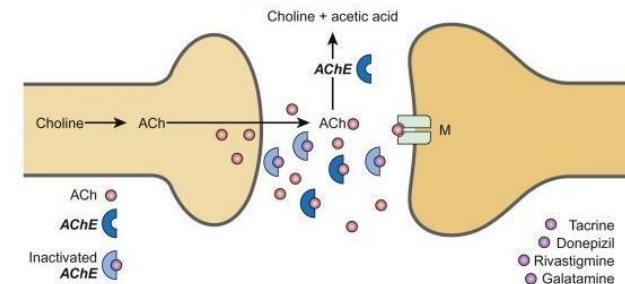


Correction of visual loss		
Stability	1 [Reference]	
Conversion	1.12 (0.27–4.71)	.877
Reversion	4.65 (1.58–13.70)	.005
Discontinuation of anticholinergic		
Stability	1 [Reference]	
Conversion	1.88 (0.69–5.13)	.218
Reversion	4.57 (1.87–11.18)	.001

## Cognitive Deficit Reversal as Shown by Changes in the Veterans Affairs Saint Louis University Mental Status (SLUMS) Examination Scores 7.5 Years Later

Medications with anticholinergic effect		
Very strong 3 points per drug	Strong 2 points per drug	Moderate 1 point per drug
Amitriptyline	Amantadine	Carbidopa-Levodopa
Atropine	Baclofen	Entacapone
Benztropine	Cetirizine	Haloperidol
Carisoprodol	Cimetidine	Metocarbamol
Ciproheptadine	Clozapine	Metoclopramide
Chlorpheniramine	Cyclobenzaprine	Mirtazapine
Chlorpromazine	Desipramine	Paroxetine
Dicyclomine	Loperamide	Pramipexole
Diphenhydramine	Nortriptyline	Quetiapine
Fluphenazine	Olanzapine	Ranitidine
Hydroxyzine	Prochlorperazine	Risperidone
Hyoscyamine	Pseudoephedrine	Selegiline
Imipramine	Tolterodine	Trazodone
Meclizine		Ziprasidone
Oxybutynin		
Perphenazine		
Promethazine		
Thioridazine		
Thiothixene		
Tizanidine		
Trifluoperazine		

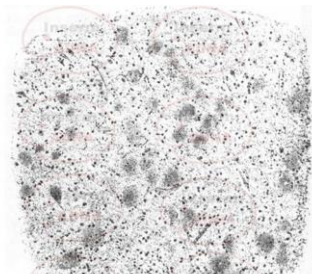
## Cholinesterase Inhibitors







Solomon Carter Fuller, 1906



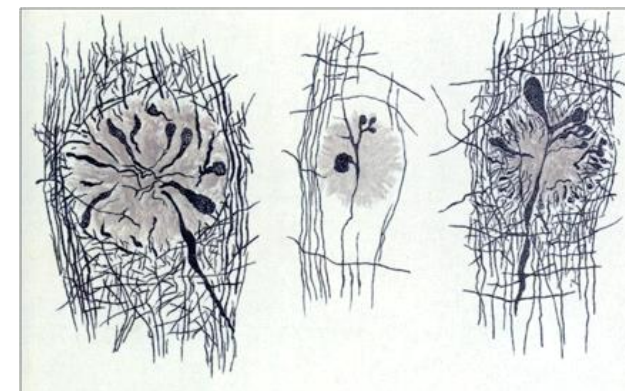
Emil Redlich 1898

# What's in a name?



Paul Blocq 1882

## Miyake 1906



12 patients with **plaque** out of 16 with senile dementia  
10 controls, 10 psychosis, 45 neurosyphilis – NO PLAQUES



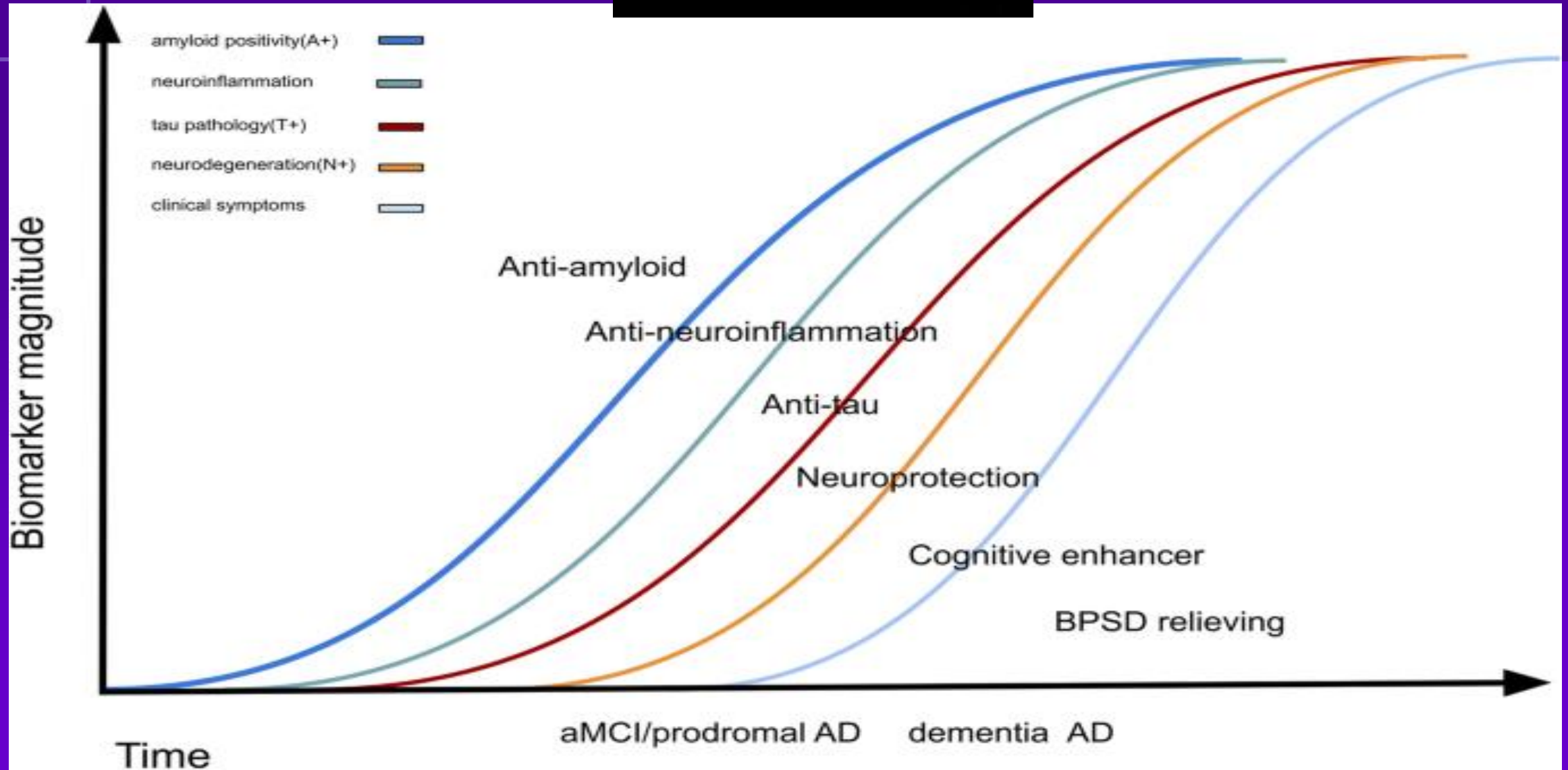
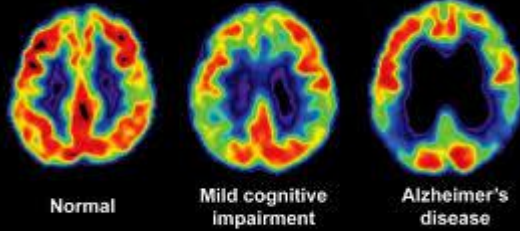
Aloysius Alzheimer, 1906/7



Auguste Deter

Oskar Fischer, 1907





# The Cholinergic Hypothesis



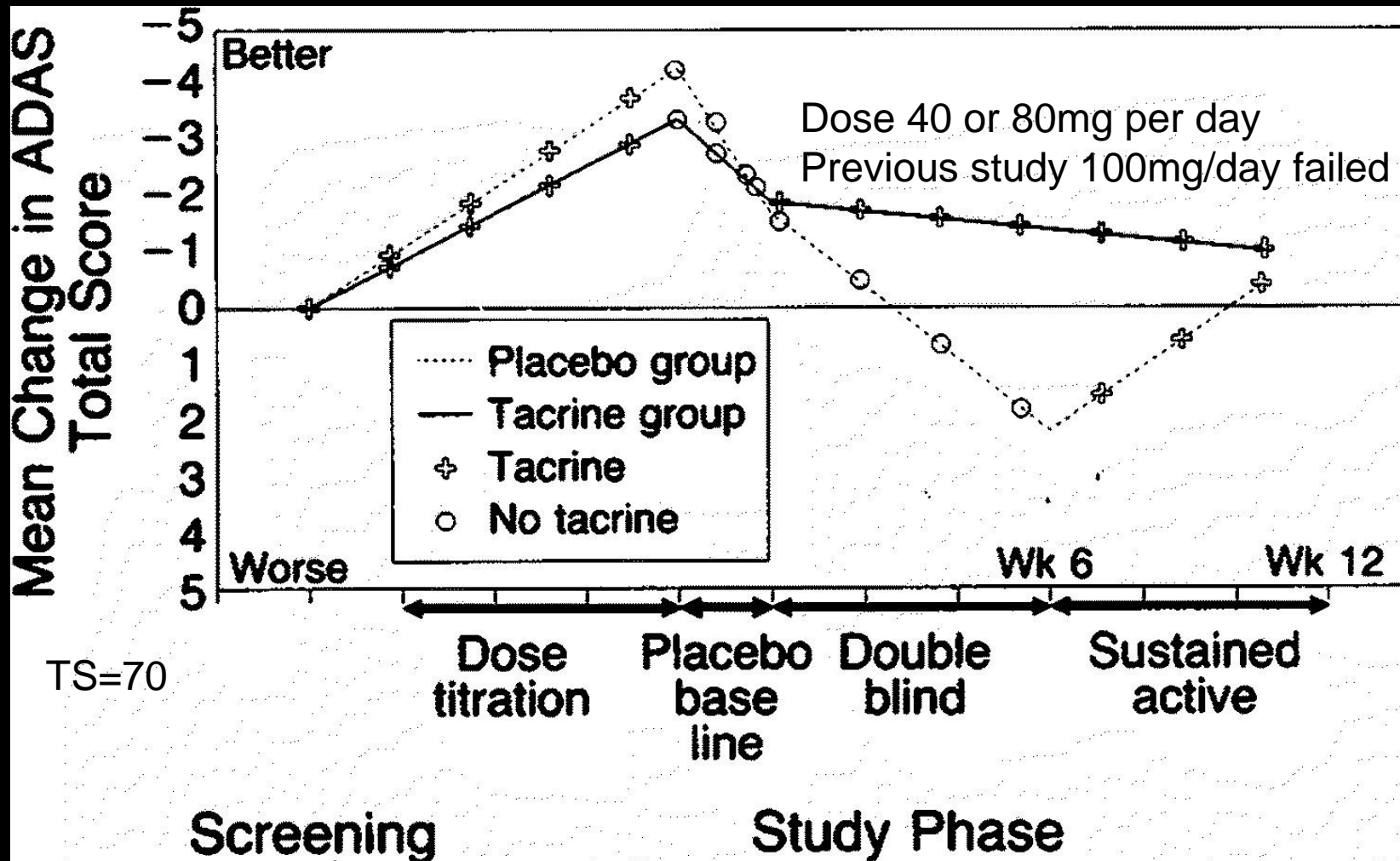
David Bowen



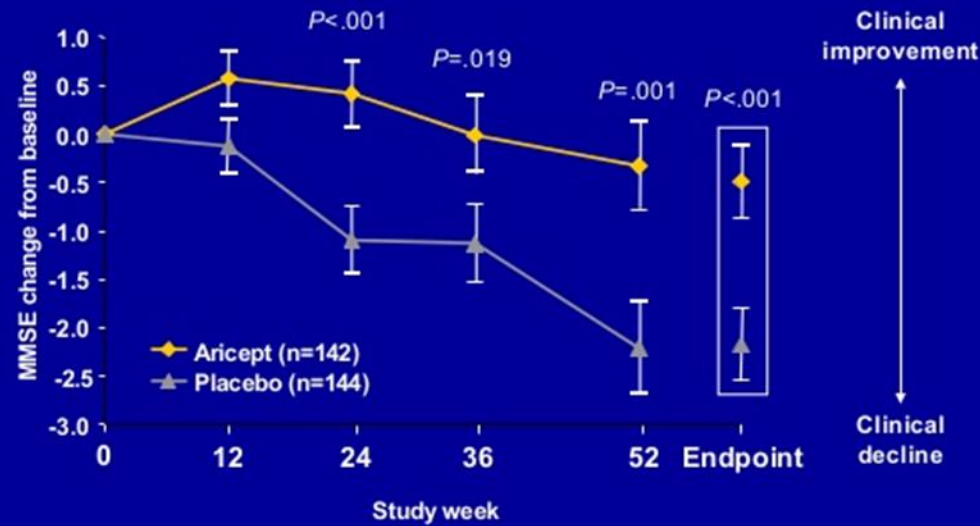
Peter Whitehouse



# Mean Change in ADAS Total Score during the Phases of the Study.

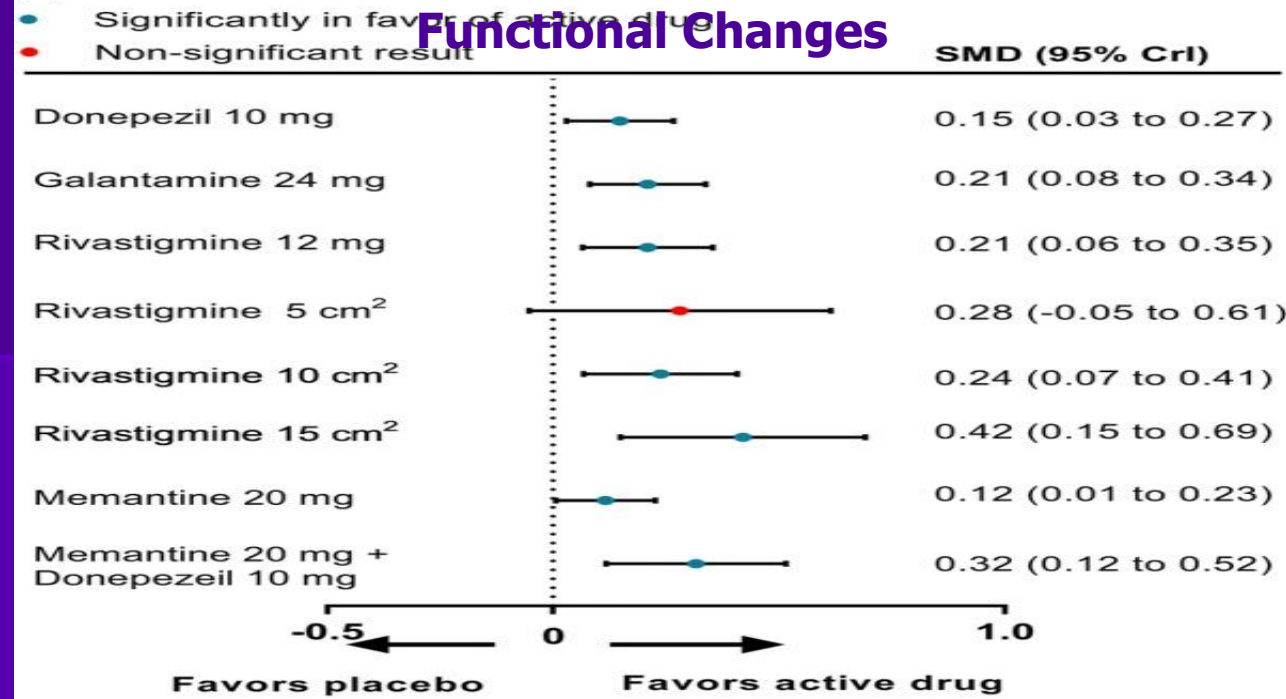


# Cognitive Benefits in Mild to Moderate AD (MMSE: 10-26)

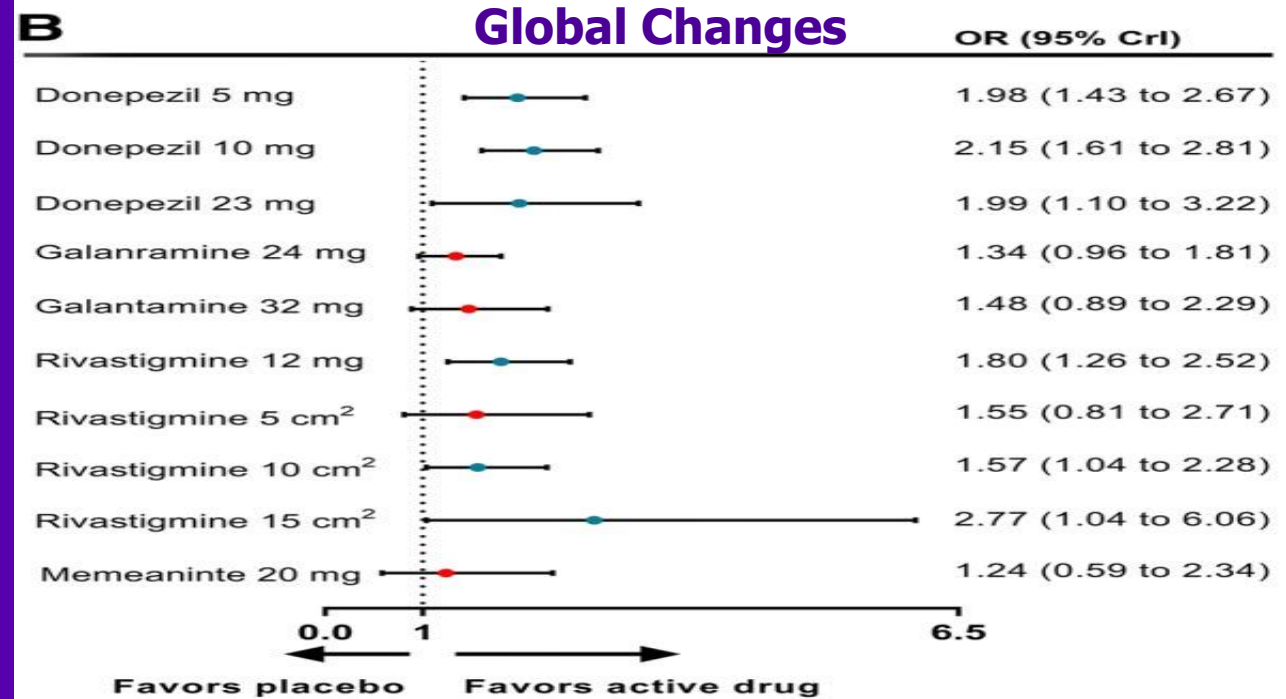


Adapted with permission from Winblad et al. *Neurology*. 2001;57:489-495.  
See Appendix for study description and safety information (Nordic).

**A**



**B**





[BMJ](#). 2005 Aug 6;331(7512):321-7.

**Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials.**

[Kaduszkiewicz H](#)<sup>1</sup>, [Zimmermann T](#), [Beck-Bornholdt HP](#), [van den Bussche H](#).

**Results** 22 trials met the inclusion criteria. Follow-up ranged from six weeks to three years. 12 of 14 studies measuring the cognitive outcome by means of **the 70 point Alzheimer's disease assessment scale**—cognitive subscale showed differences ranging from **1.5 points to 3.9 points in favour of the respective cholinesterase inhibitors**. Benefits were also reported from all 12 trials that used the clinician's interview based impression of change scale with input from caregivers(**0.26-0.54**). Methodological assessment of all studies found considerable flaws—for example, multiple testing without correction for multiplicity or exclusion of patients after randomisation.

Because of flawed methods and small clinical benefits, the scientific basis for **recommendations of cholinesterase inhibitors for the treatment of Alzheimer's disease is questionable.**

[Drugs Aging](#). 2015 Jun;32(6):453-67. doi: 10.1007/s40266-015-0266-9.

**A Risk-Benefit Assessment of Dementia Medications: Systematic Review of the Evidence.**

[Buckley JS](#)<sup>1</sup>, [Salpeter SR](#).

- 257 were included in the systematic review.
- In pooled trial data, cholinesterase inhibitors (ChEIs) produce small improvements in cognitive, functional, and global benefits in patients with mild to moderate Alzheimer's and Lewy body dementia, **but the clinical significance of these effects are unclear.**
- The efficacy of ChEI treatment appears to wane over time, with minimal benefit seen after 1 year.
- There is no evidence for benefit for those with advanced disease or those aged over 85 years.
- Adverse effects are significantly increased with ChEIs, in a dose-dependent manner. A two- to fivefold increased risk for gastrointestinal, neurological, and cardiovascular side effects is related to cholinergic stimulation, **the most serious being weight loss, debility, and syncope.**
- Those aged over 85 years have double the risk of adverse events compared with younger patients.



TABLE 1

**Cognitive enhancers approved for Alzheimer disease**

<b>Drug</b>	<b>Proprietary name (date approved)</b>	<b>Indications</b>	<b>Formulations</b>
<b>Cholinesterase inhibitors</b>			
Donepezil	Aricept (1996), generics available	Mild to moderate disease (5–10 mg), moderate to severe disease (10–23 mg)	Tablets, disintegrating tablets
Rivastigmine	Exelon (2000), generics available	Mild to moderate disease	Tablets, oral solution, transdermal patch
Galantamine	Razadyne (2001), generics available	Mild to moderate disease	Immediate-release tablets, oral solution, extended-release tablets
<b><i>N</i>-methyl-D-aspartate receptor antagonist</b>			
Memantine	Namenda (2003), generics available	Moderate to severe disease	Tablets, oral solution
<b>Combination drug</b>			
Donepezil + memantine	Namzaric (2014), generics available	Moderate to severe disease	Extended-release capsules

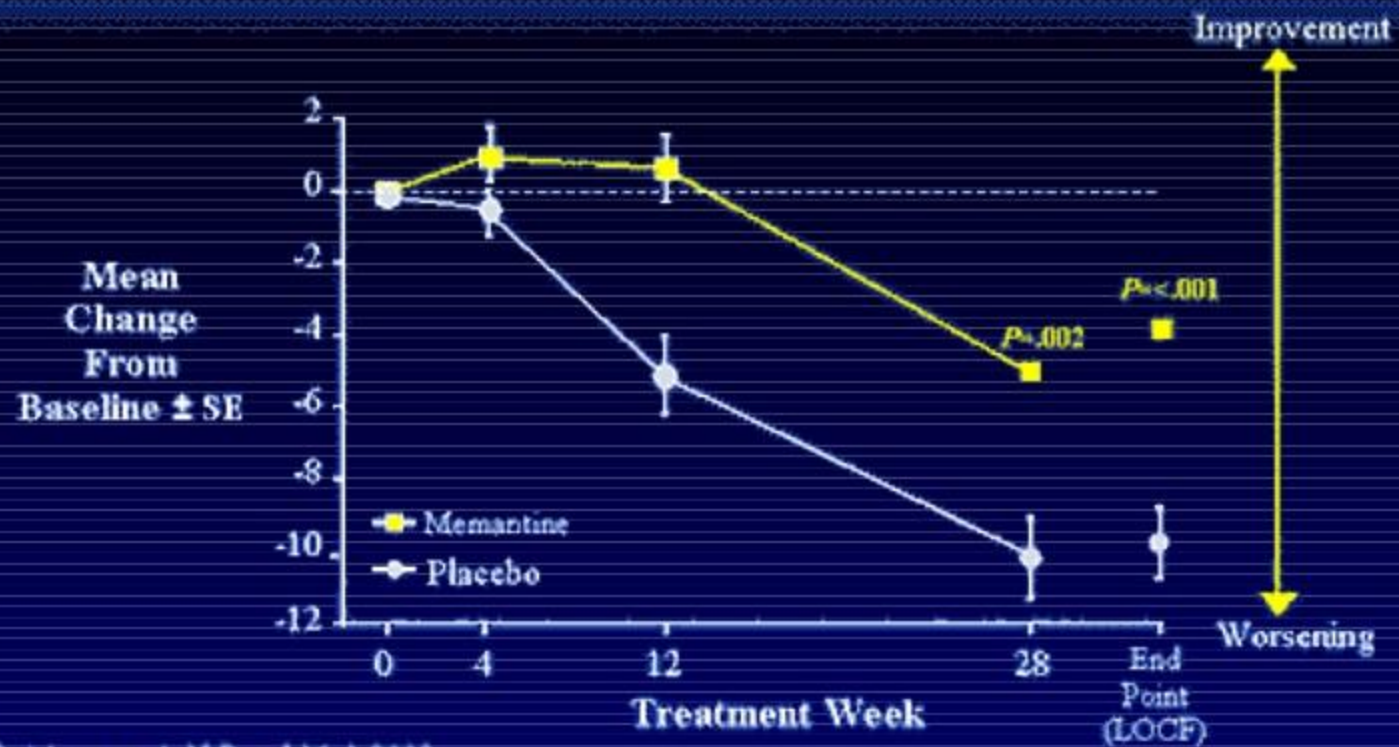
TABLE 3

**Adverse effects of cognitive enhancers: Percent of patients affected**

	Cholinesterase inhibitors			NMDA receptor antagonist	
	Donepezil	Galantamine	Rivastigmine	Rivastigmine transdermal	Memantine
<b>Nausea</b>	3%–19% <sup>a</sup>	21%	17%–47%	2%–4%	Not available
<b>Diarrhea</b>	5%–15% <sup>a</sup>	7%	5%–19%	≤ 7%	5%
<b>Constipation</b>					3%–5%
<b>Anorexia</b>	2%–8%	7% (decreased appetite)	≥ 17% 3%–26% (weight loss)	≤ 3%	< 1% 3% (weight gain) (extended-release formulation)
<b>Vomiting</b>	3%–9% <sup>a</sup>	11%	13%–31%	3%–9%	2%–3%
<b>Insomnia</b>	2%–14%	Not available	1%–9%	Not available	Not available
<b>Headache</b>	3%–10%	7%	4%–17%	≤ 4%	6%
<b>Dizziness</b>	2%–8%	8%	6%–21%	≤ 6%	5%–7%
<b>Fatigue</b>	1%–8%	4%	4%–9%	2%–4%	2%
<b>Syncope</b>	2%	1%	3% (falling) 6%–12%	Not available	Not available
<b>Bradycardia</b>	≥ 1%	1%	< 1%	< 1%	< 1%
<b>Infection</b>	11%	< 1%	1%–10% (urinary tract infections)	Not available	4% (influenza)

<sup>a</sup>Dose-related.NMDA = *N*-methyl-D-aspartate

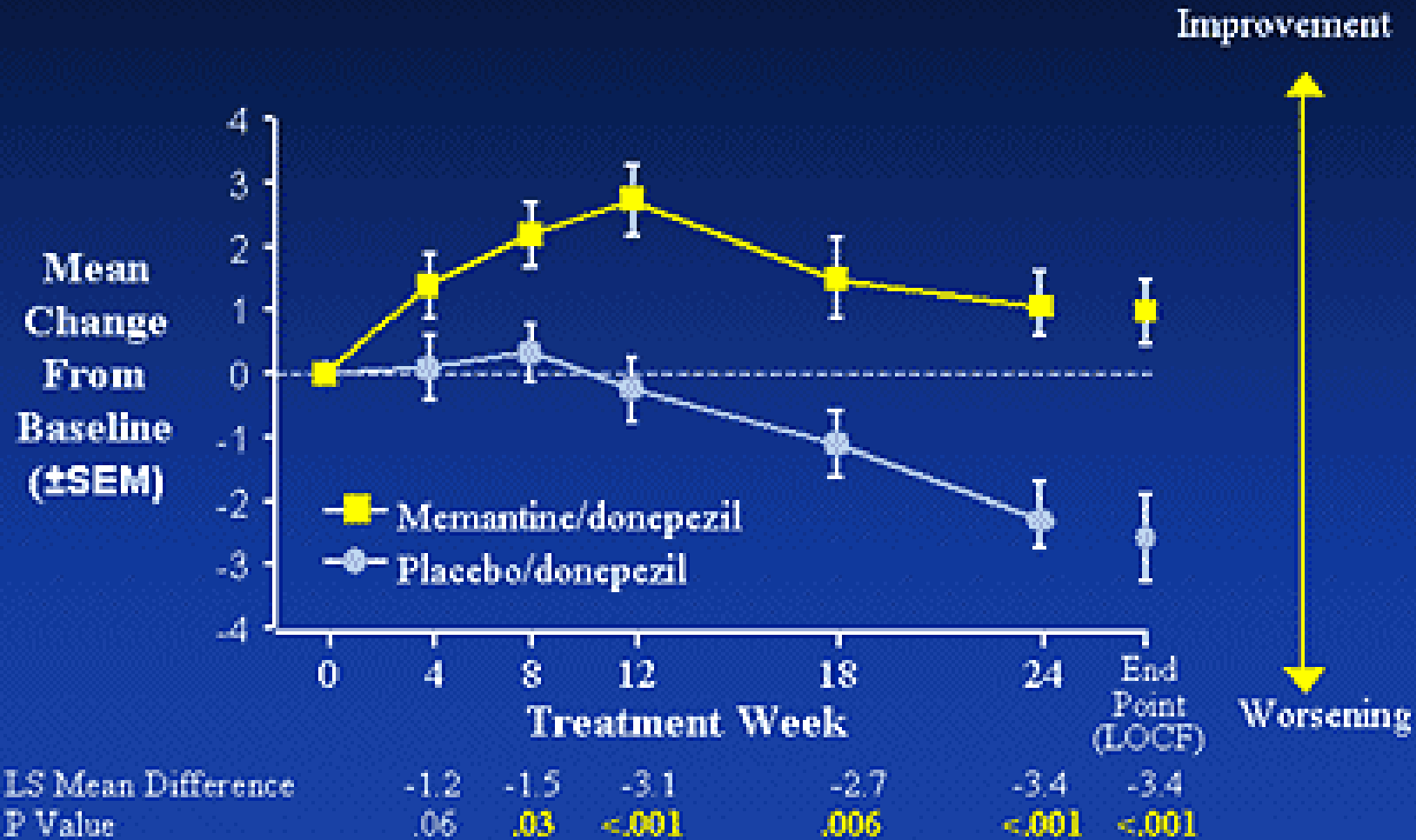
# Memantine in severe AD



Reisberg et al. *N Eng J Med*, 2003.



# Memantine Plus Donepezil in Moderate to Severe AD: Cognitive – SIB



Tariot et al. *JAMA*, 2004.



Common adverse effects	Uncommon adverse effects	Very rare/unknown adverse effects
Drug hypersensitivity	Fungal infections	Seizures (very rare)
Somnolence	Confusion	Psychotic reactions
Dizziness	Hallucinations (mostly people with severe AD)	(unknown—isolated cases reported post-marketing)
Balance disorders	Abnormal gait	Pancreatitis (unknown—isolated cases reported post-marketing)
Hypertension	Cardiac failure	Hepatitis (unknown)
Dyspnoea	Venous thrombosis/ thromboembolism	
Elevated liver function test	Vomiting	
Constipation	Fatigue	
Headache		

Adapted from Summary of Product Characteristics



# Mediterranean Diet associated with reduced risk of Alzheimer's Disease

Journal of Alzheimer's Disease xx (20xx) x–xx  
 DOI 10.3233/JAD-130830  
 IOS Press

## Association of Mediterranean Diet with Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis

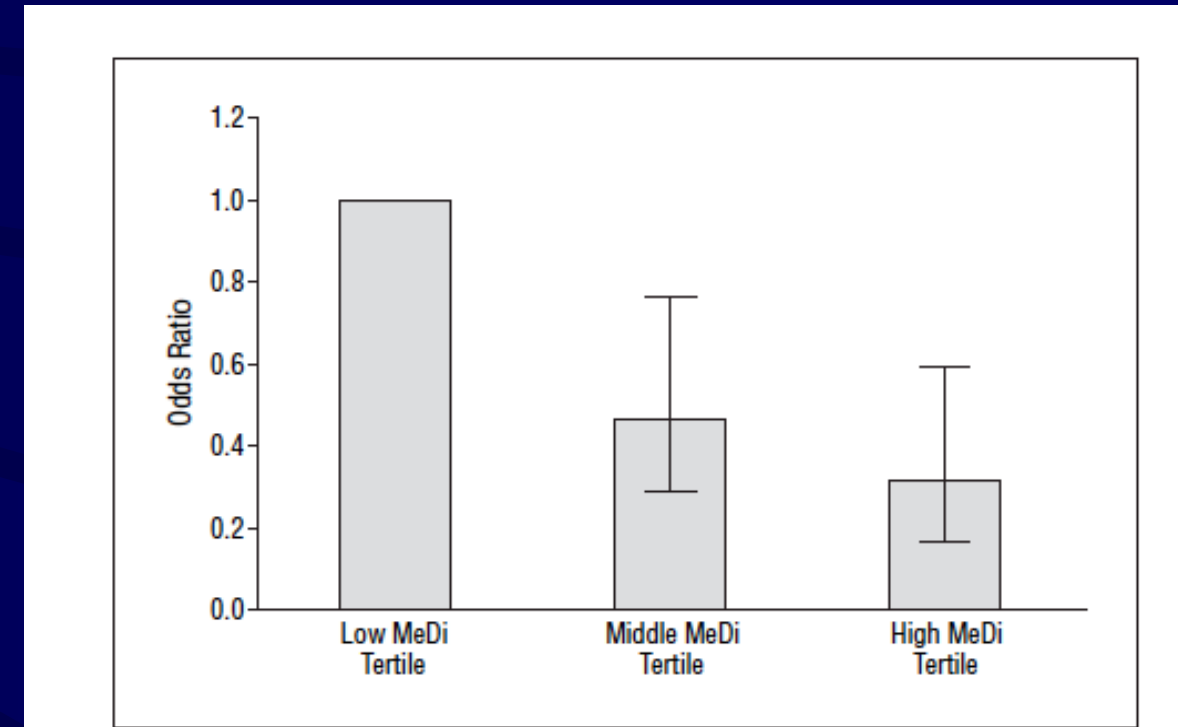
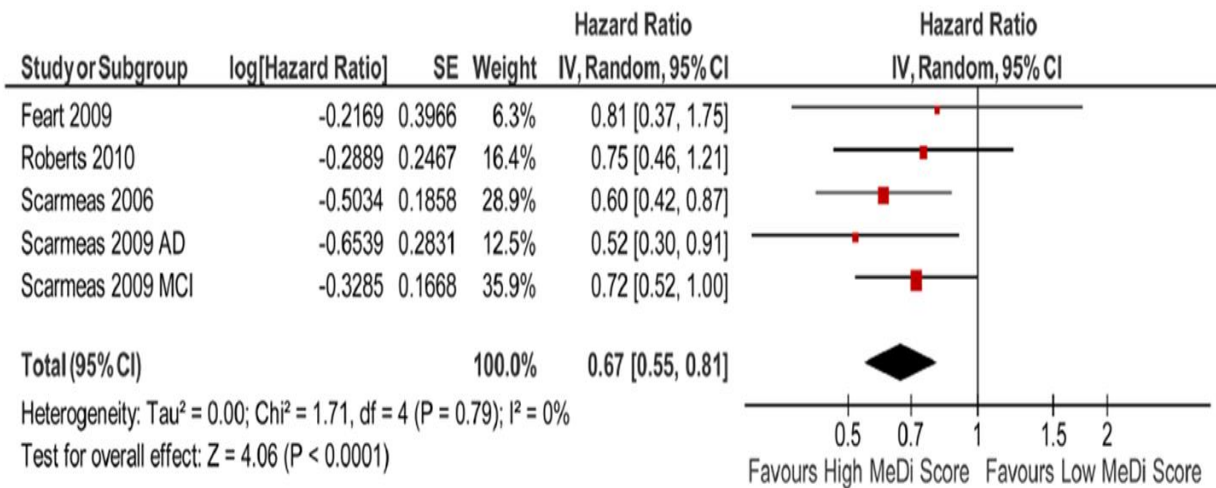
Balwinder Singh<sup>a,d</sup>, Ajay K. Parsaik<sup>a</sup>, Michelle M. Mielke<sup>b</sup>, Patricia J. Erwin<sup>c</sup>, David S. Knopman<sup>a</sup>, Ronald C. Petersen<sup>a,b</sup> and Rosebud O. Roberts<sup>a,b,\*</sup>

<sup>a</sup>Department of Neurology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

<sup>b</sup>Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

<sup>c</sup>Mayo Medical Libraries, Mayo Clinic, Rochester, MN, USA

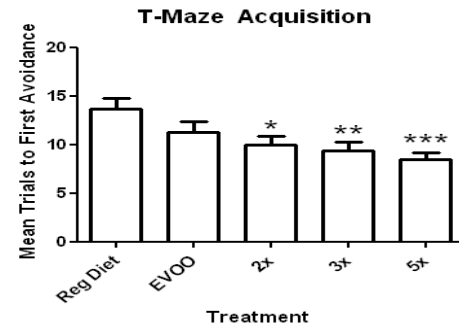
<sup>d</sup>Department of Clinical Neuroscience, University of North Dakota School of Medicine and Health Sciences, Fargo, ND, USA



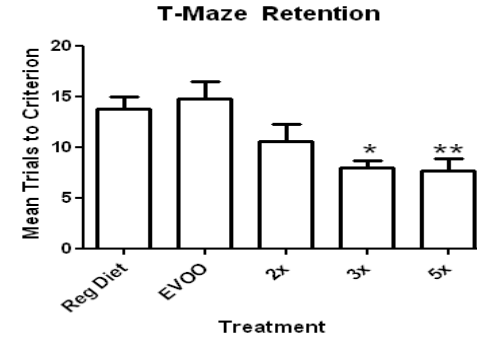


# Extra Virgin Olive Oil Extracts

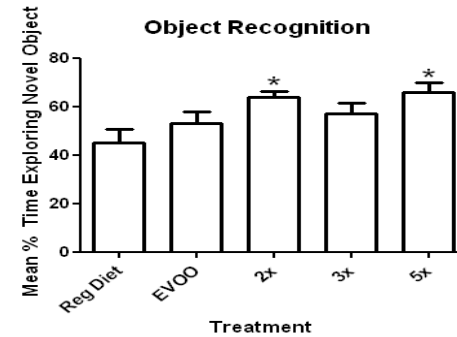
A



B



C



**Polyphenyls block oxidative damage**

## Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial

Elena H Martínez-Lapiscina,<sup>1,2</sup> Pedro Clavero,<sup>3</sup> Estefania Toledo,<sup>1,4</sup> Ramon Estruch,<sup>4,5</sup> Jordi Salas-Salvadó,<sup>4,6</sup> Beatriz San Julián,<sup>1</sup> Ana Sanchez-Tainta,<sup>1</sup> Emilio Ros,<sup>4,7</sup> Cinta Valls-Pedret,<sup>4,7</sup> Miguel Á Martínez-Gonzalez<sup>1</sup>

**Table 4** Multivariable-adjusted means after a 6½-year follow-up and differences versus control (95% CIs) in each intervention group

	MedDiet+EVOO (n=224)		MedDiet+Nuts (n=166)		Control (low-fat diet) (n=132)
	Mean (95% CI)	p Value (vs control)	Mean (95% CI)	p Value (vs control)	Mean (95% CI)
MMSE	27.73 (27.27 to 28.19)		27.68 (27.20 to 28.16)		27.11 (26.61 to 27.61)
Adjusted diff. versus control (95% CI)	+0.62 (+0.18 to +1.05)	0.005	+0.57 (+0.11 to +1.03)	0.015	0 (reference)
CDT	5.31 (4.98–5.64)		5.13 (4.78–5.47)		4.80 (4.44–5.16)
Adjusted diff. versus control (95% CI)	+0.51 (+0.20 to +0.82)	0.001	+0.33 (+0.003 to +0.67)	0.048	0 (reference)

# Exercise and the Brain

- Aerobic exercise for 6 months decreased brain atrophy.....

*al*

*61:1166*

Increased cognition

Decreased dysphoria

**LIFE Study suggests need  
For HIGH DOSE exercise**

*Colcombe et*

*et al JAMA 2006;*



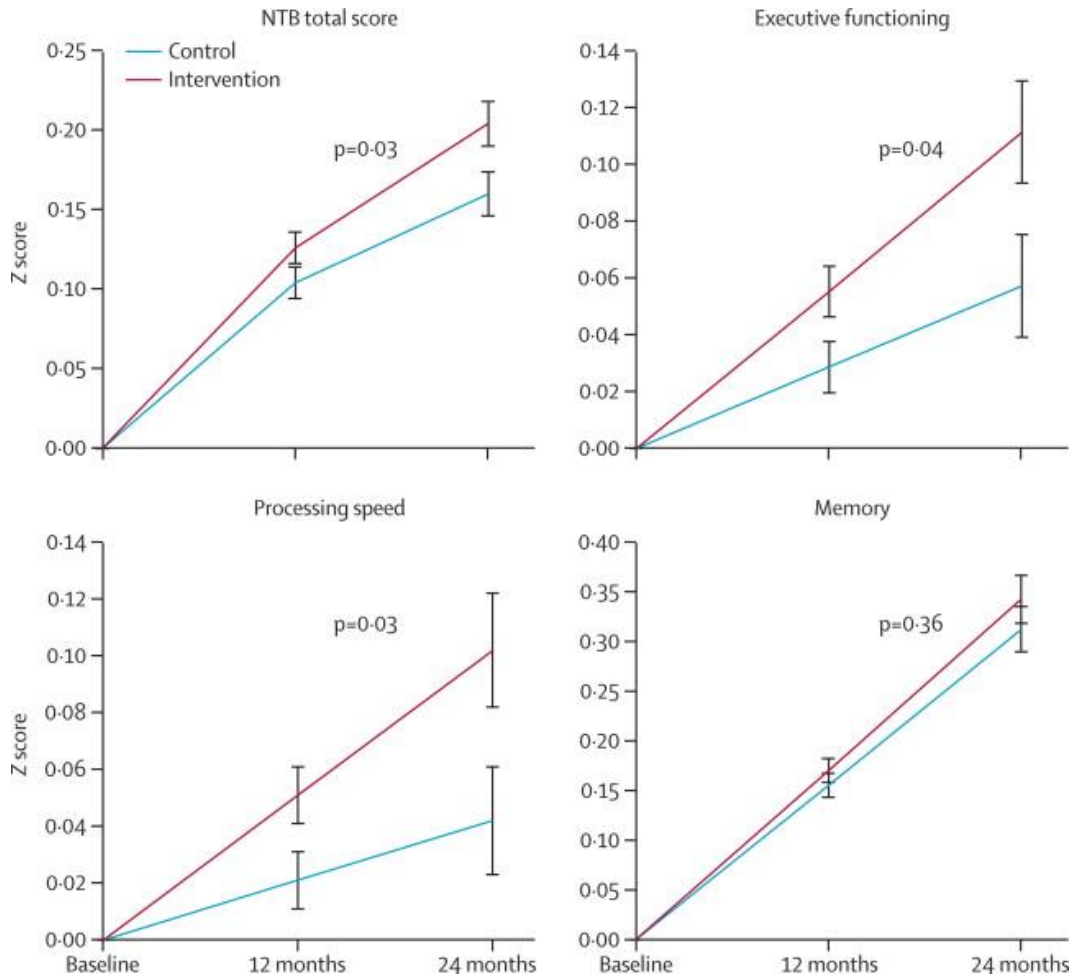


# FINGER STUDY

Aged 60-77 years recruited from previous national surveys.

A 2 year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice).

1260 to the intervention group (n=631) or control group (n=629).



**A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial**

Tiia Ngandu , Jenni Lehtisalo , Alina Solomon , Esko Levälähti , Satu Ahtiluoto , Riitta Antikainen , Lars Bäckma...





Improves  Cognition



# Reminiscence Therapy\*

- Discussion about the past, often using prompts (e.g. pictures, objects, music) with groups or individuals (e.g. life review books).
- Focuses on long-term memory, the last to deteriorate in dementia.
- Extremely popular - helps to avoid failure experiences, aids communication.
- Cochrane review\*\* showed marginal improvements in cognition and mood.
- [Football reminiscence for men with dementia: lessons from a realistic evaluation.](#) Tolson D, Schofield I. *Nurs Inq.* 2012 Mar;19(1):63-70

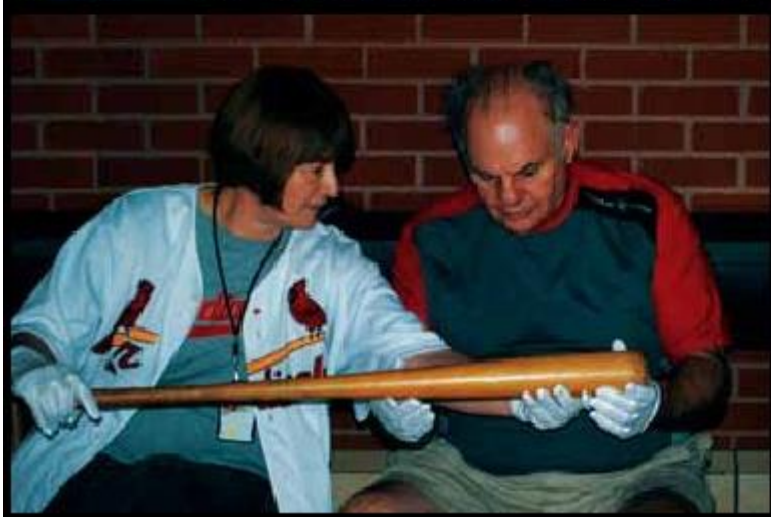


\*Butler RN & Lewis MI (1977). *Aging and Mental health: Positive psychosocial approaches*. Saint Louis: CV Mosby Company.

\*\*Woods, B., Spector, A. E., Jones, C. A., Orrell, M., & Davies, S. P. (2005). Reminiscence therapy for dementia. *The Cochrane Library*.



# Cardinals Reminiscence League



## GEC Introduces Reminiscence Leagues to St. Louis



CARDINALS  
REMINISCENCE  
LEAGUE

2011: CRL group begins at  
Jefferson Barracks VAMC

2014: CRL group begins at St. Louis Alzheimer's Association

2014: In partnership with GEC, St. Louis Alzheimer's Association develops CRL Tool Kit

2017: 5 CRL groups active in the St. Louis area



# Evidence

- Improved cognition, mood, behavior
- Reduction of caregiver strain
- Improved staff/member relationships
- Social nature of the groups may be an important factor in promoting the above benefits

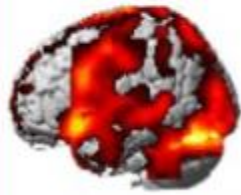
Baseball reminiscence league: a model for supporting persons with dementia. Wingbermuehle C, Bryer D, Berg-Weger M, Tumosa N, McGillick J, Rodriguez C, Gill D, Wilson N, Leonard K, **Tolson D.** J Am Med Dir Assoc. 2014 Feb;15(2):85-9.



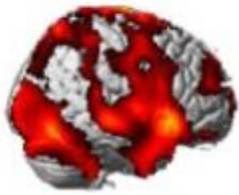


The tasks must

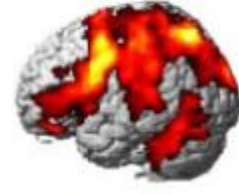
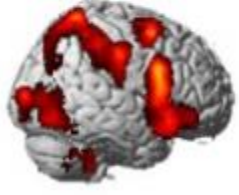
1. activate bilateral PFC
2. be simple and easy



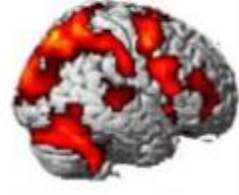
Reading aloud



Hand writing



Simple arithmetic



# SAIDO

J Am med Dir Assoc 2015;16:56

SAIDO  
Learning™

**INCREASED MMSE**

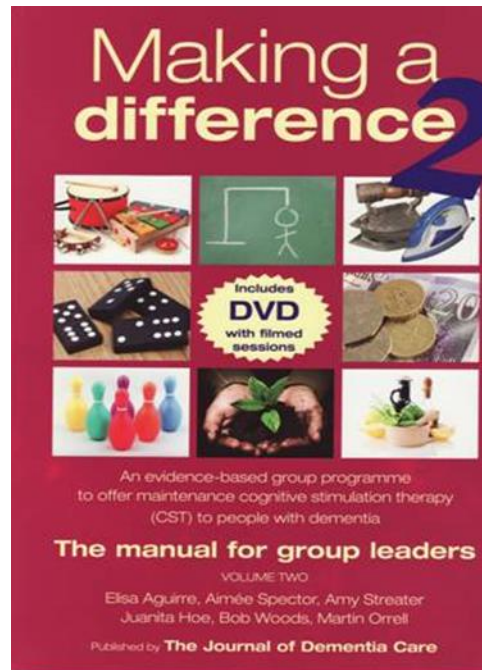




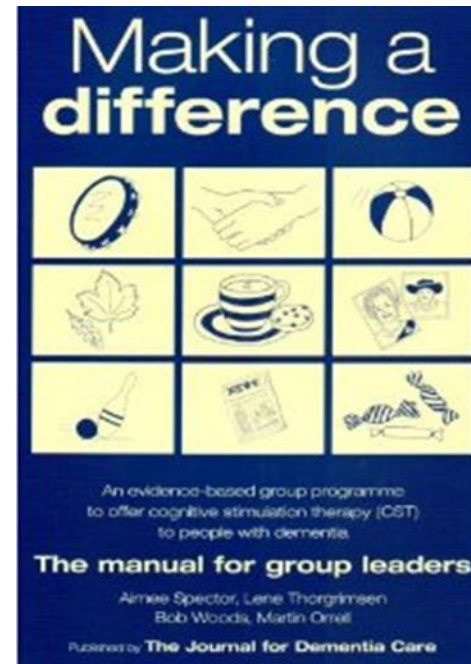
# Cognitive Stimulation Therapy

- Tacrine and psychological therapies in dementia: No contest?
- (Orrell & Woods, 1996, *British Journal of Psychiatry*)

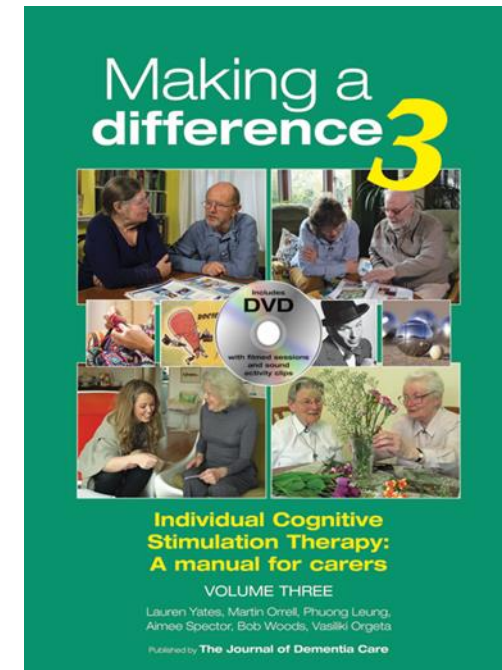
Special Thanks to:



2011



2006

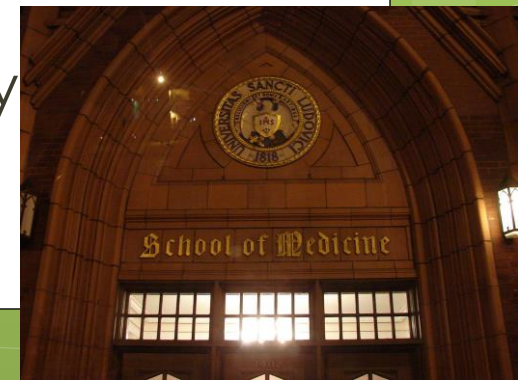


2014

# History of CST




- Created largely by Aimee Spector, Martin Orrell, and Bob Woods:
  - [www.cstdementia.com](http://www.cstdementia.com)
- Began with a review of literature on non-pharmacological therapies for mild to moderate dementia
- Grounded in reality orientation, the founders combined the most effective elements of the different therapies to create CST
- North American Training Center for CST at St Louis University



# Evidence to Support CST Effectiveness

- 2003 Pilot Study (Spector et al., 2003)
  - Analysis suggested that for improvements in cognition, CST is equally effective as several dementia drugs.
  - CST led to significant improvements in quality of life, as rated by the participants themselves using the QoL-AD. There were no reported side-effects of CST.
- 23-center RCTs (residential homes and day centers) (Spector et al., 2003)
  - CST led to significant benefits in people's cognitive functioning and language skills including naming, word-finding and comprehension.
- Qualitative work (Spector et al., 2011)
  - Participants experience greater sense of accomplishment, support, active engagement, and improvement in memory, concentration, and alertness

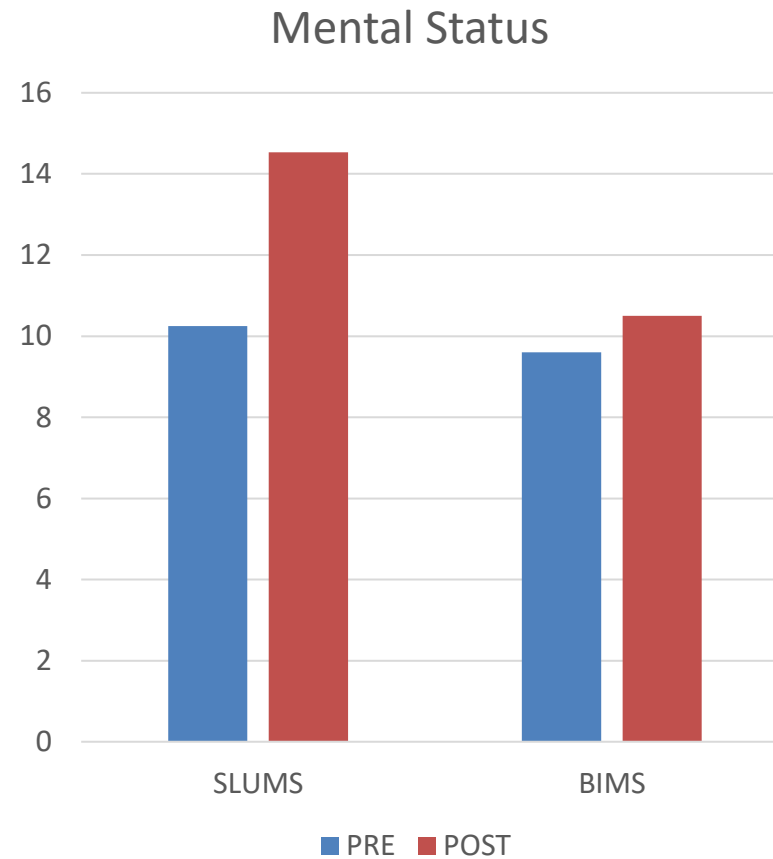




CST is endorsed as the only non-pharmacological interventions for cognitive symptoms and maintaining function by the **UK Government National Institute for Health and Care Excellence (NICE)**, regardless of drug regiment.



# Cognitive Stimulation Therapy : NHC Nursing Home



# Perry County Mean Pre & Post Scores by Test

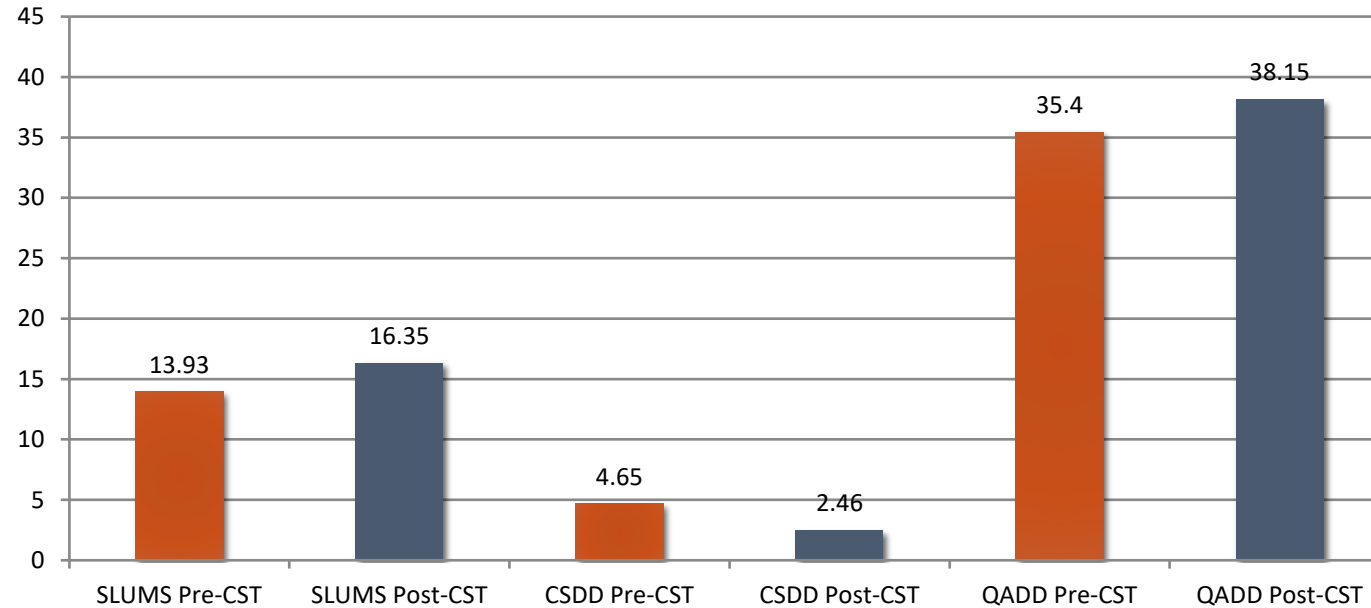
## SLUMS

Validated for  
MCI and  
dementia,  
Free and fairly  
quick to  
perform

VAMC  
SLUMS Examination  
Department of Veterans Affairs  
ST. LOUIS UNIVERSITY

1. What day of the week is it?  
2. What is the year?  
3. What time are we in?  
4. Please remember these five objects. I will ask you what they are later.  
5. You have \$100 and you go to the store and buy a dozen apples for \$3 and a pencil for \$20.  
6. Place wax on every animal on the car in one minute.  
7. What were the five objects I asked you to remember? 1 point for each one correct.  
8. I am going to give you a series of numbers and I would like you to give them in one backward.  
9. This is a clock face. Please put in the hour markers and the time at one minute to eleven o'clock.  
10. Please place an X in the triangle.  
11. I am going to tell you a story. Please listen carefully because afterwards, I'm going to ask you some questions about it.

Score Key:  
Mean Score: Excellent (25-30), Normal (20-24), Mild Deterioration (15-19), Moderate Deterioration (10-14), Severe Deterioration (5-9), Very Severe Deterioration (0-4)



## Sample Characteristics (N=164)

Variables	CST Participants
Gender	71.3% Female
Age	78.55±10.01
Race	14.9% Non-White
Education	95.1% High School Graduate & Above
Living Arrangement	61% Community Dwelling
Pre-CST SLUMS	13.93

## Paired Sample T-Test

	Mean	Std Dev	SE Mean	t value	Df	Sig (two-tailed)
SLUMS	2.061	3.716	.307	6.725	146	.000
Cornell Scale for Depression	-1.921	3.847	.318	-6.034	145	.000
Quality of Life – Alzheimer's Disease	2.545	4.658	.387	6.579	144	.000



# Examples of Participant Improvement in Clock Drawing Test

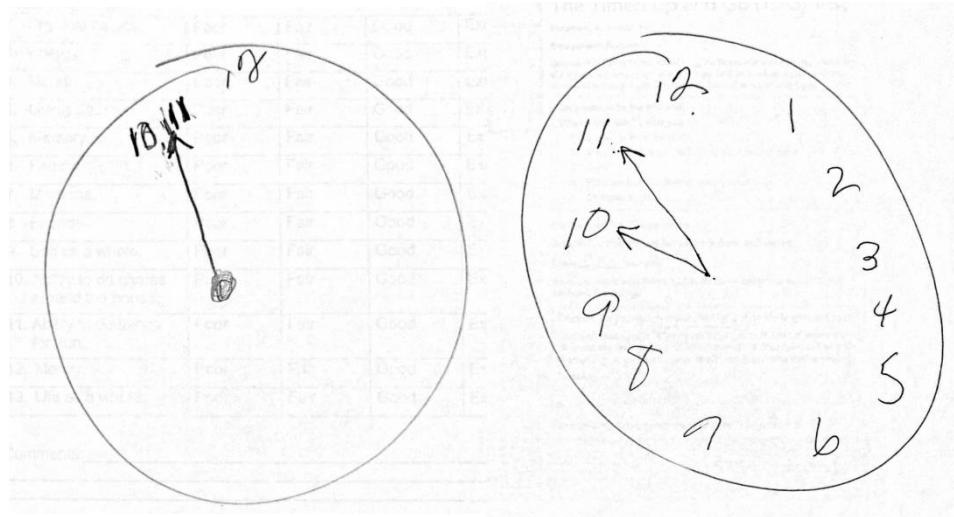


Fig. 1. Resident A Clock Drawing Test Pre- and Post-CST Results

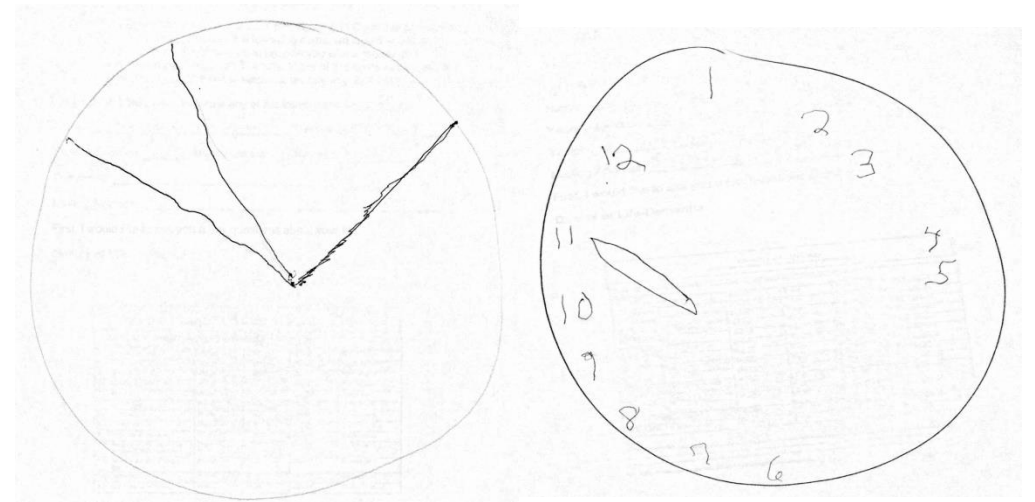
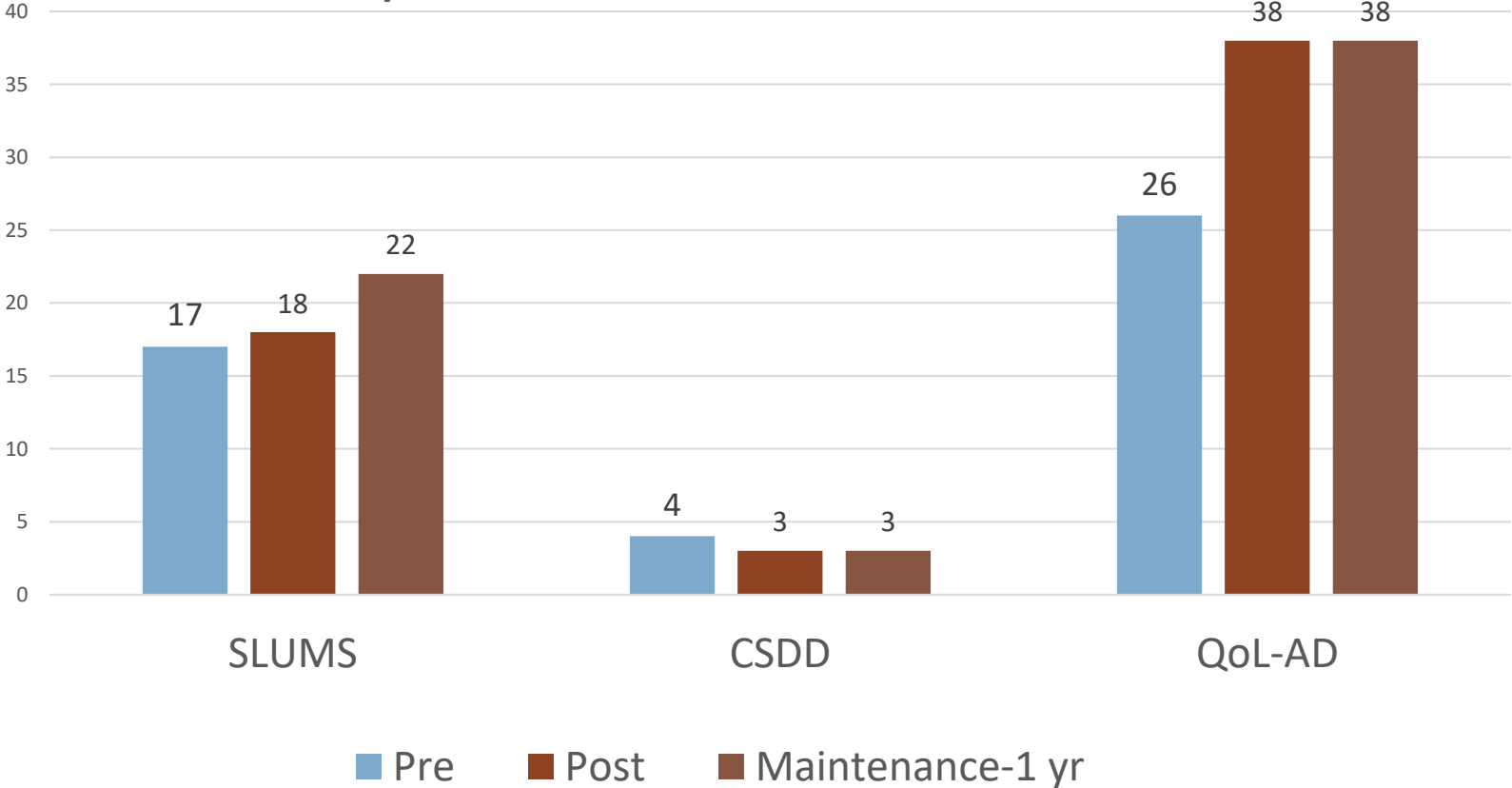


Fig. 2. Resident B Clock Drawing Test Pre- and Post-CST Results

# Maintenance Cognitive Stimulation Therapy (MCST)

Combined scores from A.T. Still University / Perry County Memorial Hospital  
Comparison of Means at 7wks & 12m



SLUMS (out of 30)---CSDD (> 12depression) ---QoL-AD (out of 52)

# Combining Physical Exercise with CST

---



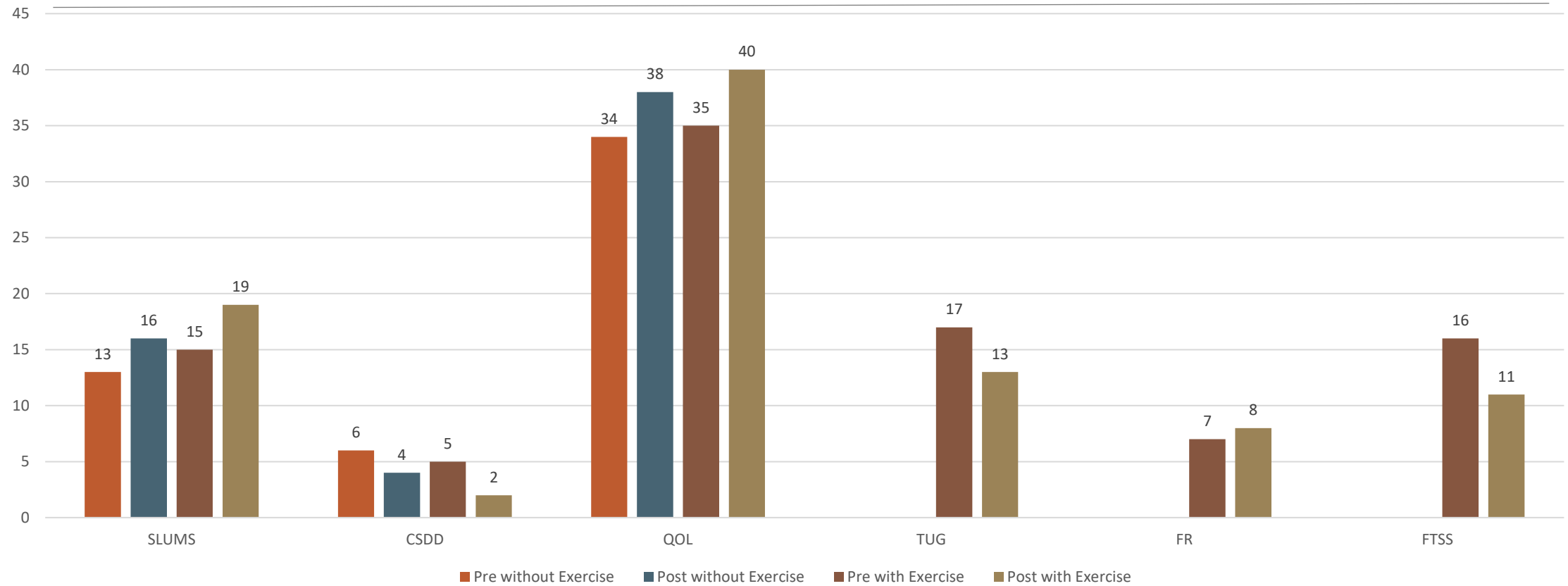


# CST Dementia: SLUMS 1-20

## Without Exercise n=34

### VS

## With Exercise n=21

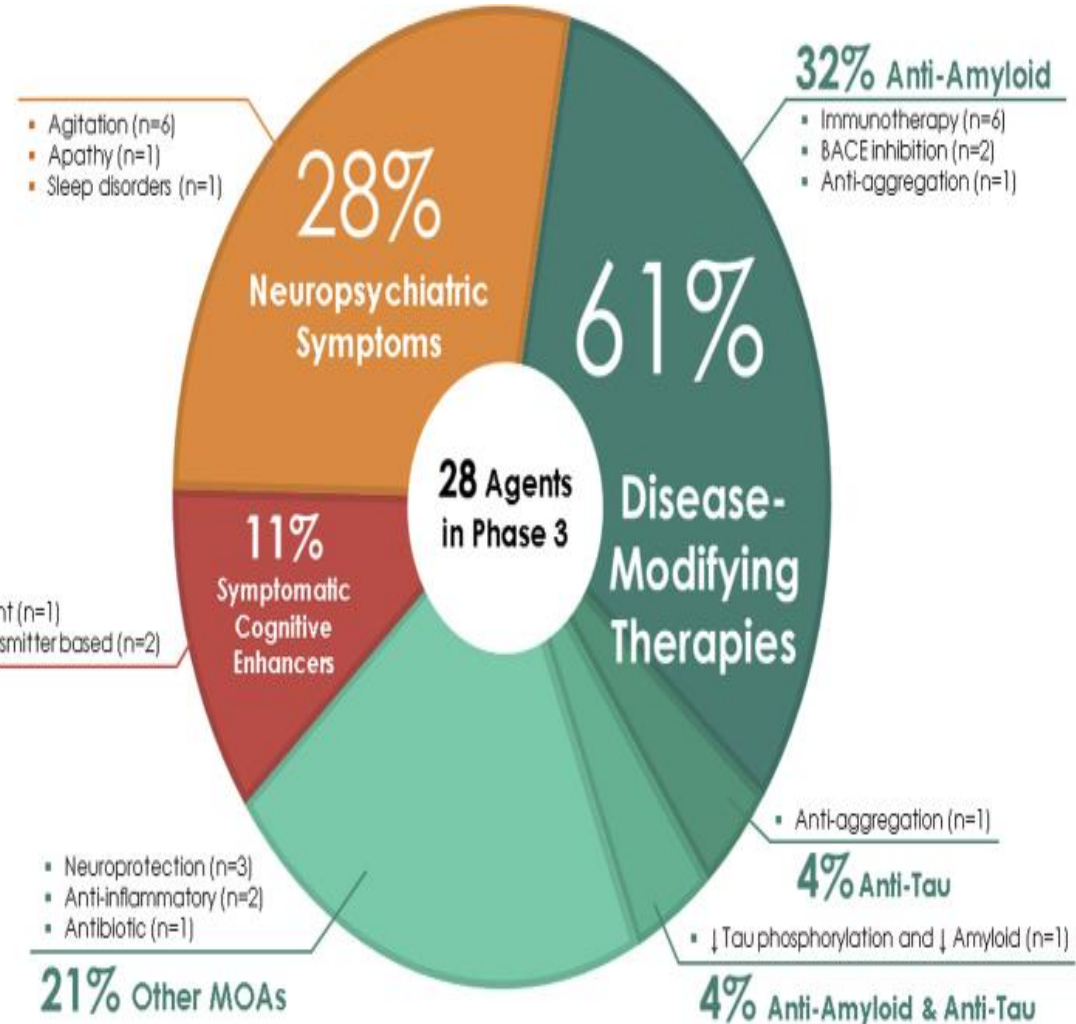
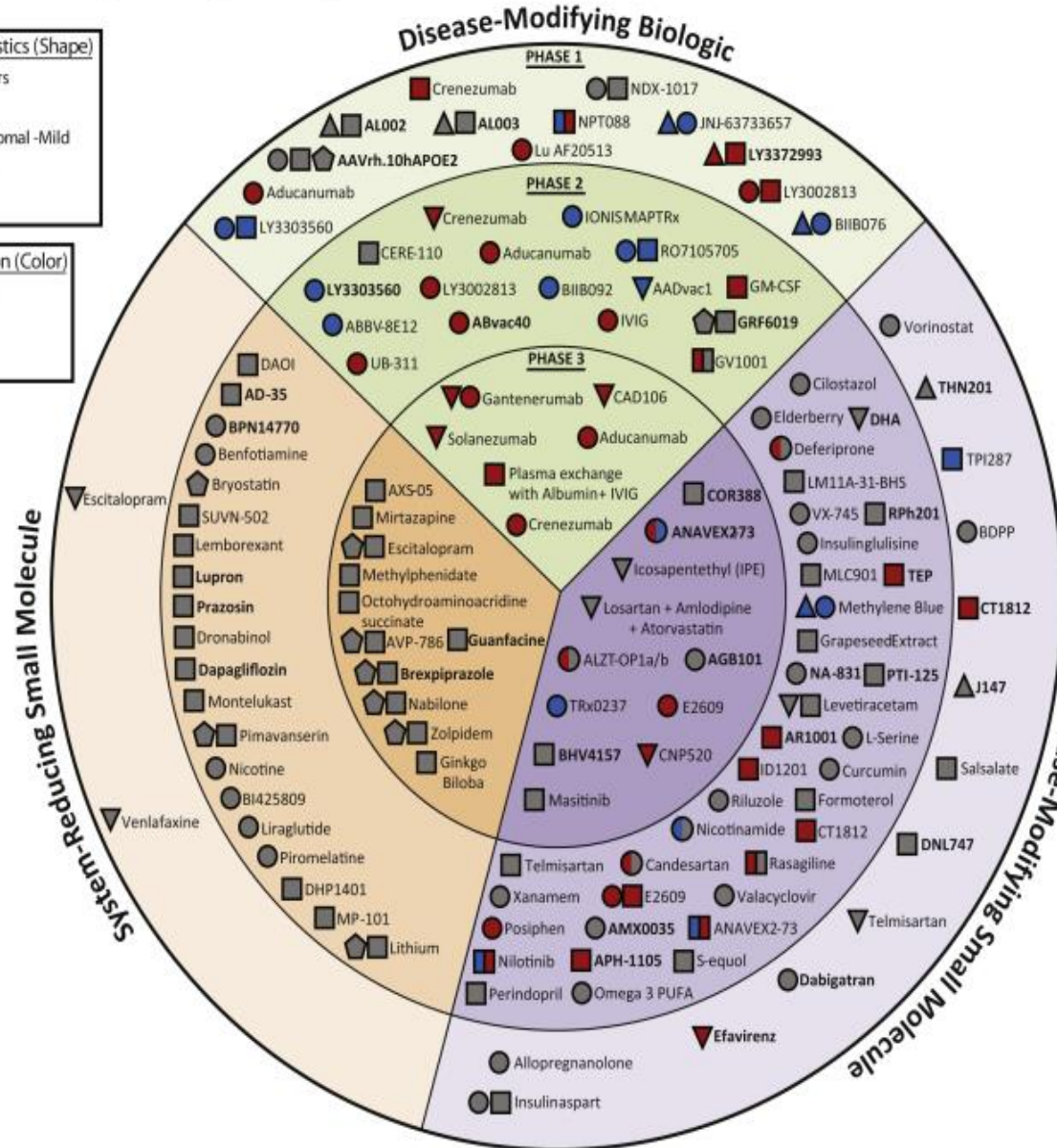


SLUMS: <20 dementia  
 CCSD: A score >12 depression  
 QoL-AD: maximum of 52

Measures high risk for falling, disability, and morbidity in older adults:  
 Timed Up & Go: ≥12 seconds  
 Functional Reach: 6 inches or less  
 Five Times Sit to Stand: > 13.6 seconds

## 2019 Alzheimer's Drug Development Pipeline

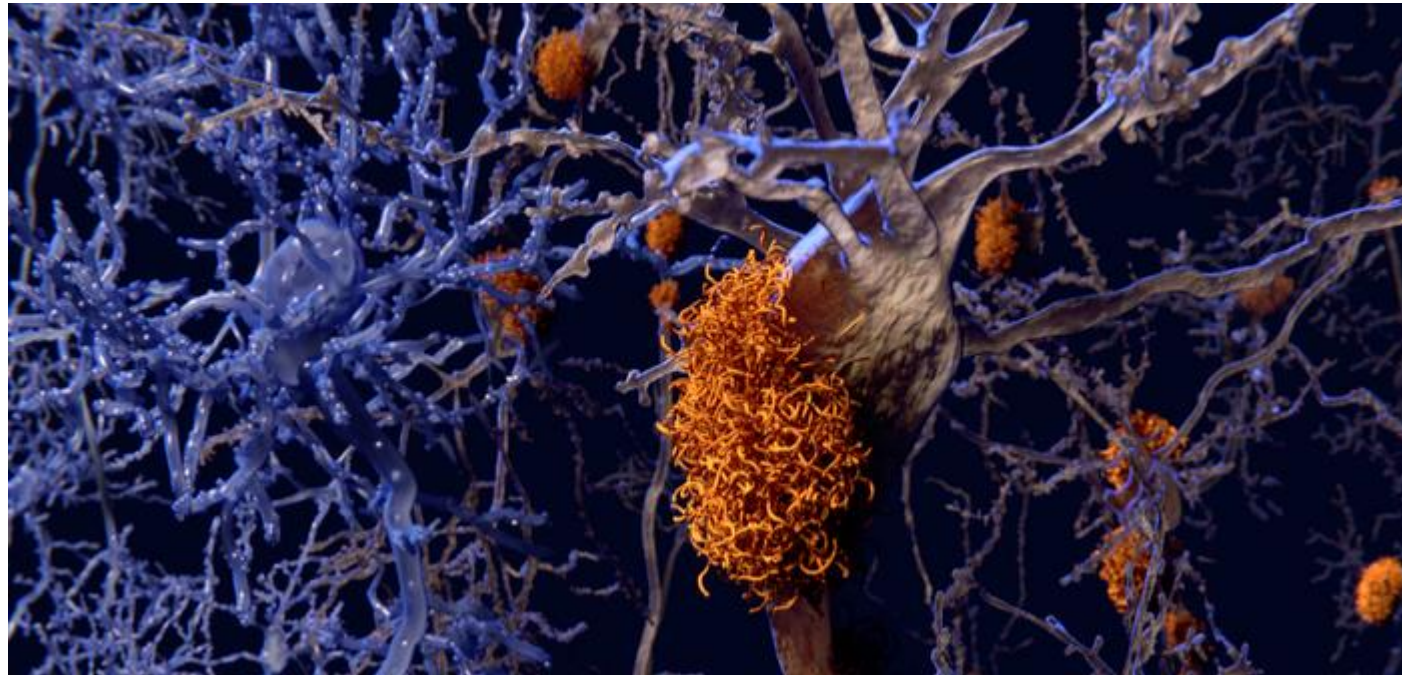
# Bryostatin : A Protein Kinase Epsilon Activator



# Oligomannate

---

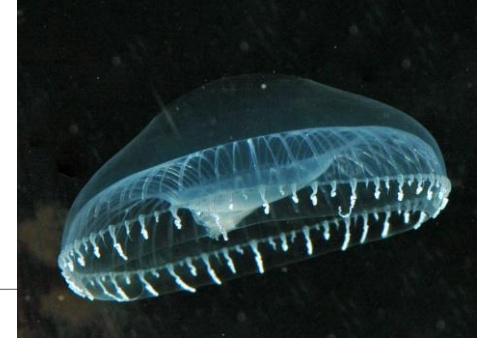
- China approves seaweed-based Alzheimer's drug.
- It's the first new one in 17 years







# PREVAGEN



- Apoaequorin is an ingredient in "Prevagen", which is marketed by Quincy Bioscience as a memory supplement.
- The US [Federal Trade Commission](#) (FTC) charged the maker with [falsely advertising](#) that the product improves memory, provides cognitive benefits, and is "clinically shown" to work.
- According to the FTC, "the marketers of Prevacen preyed on the fears of older consumers experiencing [age-related memory loss](#)".
- Prior to the suit, a clinical trial run by researchers employed by Quincy Bioscience "found no overall benefit compared to a placebo for its primary endpoints involving memory and cognition",





# DEMENTIA TREATMENT

- **Mediterranean/MIND Diet + Olive Oil**
  - **Exercise**
  - **Behavioral Therapy / Keep Mind Active**
  - **Drugs**
  - **?Update vaccinations**
- 