Dementia Pharmacotherapy

AUGUST 27, 2021, PRESENTATION BY IAN NEEL, MD

Alzheimer's Project Clinical Roundtable

LIVE WELL SAN DIEGO

Disclosures

- 2019 – Served on the Biogen Alzheimer’s Disease Advisory Board

Introduction

Major Neurocognitive Disorder as per DSM-V:

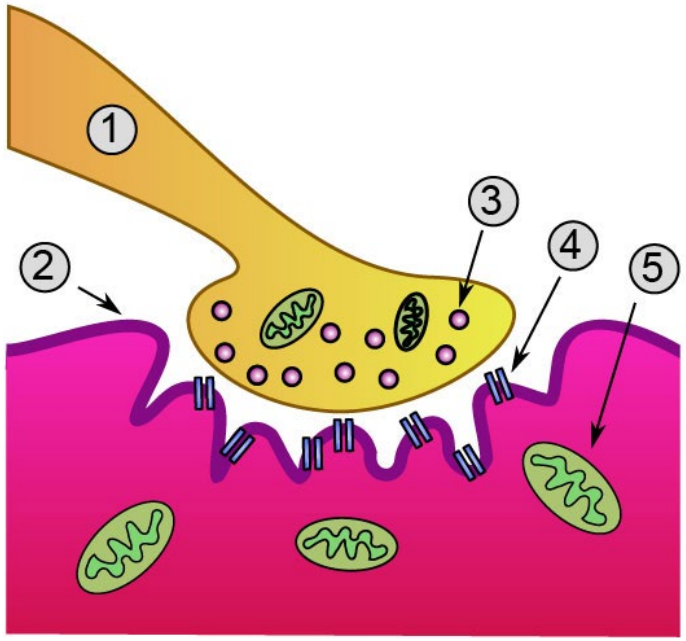
- Cognitive deficits in an area of cognition (memory, apraxia, aphasia, agnosia, or executive function)
- Cognitive defects must impair social or occupational functioning
- Gradual onset and progressive cognitive decline
- Not due to other CNS cause of dementia, substance abuse, or systemic conditions that can cause dementia
- Not due to delirium
- Not accounted for by another Axis 1 disorder

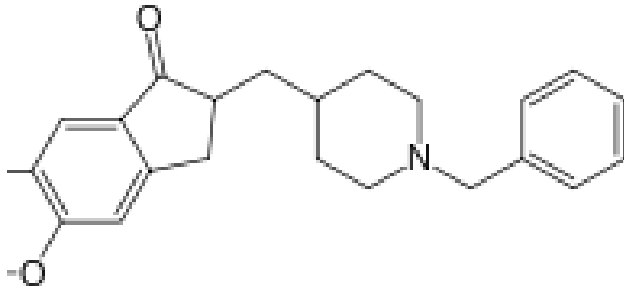
Introduction

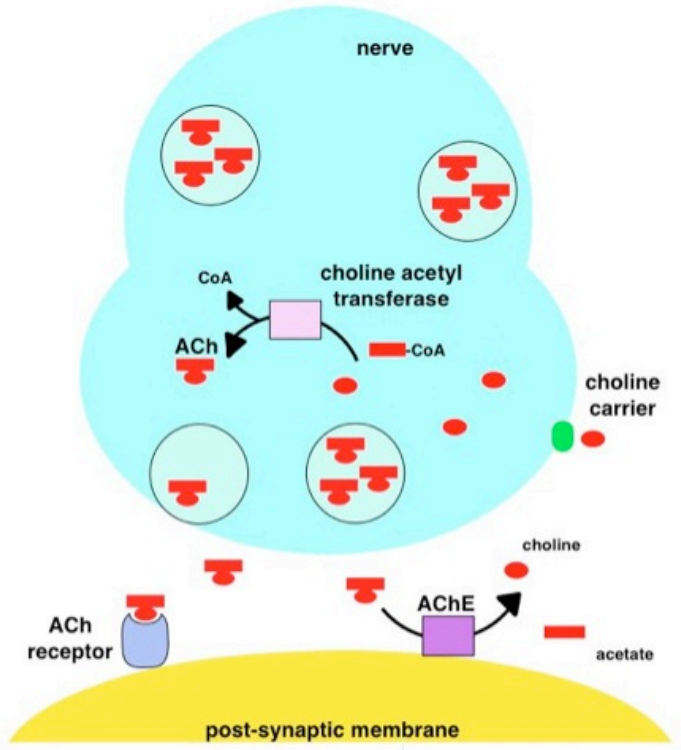
Alzheimer's disease:

- One subtype of the a major neurocognitive disorder. The diagnosis of major neurocognitive disorder, probable Alzheimer's disease requires the following:
- All three of the following:
  - Evidence of decline in memory and learning and at least one other cognitive domain
  - Slow, progressive decline
  - No evidence of mixed etiology
- Or, evidence of a causative Alzheimer's disease genetic mutation from family history of genetic testing

Acetylcholinesterase inhibitors







AD 2000 Trial

	Donepezil (n=283)	Placebo (n=283)
Characteristic		
Dementia severity		
Mild (MMSE 19–26)	143 (51%)	148 (52%)
Moderate (10–18)	140 (49%)	135 (48%)
Men	118 (42%)	113 (40%)
Age, years (median [range])	76 (54–93)	75 (46–90)
Age-group		
<60	8 (3%)	10 (4%)
60–69	45 (16%)	49 (17%)
70–79	163 (58%)	155 (55%)
⩾80	67 (24%)	69 (24%)
Vascular dementia present	51 (18%)	42 (15%)
Parkinsonism present	11 (4%)	11 (4%)
Psychotic symptoms present	25 (9%)	29 (10%)
Comorbidity present	149 (53%)	138 (49%)
MMSE score (median [range])	19 (10–27)*	19 (10–26)
BADLS score (median [range])	13 (0–42)	15 (0–38)
NPI score (median [range])	15 (0–84)	15 (0–74)
GHQ-30 score (median [range])	4 (0–27)	4·5 (0–29)
Number of APOE ε4 alleles		
0	76 (34%)	74 (33%)
1	109 (49%)	116 (51%)
2	36 (16%)	37 (16%)
Unknown	62	56

Data are number of patients (%) unless otherwise indicated. *One patient was randomised on paper and later found to have an MMSE score of 27.

Table 1: **Patients' characteristics at entry to trial**

Primary Endpoints

- Entry into institutional care
- Progression of disability (loss of 2/4 ADLs or 6/11 iADLs)

Secondary Outcomes

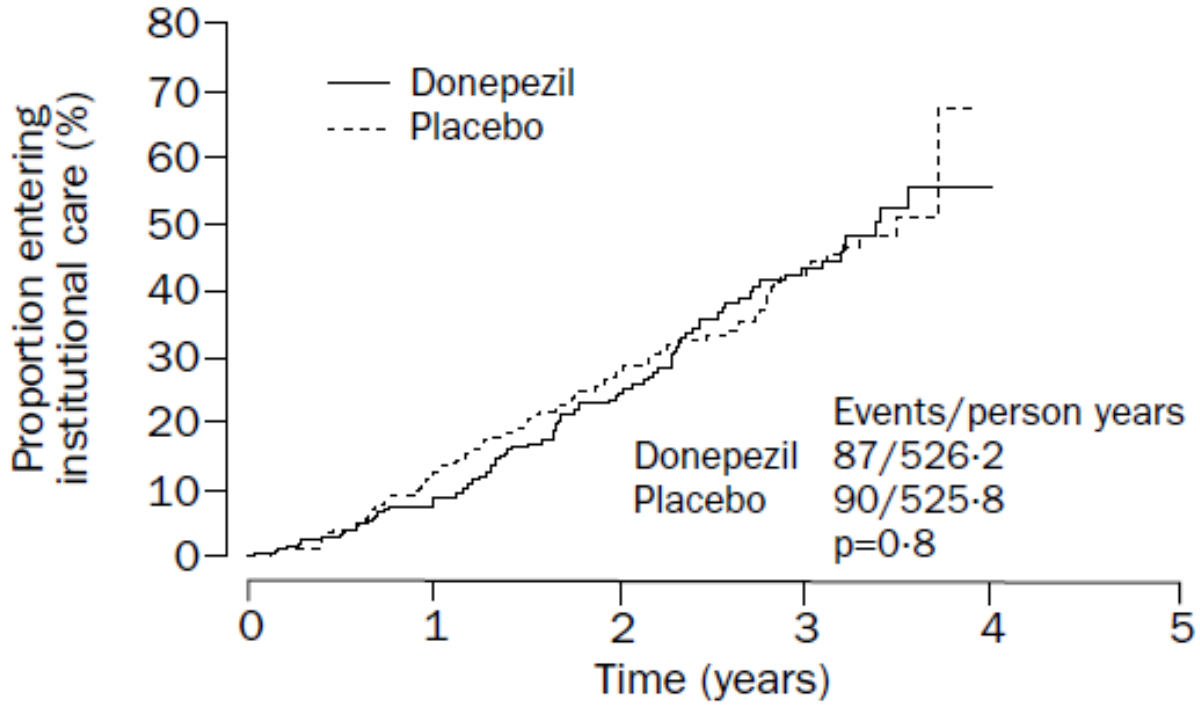
- Functional ability (BADLS)
- Presence and severity of behavioral and psychological symptoms (NPI)
- Cognition (MMSE)
- Psychological wellbeing of the caregiver (GHQ-30)
- Death from AD
- Safety
- Compliance

- **No significant difference**

9% vs 14% at 1 year, p=0.15

- RR of institutionalization for Donepezil vs. placebo was **not statistically significant at** 0.97

95% CI 0.72-1.30, p=0.8

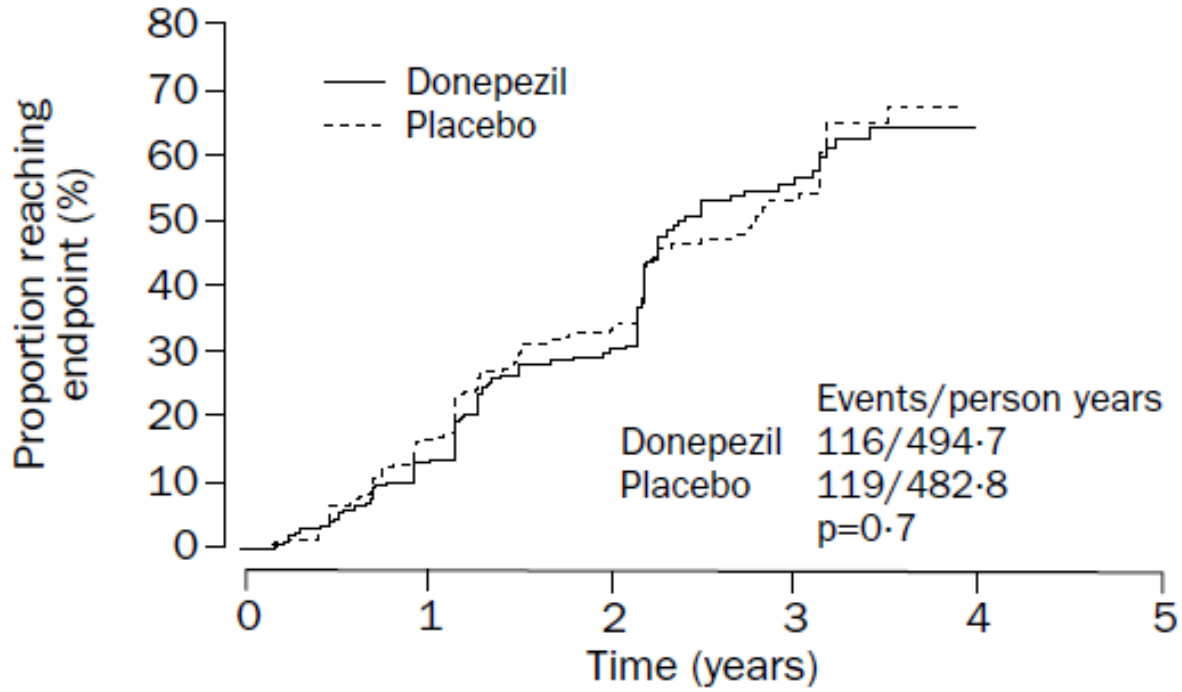


Number at risk

Donepezil	282	212	134	57	1
Placebo	283	209	135	60	0

Figure 2: **Entry to institutional care**

- 13% donepezil vs 19% placebo had progression of disability at 1 year, p=0.3 **not statistically significant**



Number at risk

Donepezil	281	203	126	45	1
Placebo	282	199	122	50	0

Figure 3: **Time to loss of activities of daily living*, institutional care, or both**

*Loss of two basic, or six instrumental, activities of daily living.

- No difference in BADLS score at 12 weeks, but after donepezil group had better scores.
- Average difference was 1.0 BADLS points (0.5-1.6; p 0.0004) **which was statistically significant**
- BADLS scores 1.0 points better with 10mg vs 5mg donepezil (-0.-2.6; p0.24) **which was not statistically significant**

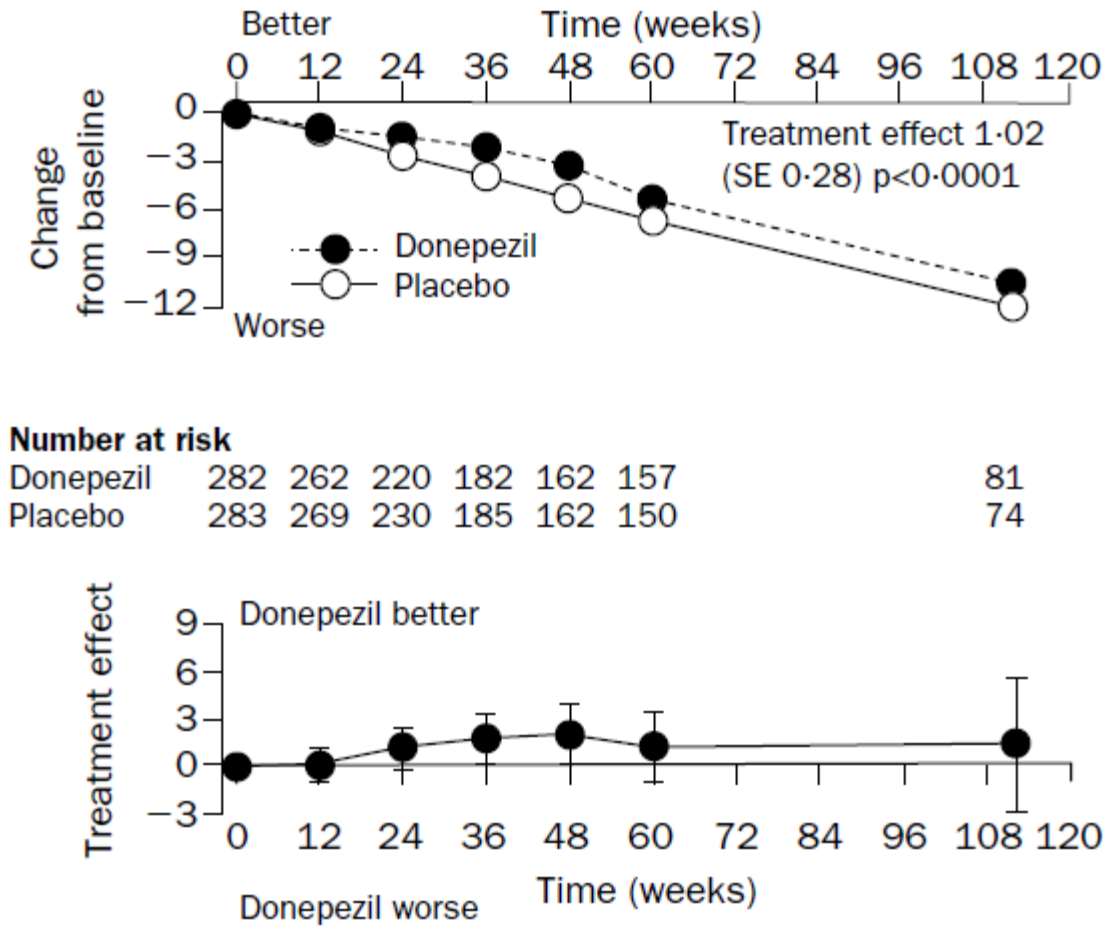


Figure 4: **Change in BADLS (upper) and effect of donepezil (lower)**

- During the first 12 weeks, donepezil averaged 0.9 MMSE points above baseline, compared to no improvement in placebo

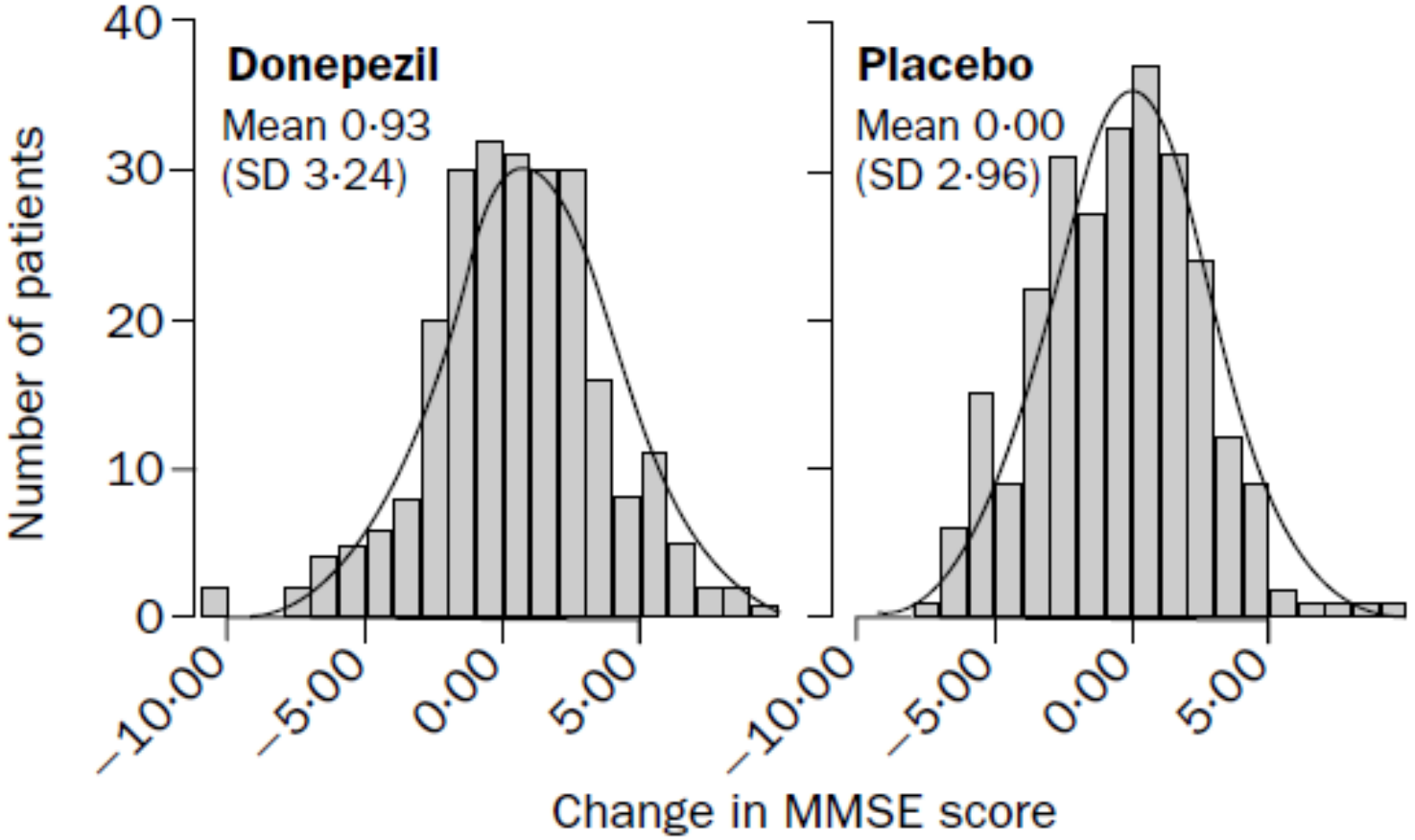


Figure 5: **Improvement in MMSE from 0 to 12 weeks**

- Over 2 years the donepezil group averaged **a statistically significant 0.8 higher than placebo** (95% CI 0.5-1.2 p<0.0001) with no significant attrition of benefit
- Cognition scores averaged 0.2 MMSE points (-0.8-1.2; p 0.4) better with 10mg than 5mg **but not statistically significant**
- No delay found in reaching severe cognitive disability (MMSE <10)

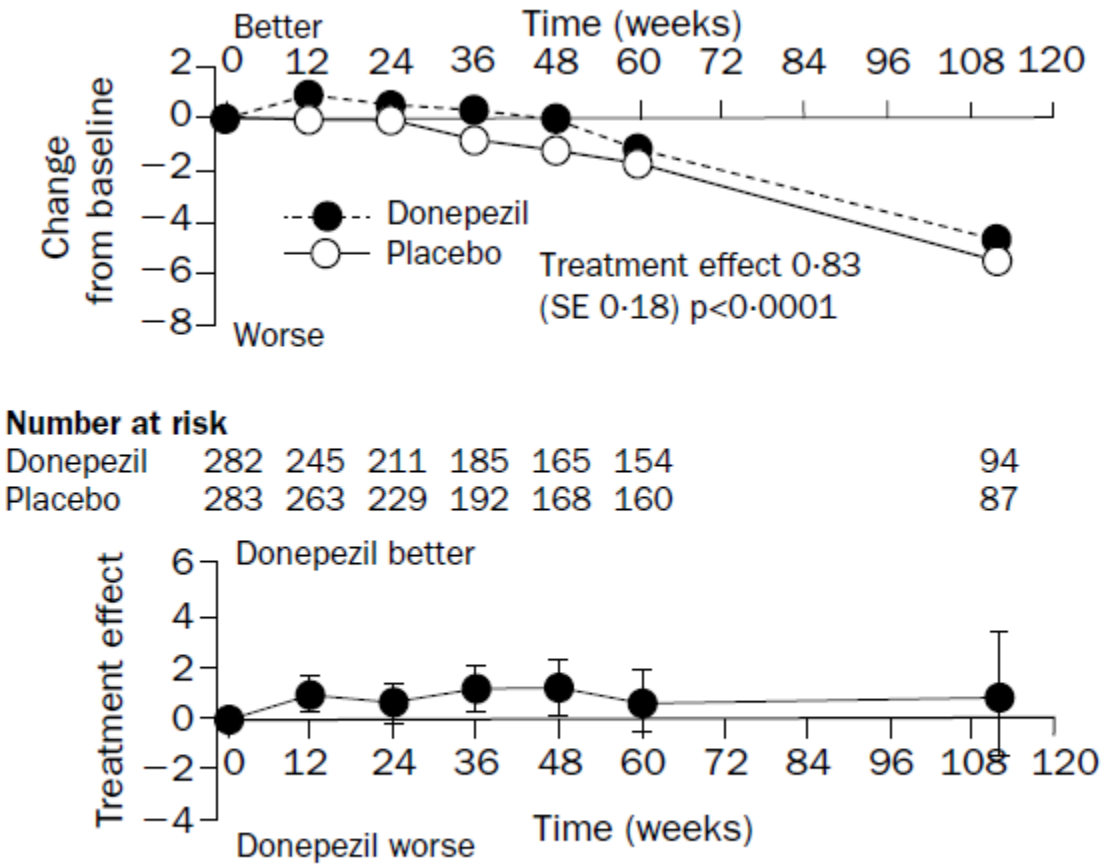


Figure 6: **Change in MMSE (upper) and effect of donepezil (lower)**

- Donepezil 0.3 NPI points better on average but no significant difference in NPI at any time point or overall (-0.9-1.5; p 0.6) **but not statistically significant**

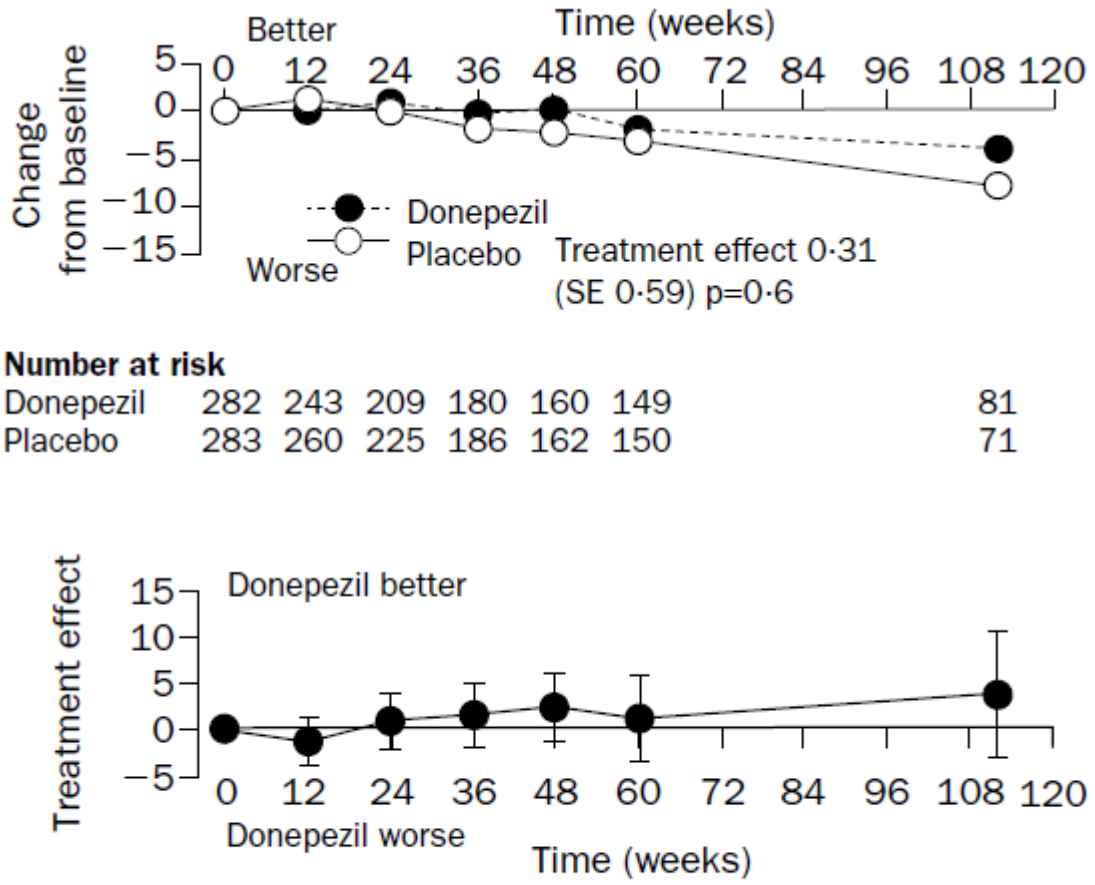


Figure 7: **Change in NPI (upper) and effect of donepezil (lower)**

- Caregivers had 0.3 GHQ points lower with donepezil vs. placebo (-0.3-0.9; p 0.3) **but not statistically significant**
- Half of caregivers had scores of 5 or more at baseline indicating probable psychological morbidity, and proportion above 5 increased at same rate in both groups

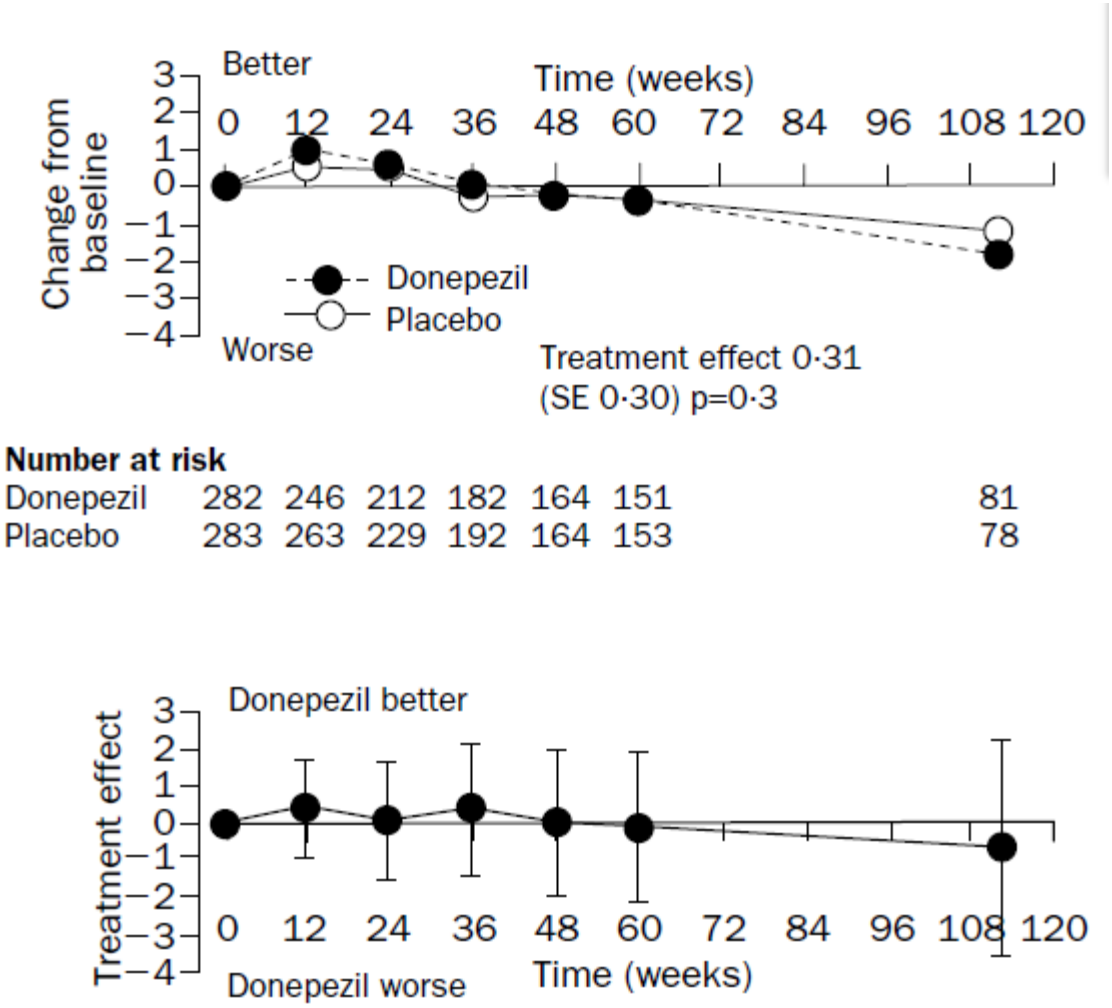


Figure 8: **Change in carer's GHQ score (upper) and effect of donepezil (lower)**

- Active caregiver time was 0.2 hours less (-0.1-0.5; p=0.2) and passive caretime was 0.4 hours less (-0.1-1.2; p=0.4) **but neither were statistically significant**

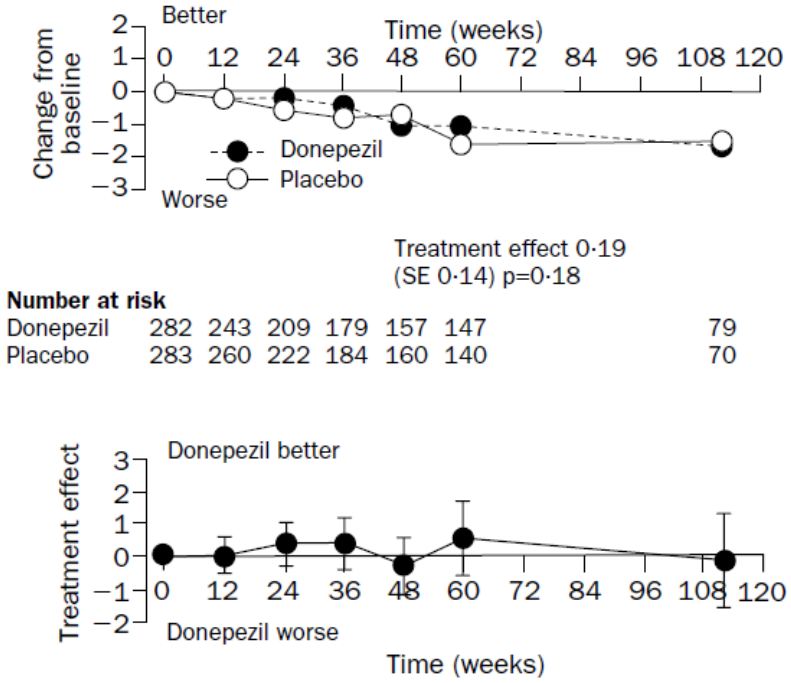


Figure 9: **Change in active care time (upper) and effect of donepezil (lower)**

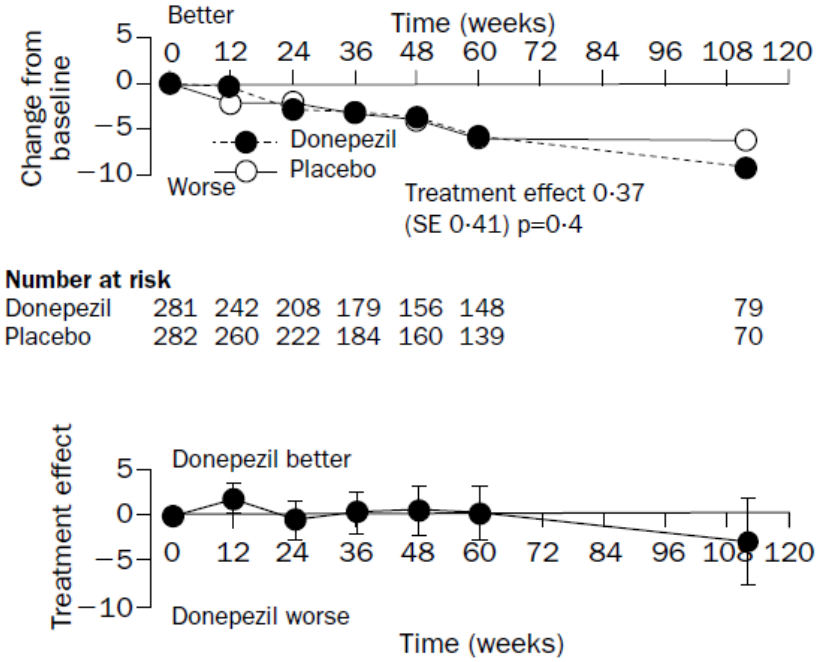


Figure 10: **Change in passive care time (upper) and effect of donepezil (lower)**

	Total units reported		Average use per 12-week period per patient		Estimated annual cost per patient (£/year)		£/year saving with donepezil (SE)	p
	Donepezil (n=997)	Placebo (n=1013)	Donepezil	Placebo	Donepezil	Placebo		
Number and resource type (cost per unit)*								
1 Visiting nurse (£25 per visit)	375	210	2·4	1·4	232	155	–77 (48)	0·11
2 Social worker (£83 per hour)	28	37	0·2	0·2	49	95	45 (25)	0·07
3 Domestic help (£12 per hour)	905	1058	5·9	6·8	285	329	44 (80)	0·6
4 Meals on wheels (£3 per meal)	271	271	1·8	1·7	19	18	–1 (6)	0·9
5 Day care centre (£38 per session)	710	579	4·6	3·7	674	675	1 (108)	0·99
6 Day hospital (£69 per session)	199	211	1·3	1·4	380	360	–21 (86)	0·8
7 Visits to family doctor (£25 per visit)	755	747	0·8	0·7	78	74	–4 (7)	0·6
8 Hospital doctor (£68 per visit)	254	254	0·3	0·2	82	69	–13 (14)	0·4
9 Hospital overnight stay (£223 per night)	844	518	0·8	0·5	825	439	–386 (223)	0·09
10 Nursing home overnight stay (£51 per night)	545	258	0·5	0·3	99	36	–63 (41)	0·12
11 Residential home overnight stay (£38 per night)	412	596	0·4	0·6	78	88	10 (37)	0·8
12 Unknown overnight stays (£100 per night)	50	14	0·1	0·0	41	6	–36 (37)	0·3
Total (all resources)					£2842	£2344	–£498 (352)	0·16

*from Netten and Curtis.[29] Items 1–6 cover the previous 2 weeks and items 7–12 the previous 12 weeks. Cost for item 1 assumes visit lasts less than 4 h, and 6 assumes visits longer than 4 h; 7 assumes visit in surgery; 8 assumes outpatient visit; 12 is weighted average of hospital, nursing home, and residential home rates.

Table 2: **Health resource use over weeks 0–60**

- Mean annual cost per patient in the community was higher with donepezil than placebo **but not statistically significant** (£2842 vs 2344, p=0.16)

Discussion

The only statistically significant effects shown by the AD 2000 study were a 0.8 point increase in MMSE, and a 1.0 point improvement on the BADLS.

No reduction in rate of institutionalization or progression of disability

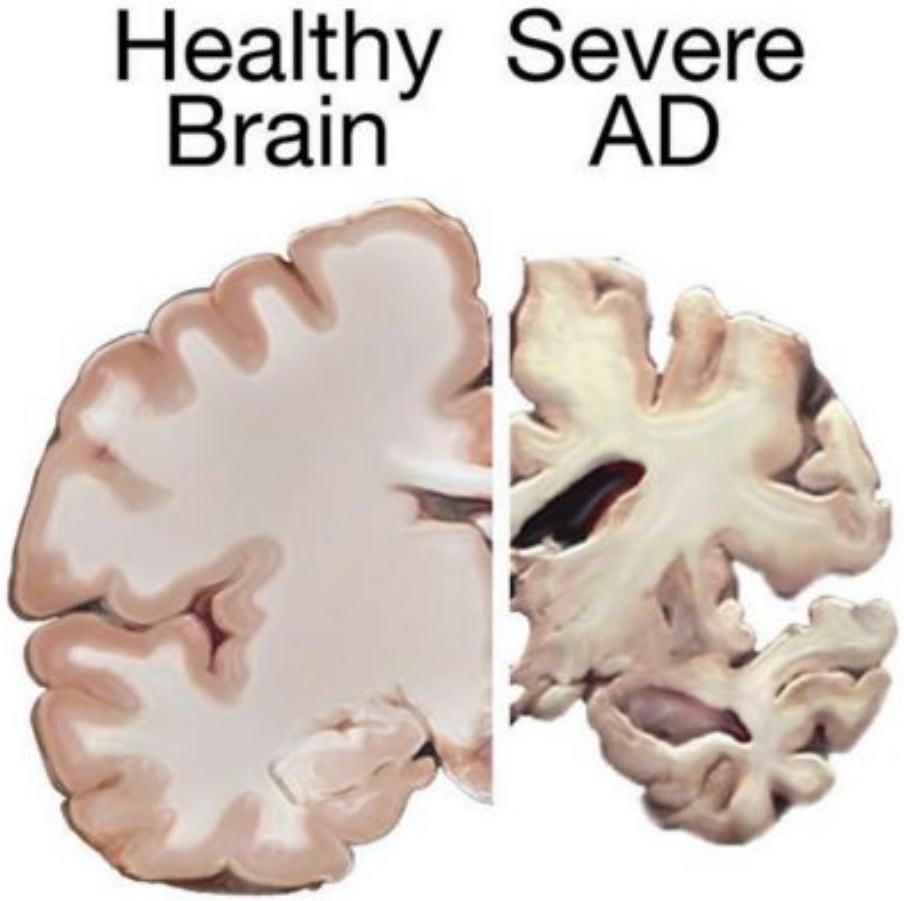
Hence no cost savings were shown and the cost-neutral hypothesis was rejected

Given the modest patient size (study projected to have 3000 patients) some argue it was underpowered to make definitive conclusions regarding primary endpoints

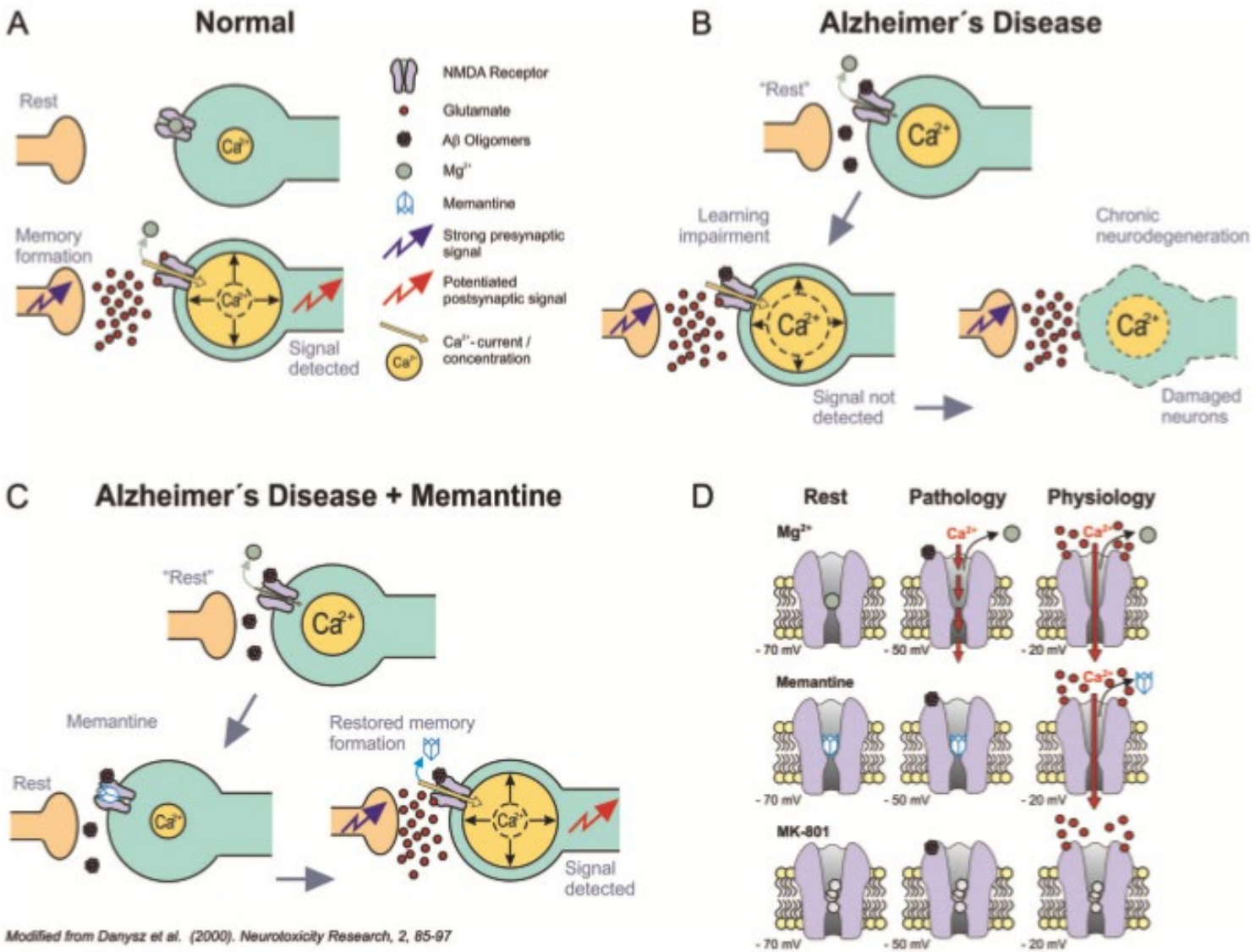
Acetylcholinesterase Inhibitor Adverse Effects

- Nausea, vomiting
- Diarrhea
- Abdominal pain
- Constipation
- Fecal incontinence
- Dyspepsia
- Weight loss
- Peripheral edema
- Agitation
- Bradycardia
- Hypotension
- Heart failure
- Anemia
- Arthralgias
- Anxiety
- Tremor
- Vertigo
- Wandering
- Gait disturbance
- Falls
- Cough
- Rash
- Pruritis
- Conjunctivitis
- Blurred vision
- Urinary tract infections
- Flu-like syndrome

Alzheimer’s dementia is a disease of cell death



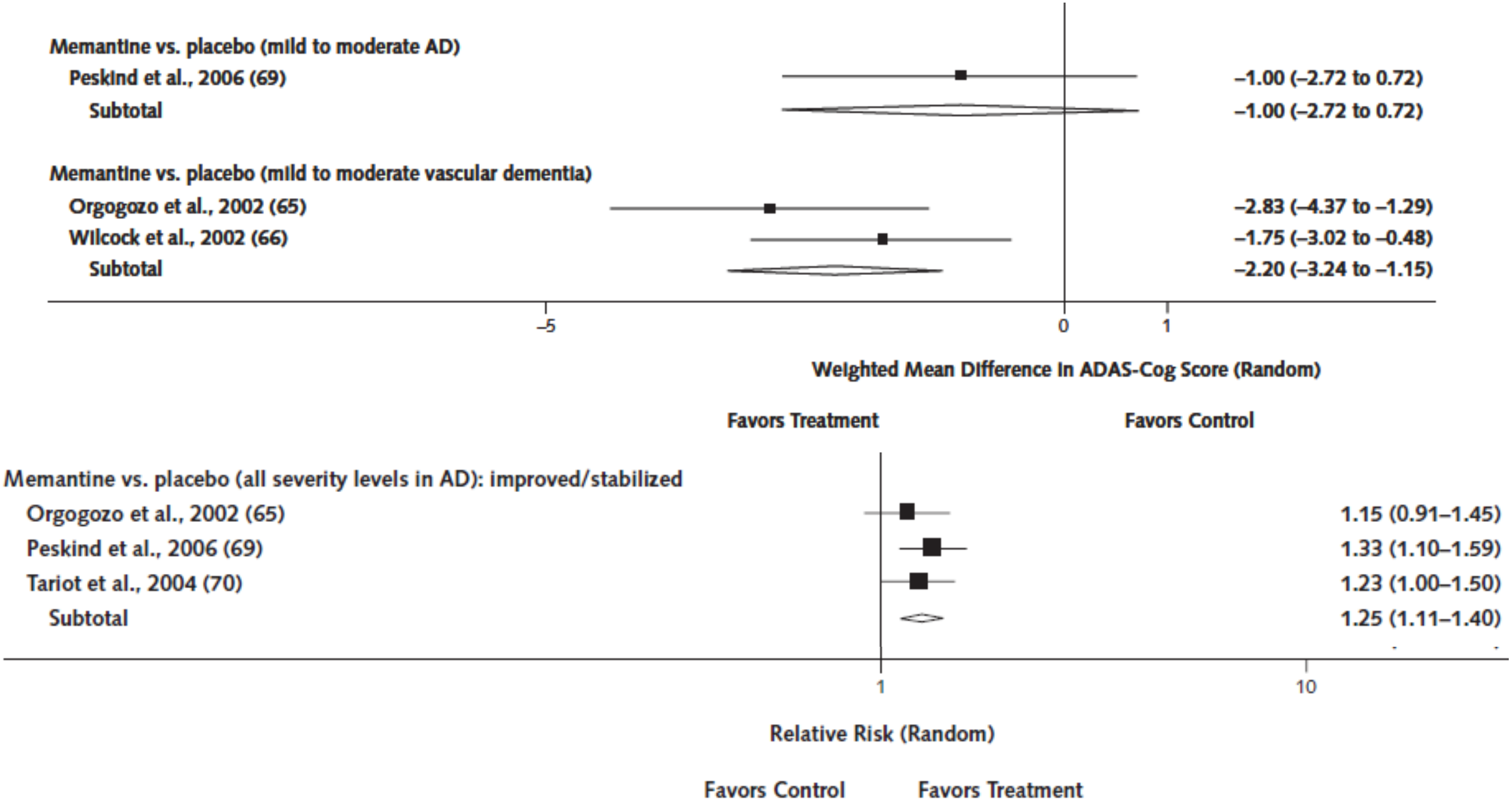
Namenda
memantine HCl tablets



Modified from Danysz et al. (2000). Neurotoxicity Research, 2, 85-97

Namenda

- Approved for moderate to severe Alzheimer's Dementia
- Technically has been shown to increase cognition and global assessment of function based on a 2008 meta-analysis
- Does it truly have clinical significance?


Memantine vs. placebo (mild to moderate AD)
Peskind et al., 2006 (69)
Subtotal
–1.00 (–2.72 to 0.72)
–1.00 (–2.72 to 0.72)
Memantine vs. placebo (mild to moderate vascular dementia)
Orgogozo et al., 2002 (65)
Wilcock et al., 2002 (66)
Subtotal
–2.83 (–4.37 to –1.29)
–1.75 (–3.02 to –0.48)
–2.20 (–3.24 to –1.15)
–5
0
1
Weighted Mean Difference in ADAS-Cog Score (Random)
Favors Treatment
Favors Control
Memantine vs. placebo (all severity levels in AD): improved/stabilized
Orgogozo et al., 2002 (65)
Peskind et al., 2006 (69)
Tariot et al., 2004 (70)
Subtotal
1.15 (0.91–1.45)
1.33 (1.10–1.59)
1.23 (1.00–1.50)
1.25 (1.11–1.40)
1
10
Relative Risk (Random)
Favors Control
Favors Treatment

Adverse Effects of Memantine

- Fatigue
- Pain
- Hypertension
- Dizziness
- Headache
- Constipation
- Vomiting
- Cough
- Dyspnea
- Confusion
- Somnolence
- Hallucinations
- Anxiety
- Depression
- Aggression

Namenda

- While statistically significant benefits have been shown with regard to ADAS-COG and clinician assessment of condition, these effects have not shown a proven clinical effect on quality of life or other domains of function
  - NEJM 2012 “Donepezil and Memantine for Moderate-to-Severe Alzheimer’s Disease” showed prior pharma study results of statistically significant improvement in neuropsychiatric index scores but not enough to reach minimal clinical significance.
- Ultimately the best recommendation available for Namenda is that it has a lower side effect profile than acetylcholinesterase inhibitors, and may have some benefit, so treatment decision should be on an individual basis taking into account cost and patient preferences

JAGS, Comparative Effectiveness and Safety of Cognitive Enhancers for Treating Alzheimer's Disease: Systematic Review and Network Metaanalysis

- 2018 metaanalysis reviewed 142 studies, 110 RCTs, 21 non-RCTs, 11 cohort studies
- Studies included donepezil, galantamine, transdermal or oral rivastigmine, or memantine

- No treatments found to be superior to placebo in terms of functional status.
- Donepezil, donepezil+memantine, and transdermal rivastigmine improved cognitive test scores
- Only donepezil reached the minimal clinically important difference threshold for cognitive test score improvements

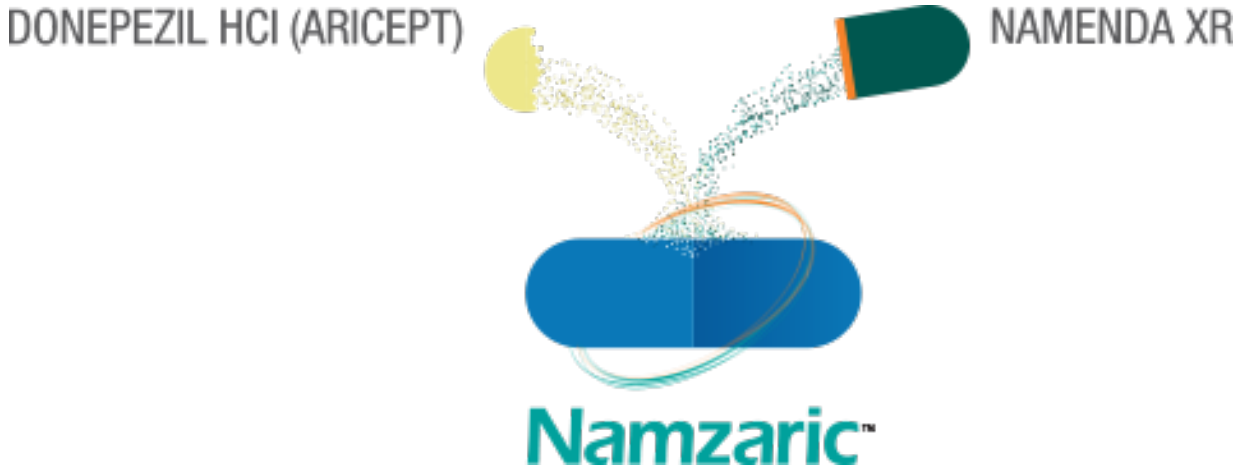
Acetylcholinesterase inhibitors and Memantine for Behavioral Disturbance

- Emerging body of evidence suggests memantine may be effective for managing/delaying onset of behavioral agitation in Alzheimer's and Vascular dementias.
- Rivastigmine possibly has efficacy at reducing behavioral agitation as per the neuropsychiatric inventory, however evidence is limited and literature finding this usually has behavioral symptoms as secondary endpoints

Namenda/Donepezil Combo Pills

Pros:
-Ease of dosing

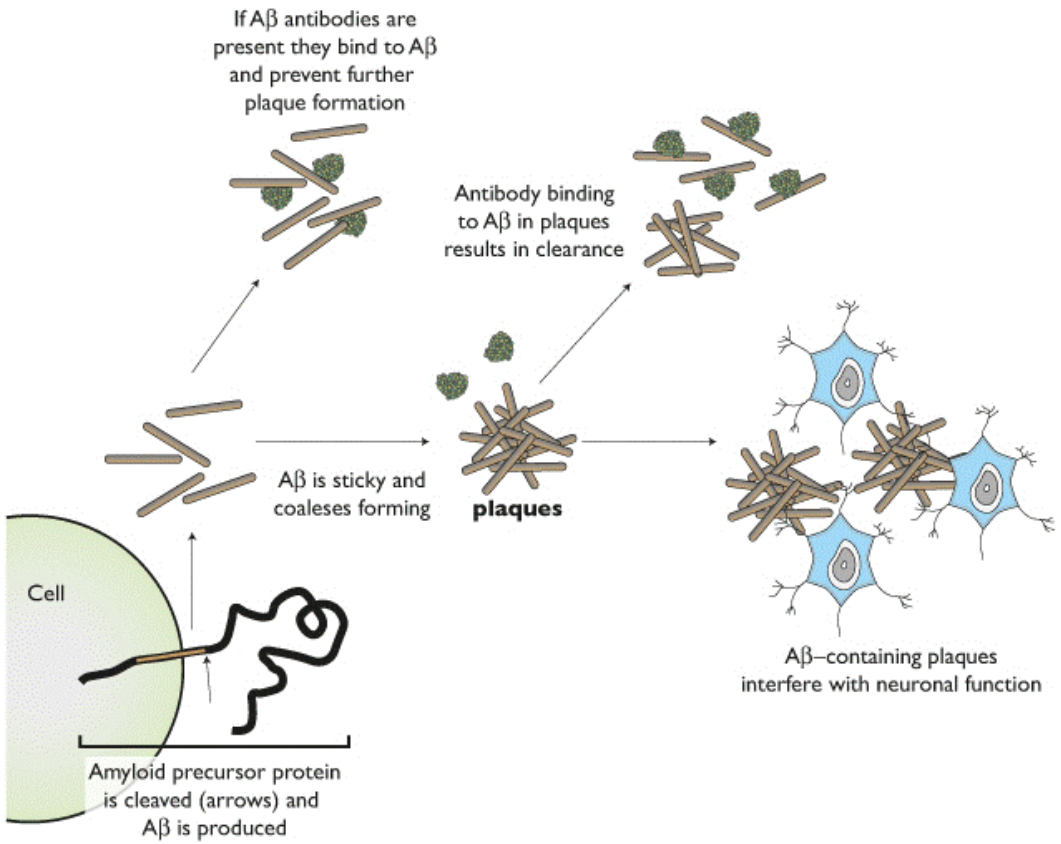
Cons:
-Higher cost
-Data varies on whether combos are efficacious or not, although best done study showed no clear additive benefits of the two drugs together
-Side effects



Neutraceuticals

- To date, no neutraceutical has been found to have clinical or statistical benefit for dementia
- Souvenaid, a medical food, (eicosapentaenoic acid, docasohexaenoic acid, phospholipids, choline, uridine, vitamin E, vitamin C, selenium, vitamin B12, vitamin B6, and folic acid) technically showed efficacy in a randomized trial of 259 patients in Europe which showed a statistical but not clinical benefit in neuropsychiatric inventory over 24 weeks.
  - Given limited sample size and minimal benefits, more study would be needed before recommending this agent

Bapineuzumab



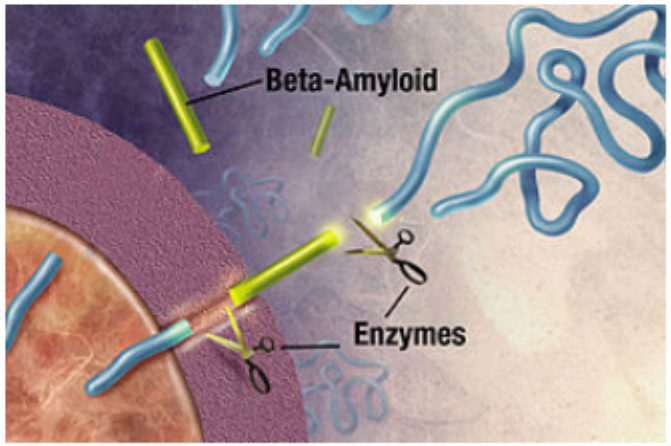
Forbes / Pharma & Healthcare

AUG 7, 2012 @ 01:09 PM 15,466 VIEWS

The Lessons Of Failure: What We Can Learn From Bapineuzumab's Blowup

Nathan Sadeghi-Nejad
CONTRIBUTOR

I write about drugs, devices, services and healthcare policy.



Enzymes are thought to cut fragments of beta-amyloid in Alzheimer's disease (Photo credit: Wikipedia)

The amyloid hypothesis is dead, at least for now.

Eli Lilly Alzheimer's Drug Fails Trial

Drugmaker's shares plunge as study shows solanezumab didn't significantly help patients

A drug developed by Eli Lilly to treat patients with Alzheimer's disease symptoms failed a closely watched clinical trial. WSJ's Jeanne Whalen explains the impact of the failure on Eli Lilly stock and the rest of the pharmaceutical sector, which had rested its hopes on the success of the drug. Photo: Kris Tripplaar/Sipa USA

By PETER LOFTUS

Updated Nov. 23, 2016 4:34 p.m. ET

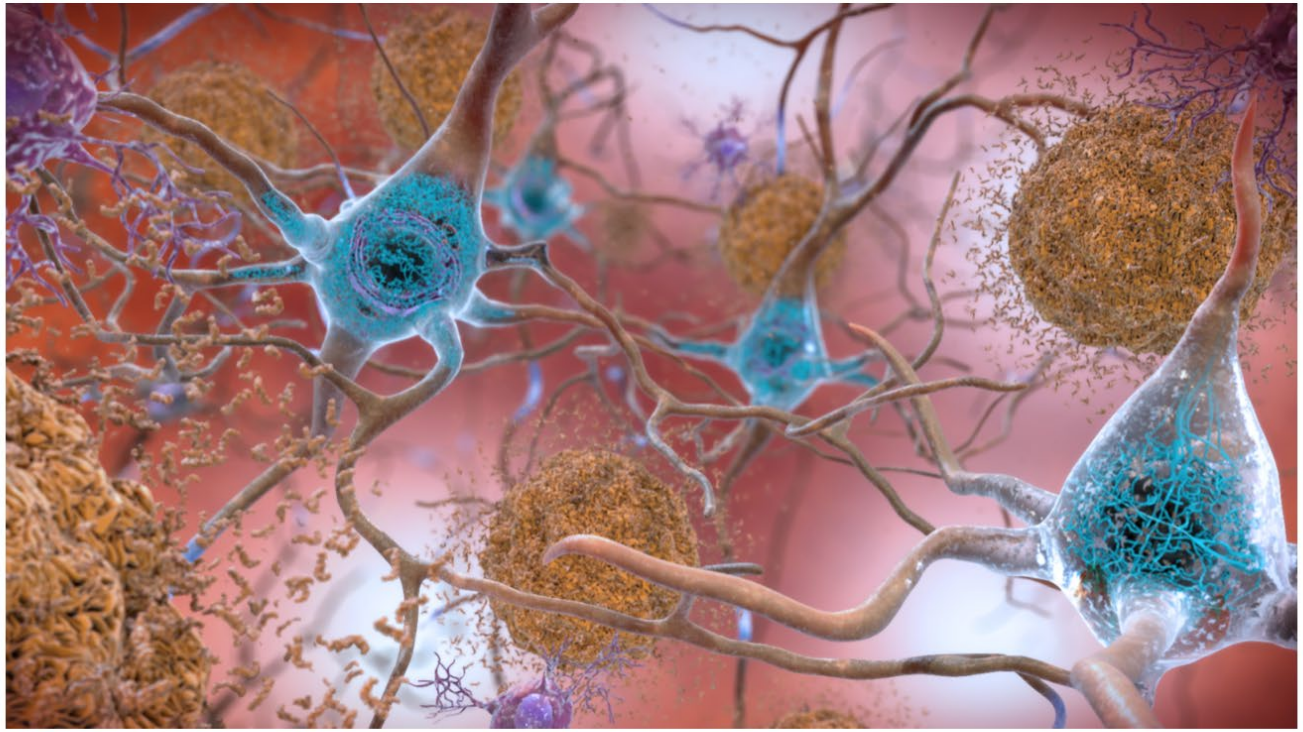
45 COMMENTS

BIOTECH

STAT+

Biogen halts studies of closely watched Alzheimer's drug, a blow to hopes for new treatment

By ADAM FEUERSTEIN @adamfeuerstein / MARCH 21, 2019

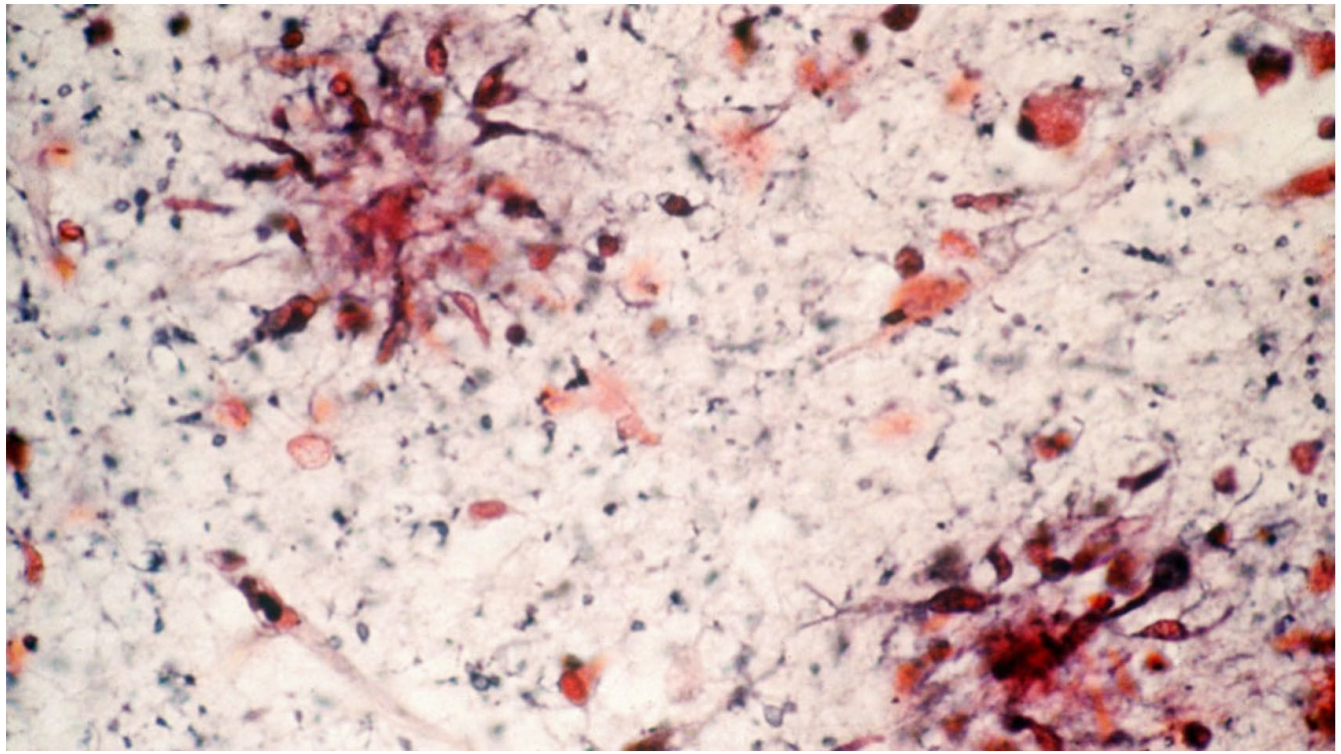


NATIONAL INSTITUTE ON AGING, NIH

NEWS HEALTH & MEDICINE

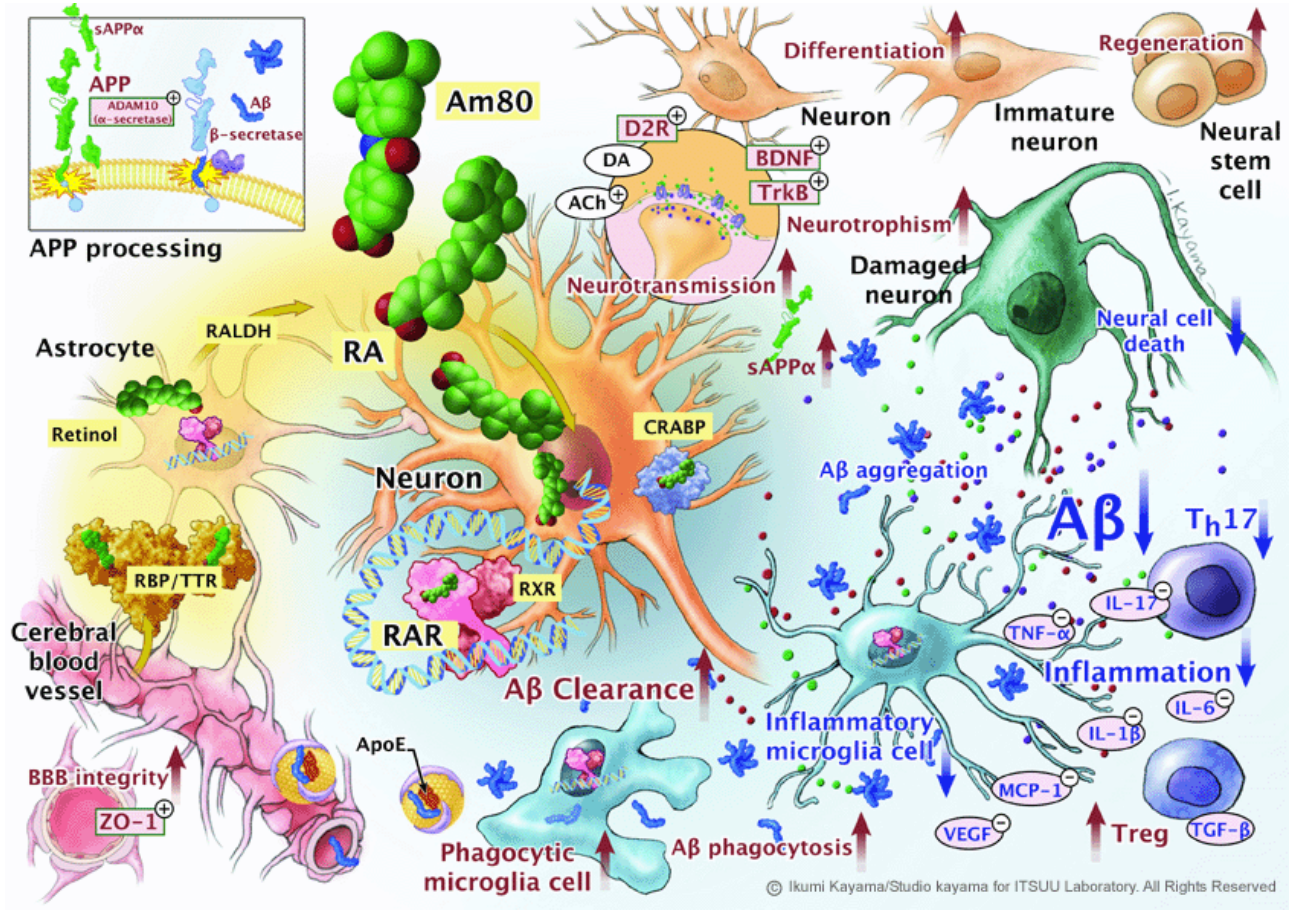
A once-scrapped Alzheimer's drug may work after all, new analyses suggest

At the highest doses, aducanumab slowed mental decline, the drug developer claims



By targeting sticky globs of amyloid (red) in the brains of people with Alzheimer's, a new drug may offer a way to slow the disease's spread.

So now what?


sAPPα
APP
ADAM10 (α-secretase)
Aβ
β-secretase
APP processing
Am80
RA
RALDH
Astrocyte
Retinol
RBP/TTR
Cerebral blood vessel
BBB integrity
ZO-1
Neuron
RXR
RAR
CRABP
D2R
DA
ACh
BDNF
TrkB
Neurotransmission
Differentiation
Neuron
Immature neuron
Regeneration
Neural stem cell
Neurotrophism
Damaged neuron
Neural cell death
sAPPα
Aβ aggregation
Aβ
Th17
IL-17
TNF-α
Inflammation
IL-6
IL-1β
Inflammatory microglia cell
MCP-1
VEGF
Treg
TGF-β
Aβ Clearance
ApoE
Phagocytic microglia cell
Aβ phagocytosis
I.Kayama
© Ikumi Kayama/Studio kayama for ITSUU Laboratory. All Rights Reserved

Risk Factors

Non-modifiable risks:

- Age
- Family History
- Gender
- Genetics

Risk Factors

Modifiable risks:

- Cardiovascular Disease
- Head injuries

Disease prevention:

- Exercise
- Stay mentally active
- Stay socially active
- Healthy diet
- Avoid tobacco or excess of alcohol

Conclusions

- Pharmacotherapy for Alzheimer's disease exists
- Any potential benefit from currently existing drugs in the acetylcholinesterase inhibitor class or NMDA-receptor antagonists are small at best.
- Monotherapy is likely as efficacious as combination therapy with fewer side effects
- Monoclonal antibody therapy against amyloid has not changed disease thus far
- Non-pharmacologic interventions likely have greater impact, although harder to study and quantify

And now, a plug

AlzDxRx

AVAILABLE ON:

GET IT ON Google Play

Download on the App Store

NPI Number

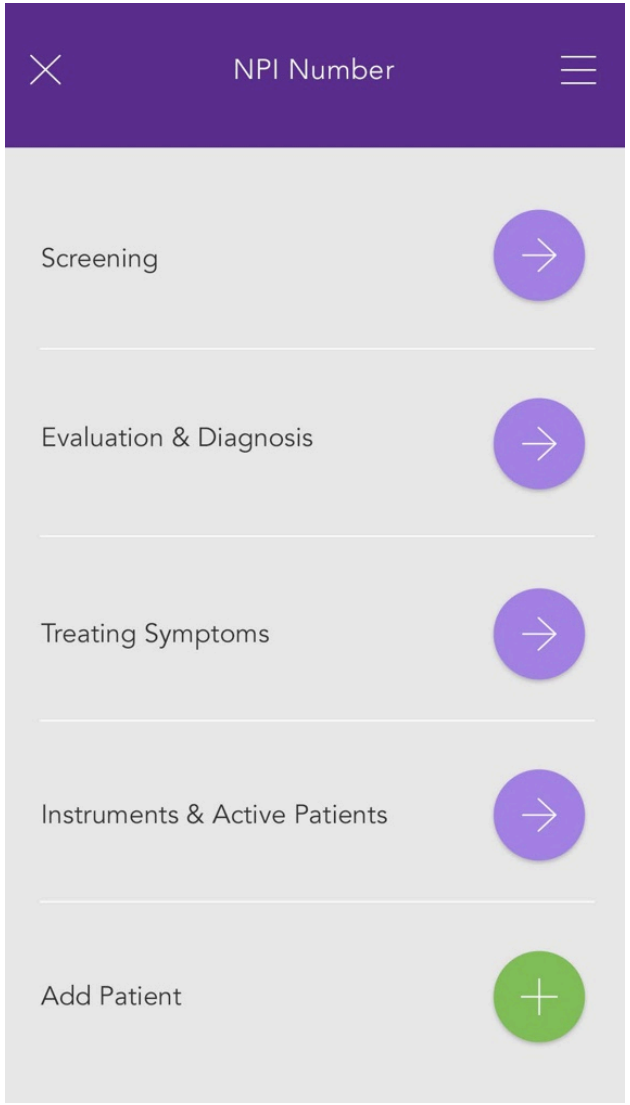
Password

Sign In

LIVE WELL SAN DIEGO

Create Account

Forgot Password


NPI Number
Screening
Evaluation & Diagnosis
Treating Symptoms
Instruments & Active Patients
Add Patient

References

AD2000 Collaborative Group, Long-Term Donepezil Treatment in 565 Patients with Alzheimer's Disease (AD2000): Randomised Double-Blind Trial, The Lancet, 363, 2105-2115. June 26, 2004.

Cummings J, Schneider E, Tariot PN, Graham SM, Memantine MEM-MD-O2 Study Group. Behavioral effects of memantine in Alzheimer disease patients receing donepezil treatment, Neurology, 67 (1). July 11, 2006.

Scheltensa P, Twiskb JWR, Blesa R, et al. Efficacy of Souvenaid in Mild Alzheimer's Disease: Results from a Randomized Controlled Trial. Journal of Alzheimer's Disease, 31; 225-236. 2014.

Howard, R, et al. Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease, New England Journal of Medicine, 366; 10, 893-903. March 8, 2012.

Raina, P, et al. Effectiveness of Cholinesterase Inhibitors andMemantine for Treating Dementia: Evidence Review for a Clinical Practice Guideline, Annals of Internal Medicine, 148; 5, 379-397. March 4, 2008.

Salloway, S, et al. Two Phase 3 Trials of Bapineuzuamb in Mild-to-Moderate Alzheimer's Disease, New England Journal of Medicine, 370; 4, 322-333. January 23, 2014.

Sommer I, Griebler U, Kien C, et al. Vitamin D deficiency as a risk factor for dementia: a systematic review and meta-analysis. *BMC Geriatr*. 2017;17(1):16. Published 2017 Jan 13. doi:10.1186/s12877-016-0405-0

Tricco , A, et al. Comparative Effectiveness and Safety of Cognitive Enhancers for Treating Alzheimer's Disease: Systematic Review and Network Metaanalysis, Journal of the American Geriatrics Society, 66: 170-178. January 2018.