THE ALZHEIMER'S PROJECT CLINICAL ROUNDTABLE

Dementia Pharmacotherapy

On-Demand webinar for Primary Care Providers
Part of the Continuing Medical Education Series on Dementia Care
produced by The Alzheimer's Project Clinical Roundtable
San Diego, CA

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Learning Objectives/Action Statements

At the conclusion of this program, you will be able to:

- Understand what factors in the brain contribute to dementia
- Know the science behind the current FDA approved drugs for treatment of dementia: cholinesterase inhibitors and memantine; and recognize the adverse effects.
- Advise patients and caregivers when it is appropriate to discontinue the use of prescription medications.
- Assess new medications as they become available for appropriateness for your patients.

Speaker Disclosures

Michael Lobatz, MD Neurologist

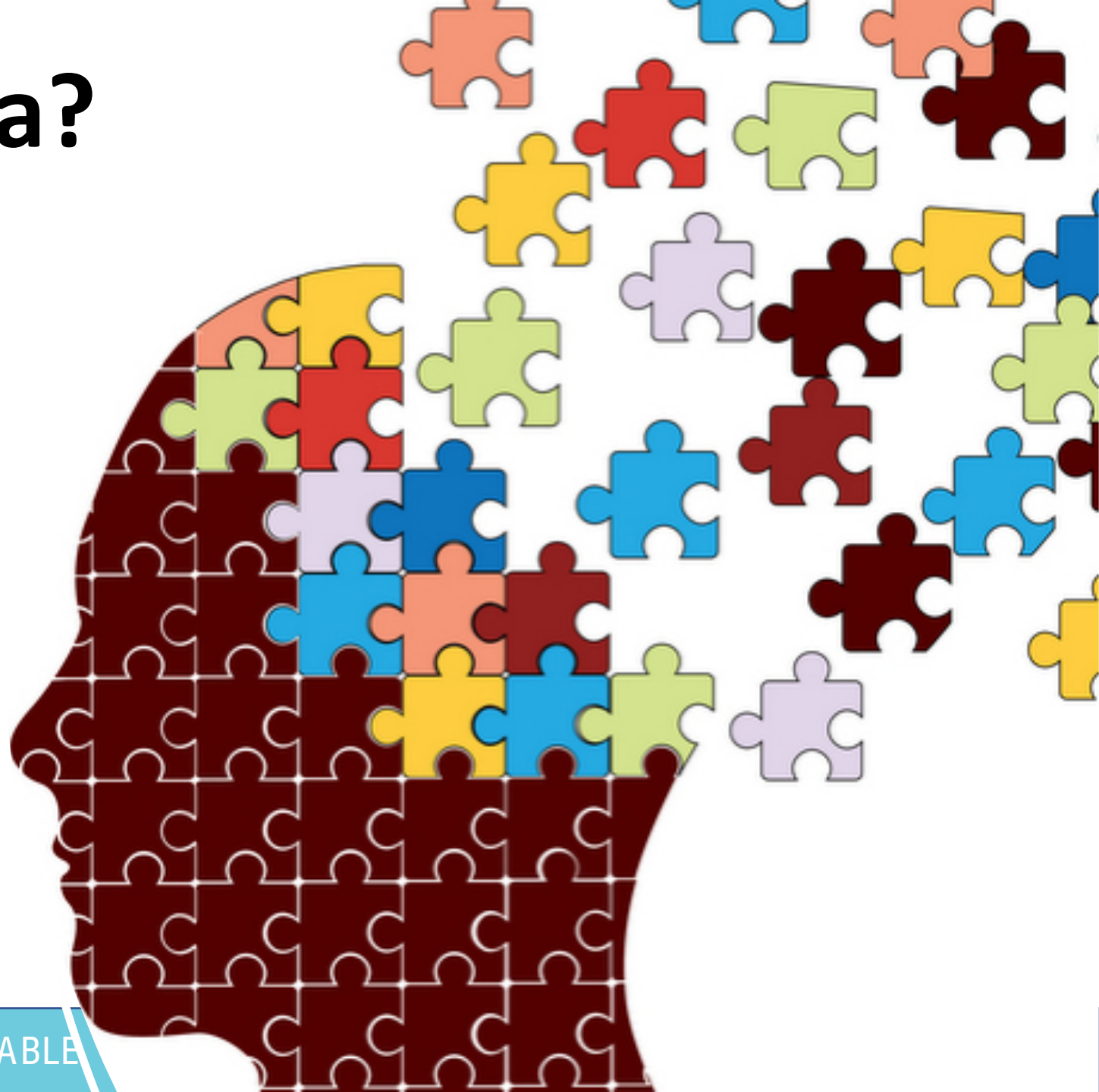
- Scripps Health 7 The Neurology Center
- No conflicts to disclose

Ian Neel, MD Geriatrician

- UC San Diego
- No conflicts to disclose

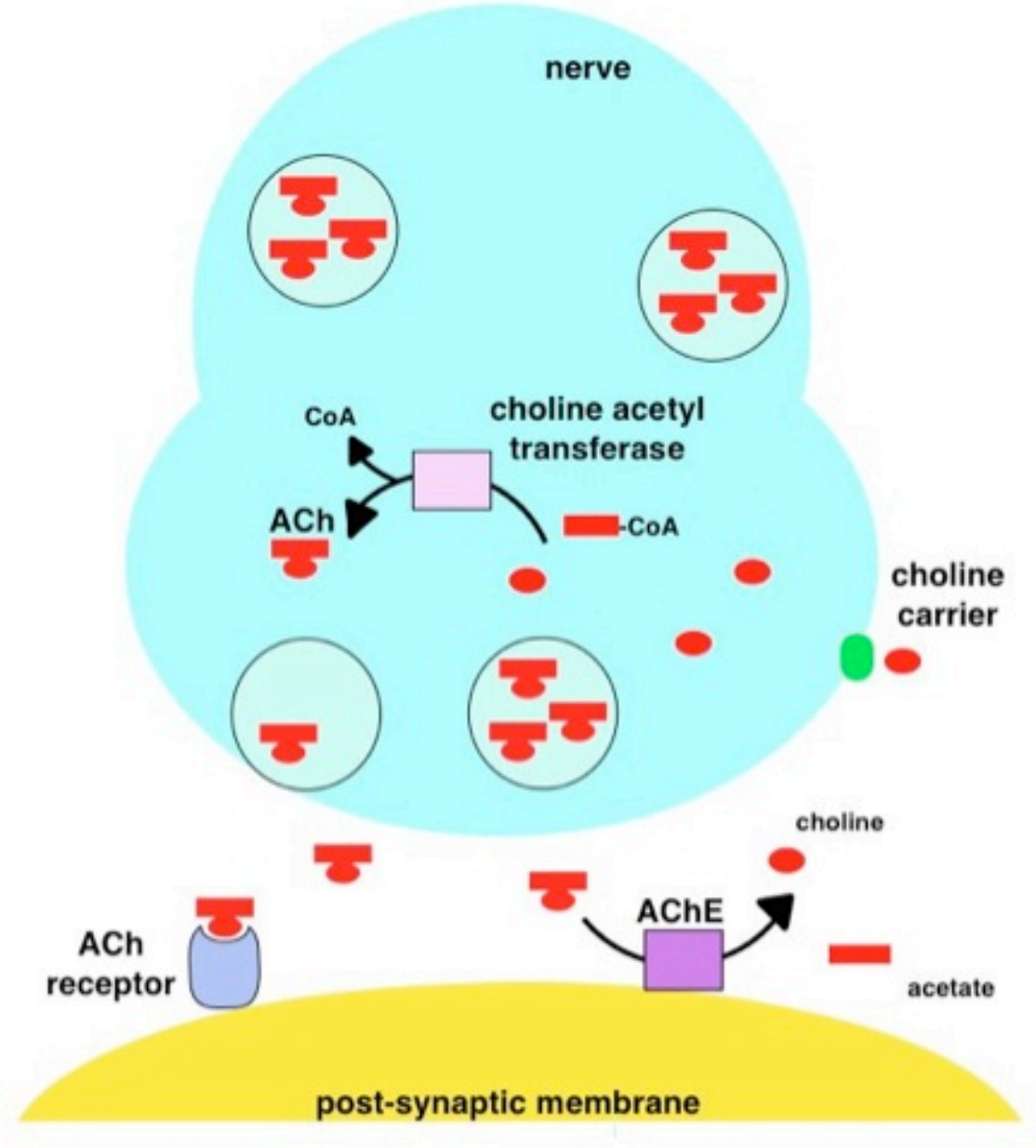
What is Dementia?

- Cognitive deficits in one or more areas of cognition, such as memory, language, visuospatial abilities, or executive function
- **Cognitive defects must impair social or occupational functioning (ADLs)**
- 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



Background

- Alzheimer's Disease pathology includes the accumulation of extracellular amyloid, forming plaques, and the aggregation of a protein called tau within neurons, forming neurofibrillary tangles
- Other pathology includes inflammatory reactions of microglia and astrocytes, loss of synapses, and neuronal death.
- Amyloid accumulates in the brain for a decade or more before the onset of symptoms of Alzheimer's
- Evidence from genetics, brain pathology and mouse models of amyloid deposition suggest that amyloid has a role in initiating Alzheimer's Disease


nerve
CoA
choline acetyl transferase
ACh
-CoA
choline carrier
choline
AChE
ACh receptor
acetate
post-synaptic membrane

Hypotheses being tested

- Treatment with donepezil is cost-neutral or better compared to the cost of donepezil with any savings from delayed admission or institutional care.
- Treatment with donepezil is cost-effective relative to placebo expressed as the additional cost of “day in a high level of disability” avoided, as defined by the primary progression of disability outcome measure.

AD 2000 Trial

- Run-in: Donepezil 5mg or placebo
- Phase 1: Re-randomized to donepezil 5mg, donepezil 10mg, or placebo
  - Donepezil 10mg group had 5mg tabs for 12 weeks before increase to 10mg tabs. Tabs were designed and packaged to look the same to avoid de-randomization
    - Used numbered 12-week long treatment packs

- Washout: Drug stopped for 6 weeks to assess for disease modifying properties
- Phase 2: Patient given option to continue treatment indefinitely with whatever drug he/she was randomized to.

	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

- Entry to institutionalization: **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
- Time to loss of activities of daily living: 13% donepezil vs 19% placebo had progression of disability at 1 year, p=0.3 **not statistically significant**

- 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)

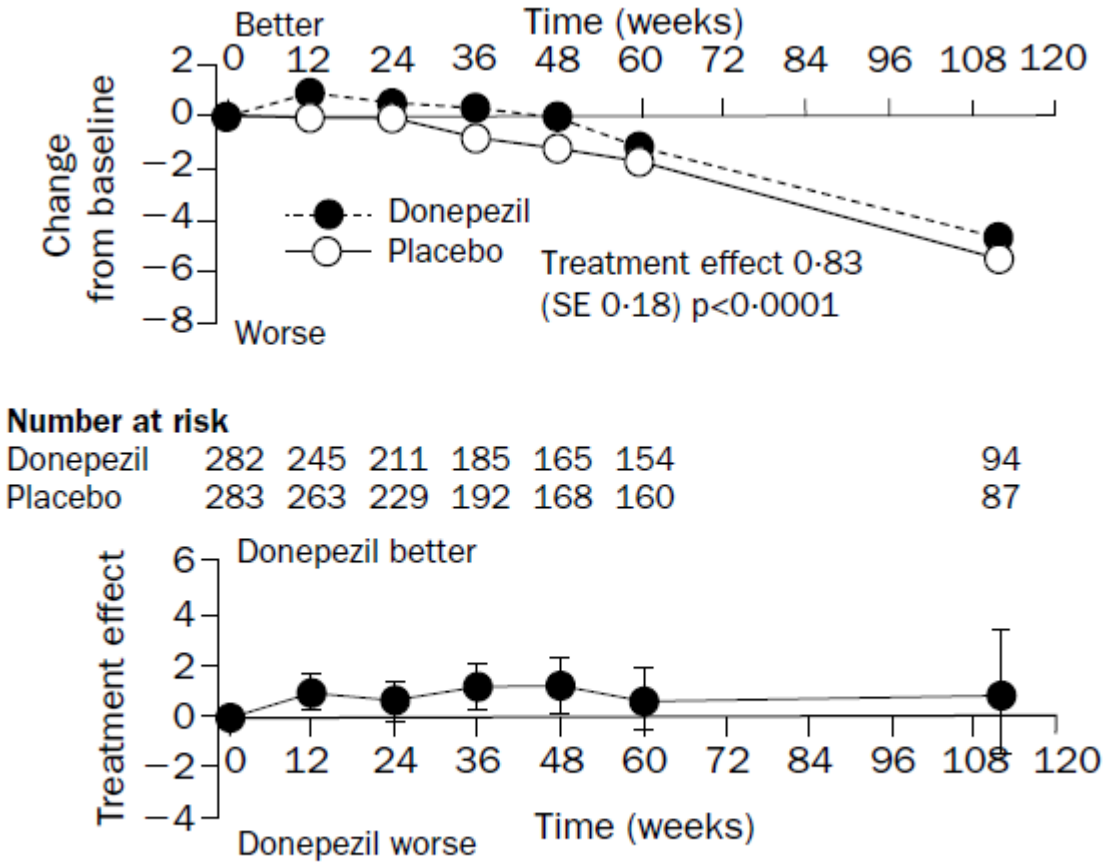
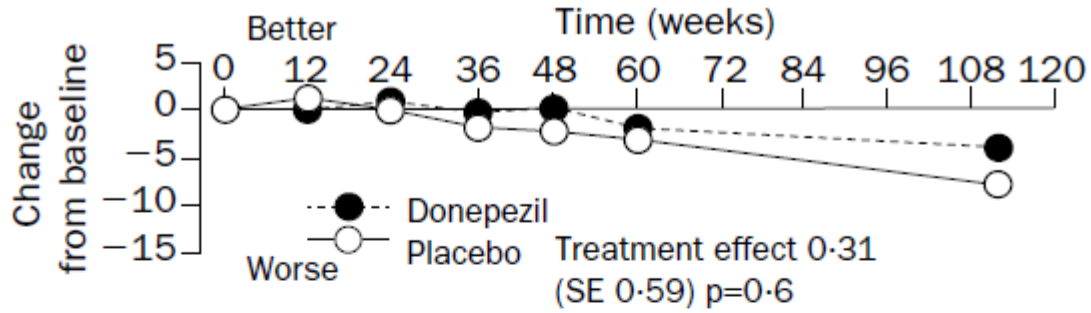


Figure 6: **Change in MMSE (upper) and effect of donepezil (lower)**

- 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**



Number at risk

Donepezil	282	243	209	180	160	149		81
Placebo	283	260	225	186	162	150		71

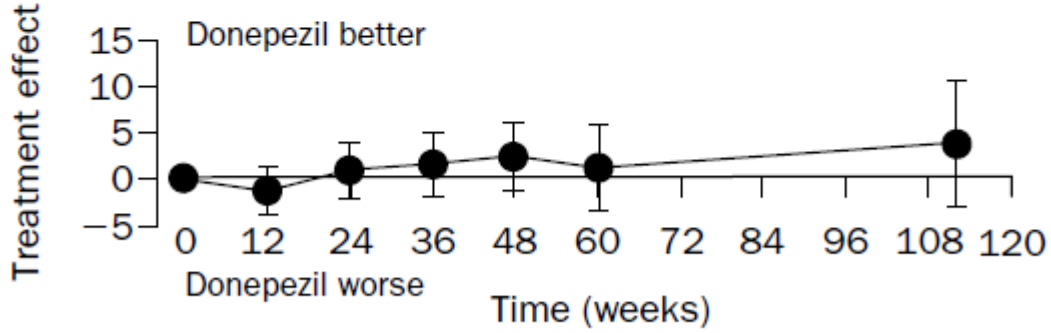


Figure 7: **Change in NPI (upper) and effect of donepezil (lower)**

- Change in Caregivers' GHQ score
- 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
- Active caregiver time was 0.2 hours less (-0.1-0.5; p=0.2) and passive care time was 0.4 hours less (-0.1-1.2; p=0.4) **but neither were statistically significant**

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

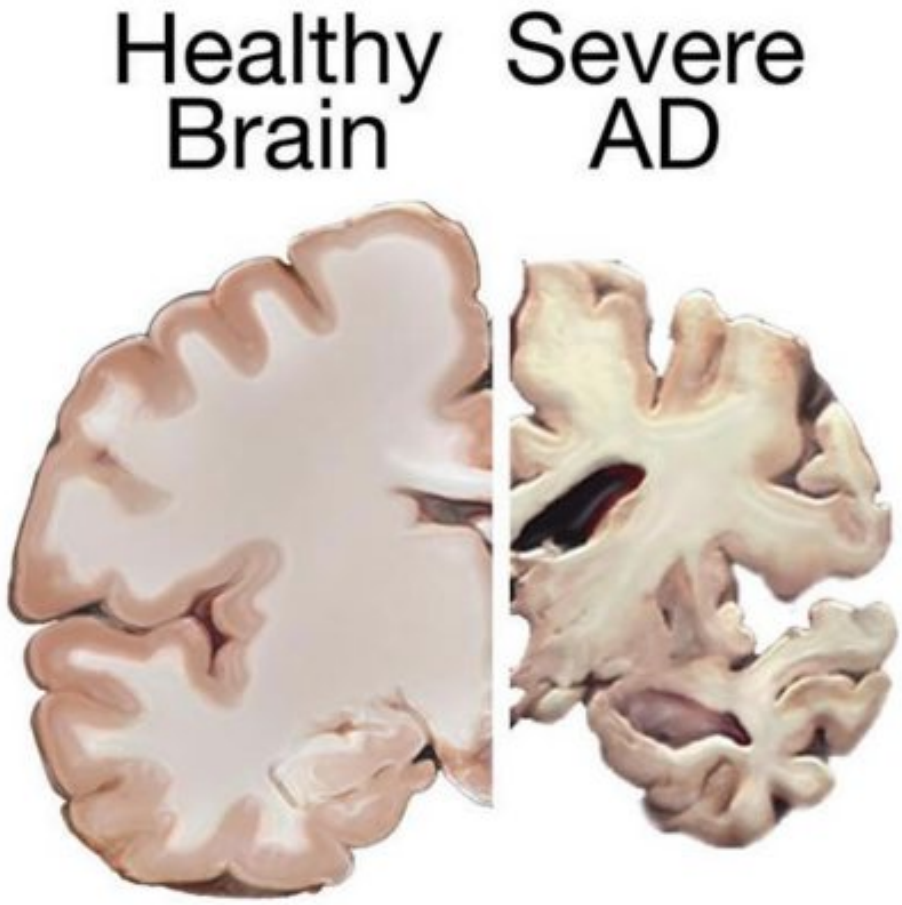
Acetylcholinesterase Inhibitor Adverse Effects

- Nausea, vomiting
- Diarrhea
- Abdominal pain
- Constipation
- Fecal incontinence
- Dyspepsia
- Weight loss
- Peripheral edema
- Agitation

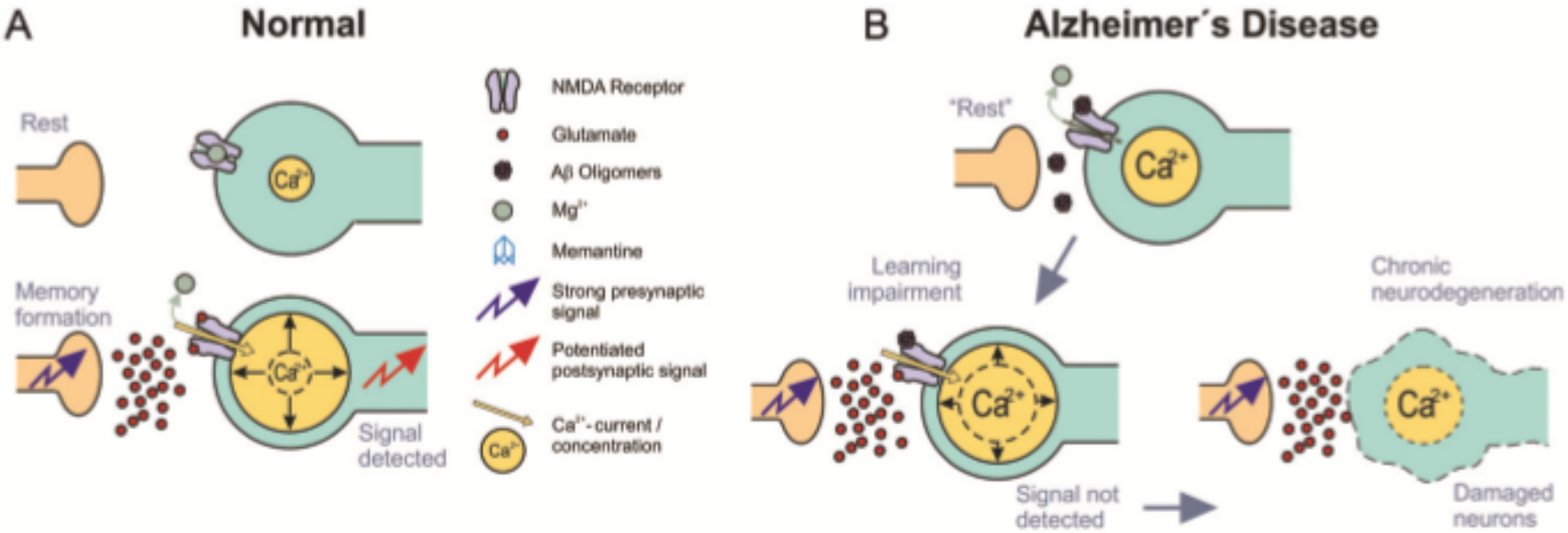
- Bradycardia
- Hypotension
- Heart failure
- Anemia
- Arthralgias
- Anxiety
- Tremor
- Vertigo
- Wandering

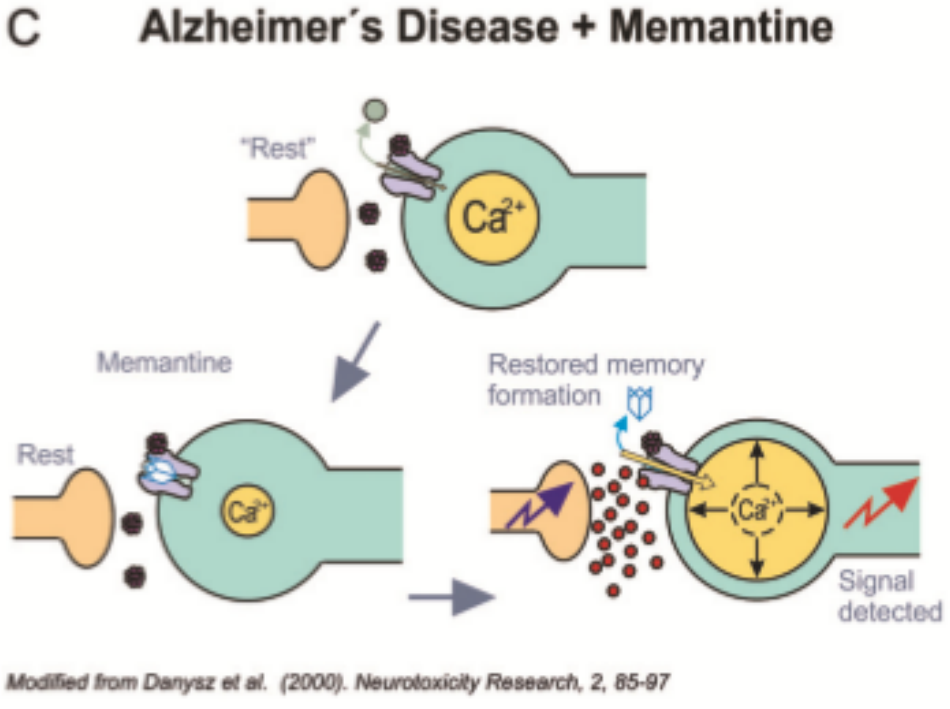
- Gait disturbance
- Falls
- Cough
- Rash
- Pruritis
- Conjunctivitis
- Blurred vision
- Urinary tract infections
- Flu-like syndrome

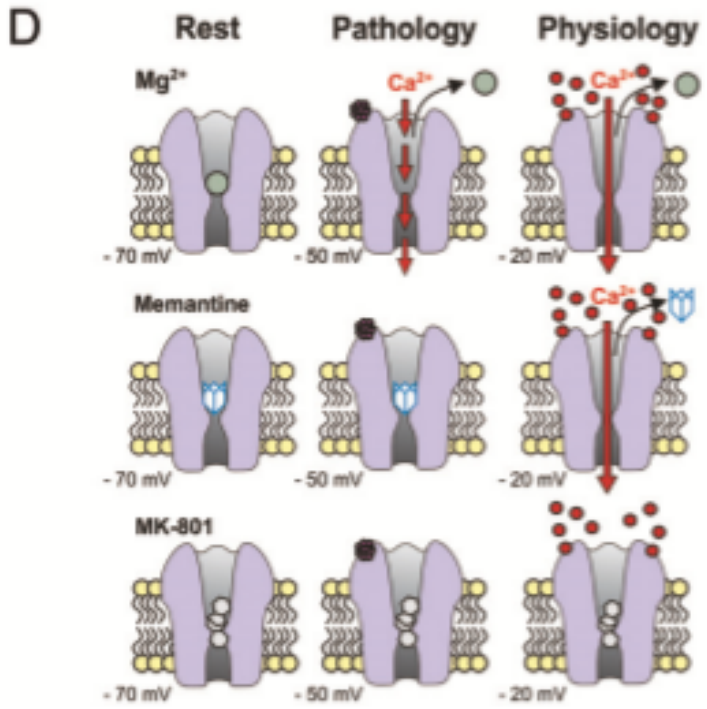
Alzheimer's dementia is a disease of cell death



How Memantine (Namenda) Works



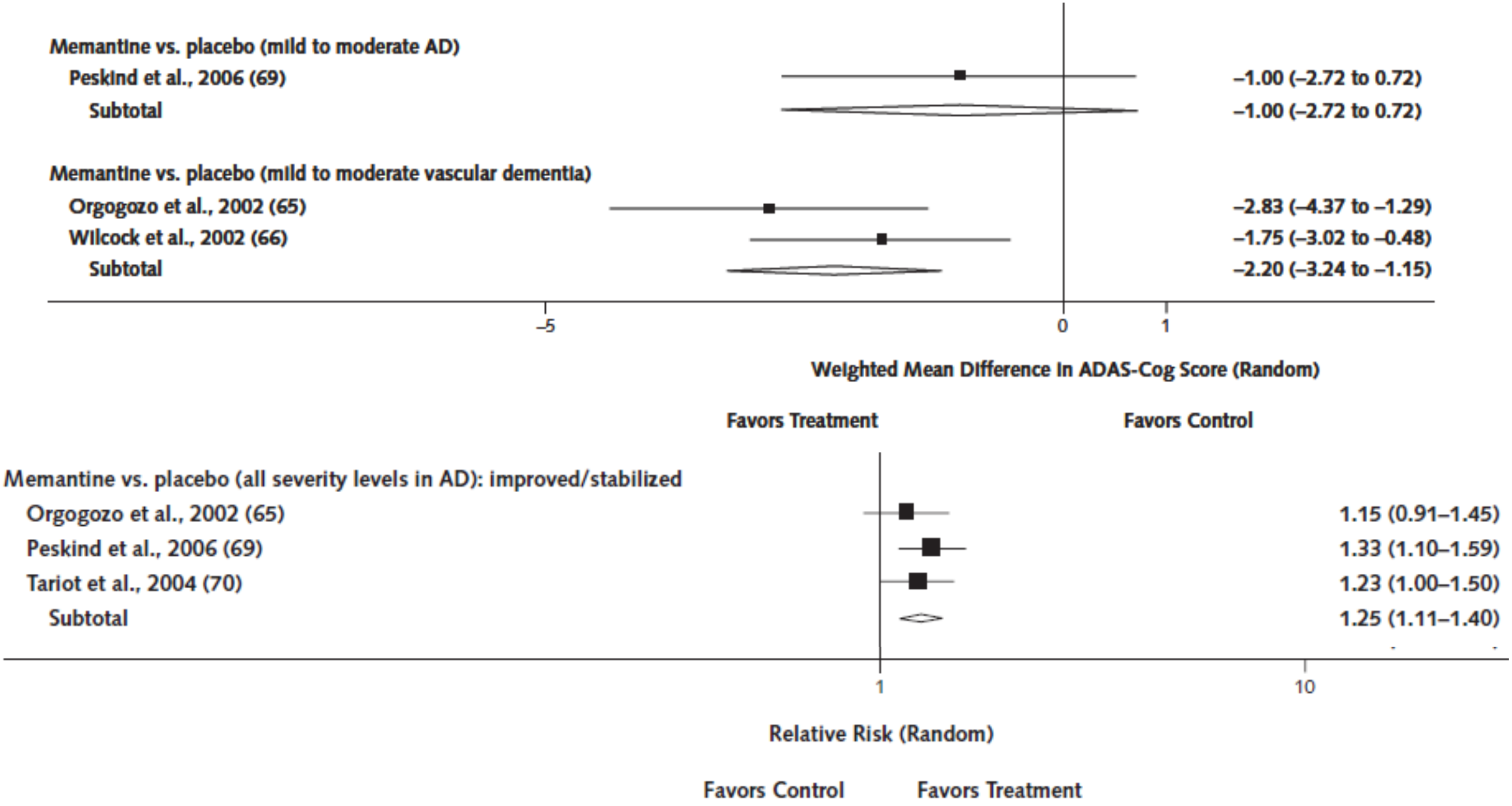

C
Alzheimer´s Disease + Memantine
"Rest"
Ca2+
Memantine
Restored memory formation
Rest
Ca2+
Ca2+
Signal detected
Modified from Danysz et al. (2000). Neurotoxicity Research, 2, 85-97


D
Rest
Pathology
Physiology
Mg2+
Ca2+
Ca2+
- 70 mV
- 50 mV
- 20 mV
Memantine
Ca2+
- 70 mV
- 50 mV
- 20 mV
MK-801
- 70 mV
- 50 mV
- 20 mV

Memantine (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

- 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.


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

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

- 2018 meta-analysis 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

Use of Medications for MCI

Cholinesterase Inhibitors and Memantine not approved for treatment of Mild Cognitive Impairment

Neutraceuticals

- To date, **no neutraceutical has been found to have clinical or statistical benefit** for dementia

Treatment strategies aimed at amyloid

- Aducanumab is an antibody that binds selectively to aggregates of amyloid beta protein and helps to remove them from the brain.
- Several other antibodies with similar actions are also in clinical trials, e.g., gantenerumab, lanenumab, donanemab.
- Antibodies like these are given intravenously, typically once per month.
- It is thought that starting treatment early may have a better chance of success

Aducanumab clinical trials

Study population
MCI or mild Alzheimer's
Amyloid positive by PET scan

Phase 1:
12 months treatment.
placebo, 1, 3, 6 and 10 mg/kg doses
N = 40 placebo and 30-32 per treatment group

extension or open label treatment

Phase 3:
2 identically designed trials, EMERGE and ENGAGE
3,000 patients, in 20 countries
18 months' treatment:
6 months of dose escalation, then dosing with placebo, 6 mg/kg or 10 mg/kg

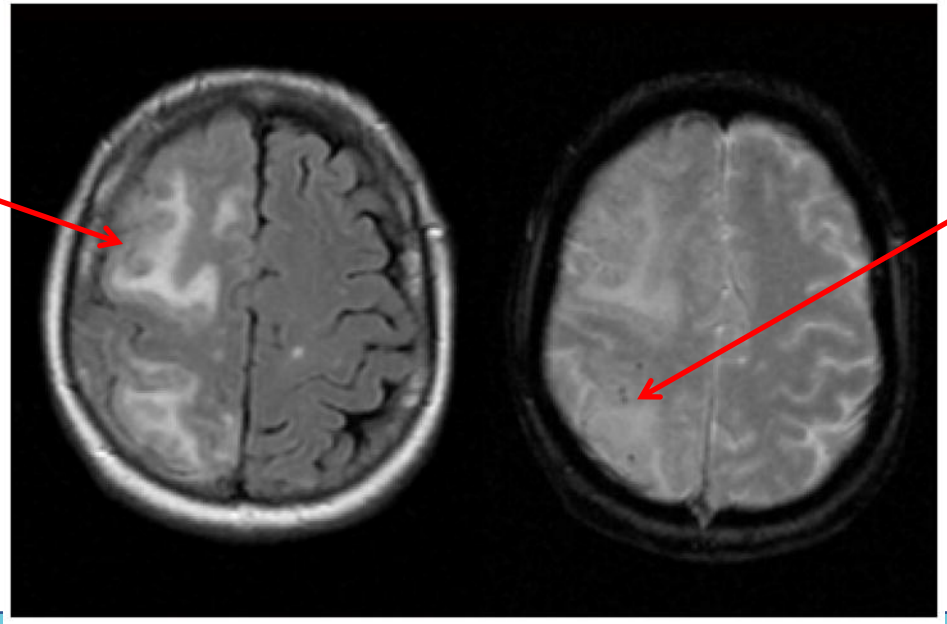
ARIA – Amyloid Related Imaging Abnormality

Amyloid can cause vascular damage, leading to hemorrhage (**ARIA-H**) or localized exudate (**ARIA-E**) with inflammation

This can occur spontaneously but is much more common when anti-amyloid antibodies are given, e.g. 41% for high dose (10 mg/kg) Aducanumab

Can be asymptomatic, or with symptoms such as headache, seizures, confusion or stroke-like symptoms

ARIA-E on T2 MRI



ARIA-H on GRE MRI

FDA accelerated / conditional approval

_____ RECENT MAJOR CHANGES _____

Indications and Usage (1) 7/2021

_____ INDICATIONS AND USAGE _____

ADUHELM is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with ADUHELM should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). (1)

Aducanumab Indications and Uses

- July 8, 2021 FDA revised approval for aducanumab: for the treatment of mild cognitive impairment due to Alzheimer's disease or mild dementia secondary to Alzheimer's disease.
- Titration is required for treatment initiation, with a recommended maintenance dose of 10 mg/kg via an hour-long infusion every month
- MRI required prior to the 7th and 12th infusions with advisement that the drug should be continued with caution if severe ARIA-H is observed only after a clinical evaluation is done and a follow-up MRI demonstrates stabilization with no change in size or number of ARIA-H
- Drug discontinuation also advised if a hypersensitivity reaction (angioedema or urticaria) develops

Amyloid Related Imaging Abnormalities

- Inform patients that ADUHELM may cause Amyloid Related Imaging Abnormalities or “ARIA”.
- ARIA most commonly presents as temporary swelling in areas of the brain that usually resolves over time.
- Some people may also have small spots of bleeding in or on the surface of the brain.
- Inform patients that most people with swelling in areas of the brain do not experience symptoms, however some people may experience symptoms such as headache, confusion, dizziness, vision changes or nausea.
- Instruct patients to notify their healthcare provider if these symptoms exist.

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

What IS Effective?

- Physical activity, particularly to reduce risk of falls
- Engaging in cognitively stimulating activities
  - Hobbies such as reading, book clubs, gardening, continuing education classes, learning a language, learning an instrument
- Social interaction and engagement
- Maintaining healthy, nutritious diet

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ChampionsforHealth.org/alzheimers

Website updated regularly with most current information

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