

Alzheimer's Disease Update

David S. Geldmacher, MD, FANA, FACP

Director, Division of Memory Disorders and Behavioral Neurology

UAB Department of Neurology

Disclosures

- Research funding (paid to UAB)
 - Biogen, Eisai, Genentech, Janssen, Lilly, NIH/NIA, and US Department of Defense
- Consulting fee (paid to speaker; all associated with Alzheimer's Disease and related disorders)
 - Eisai, Genentech, NFL Concussion Settlement Program, Premier Applied Science
- Off-label use
 - No medications are approved to treat noncognitive behavioral symptoms in dementia

Objectives

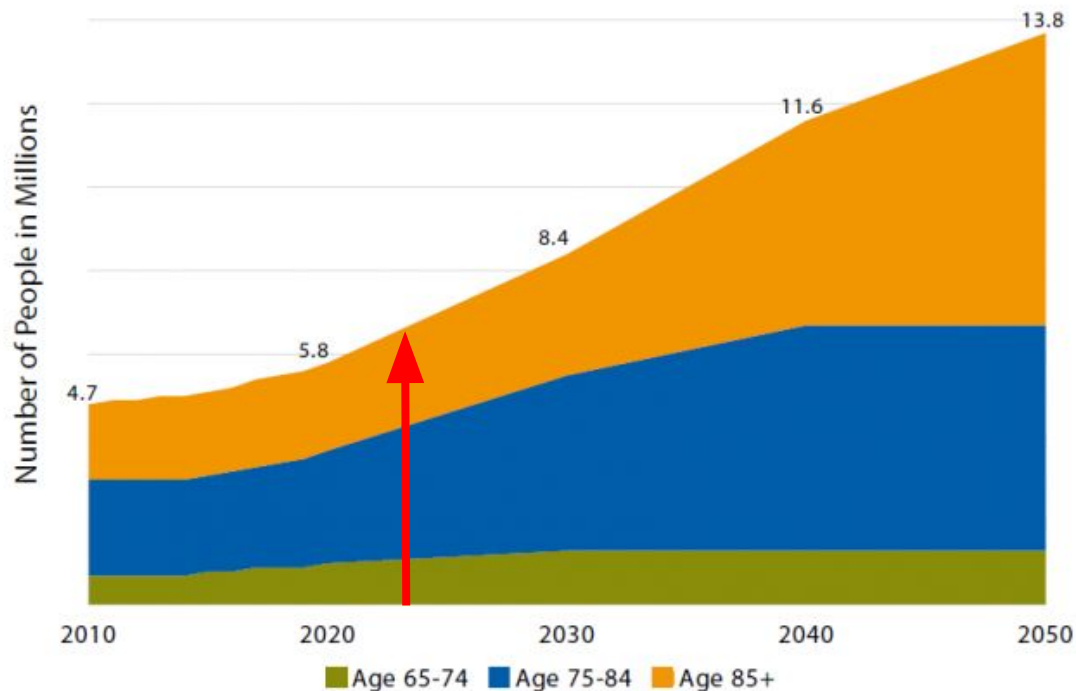
By the end of the session, the learner should be able to

1. Describe features that distinguish Alzheimer's disease from normal cognition
2. Implement use of screening tools to identify cognitive impairment
3. Discuss current understanding of the amyloid peptide in the pathophysiology of Alzheimer's disease
4. Discuss reasonable treatment expectations for people with Alzheimer's disease

So what's the big deal?
Why should I worry about Alzheimer's?

Alzheimer's Disease: The looming crisis

Projected Number of People Aged 65 or Older With Alzheimer's Disease, by Age Group, United States, 2010–2050



In 2022 >**500,000** new cases of AD are expected in the US

>**7,000** new cases projected in Alabama

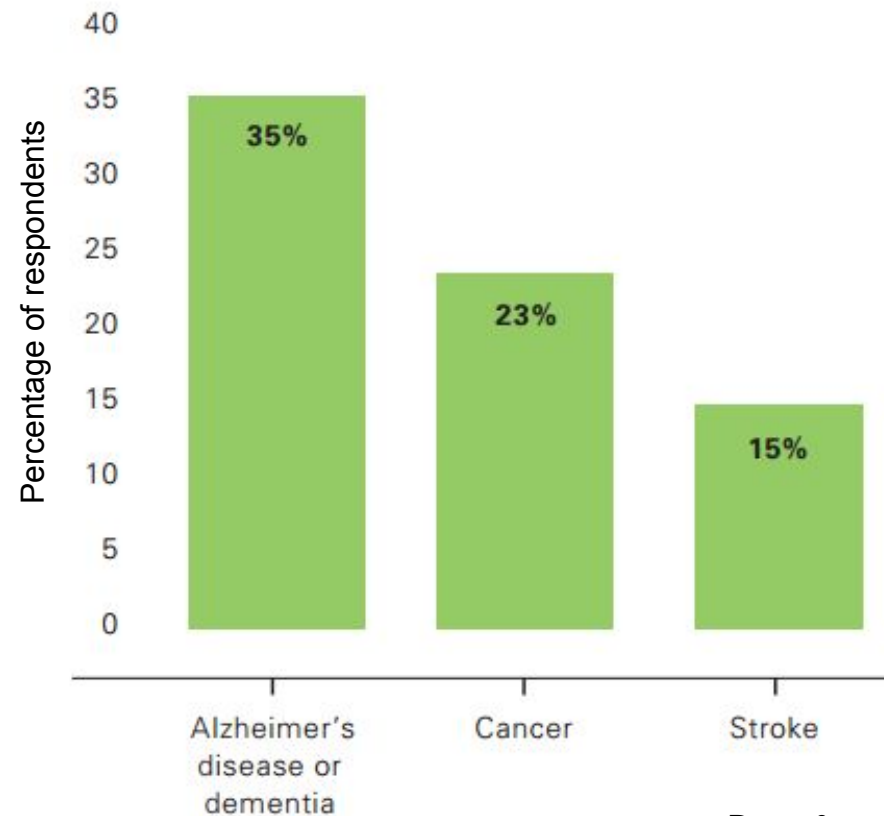
In perspective:

At its peak in 1993, the annual **nationwide** incidence of AIDS was ~20,000 cases

Source: Created from data in Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 Census. *Neurology*. 2013;80(19):1778–1783.

Alzheimer's disease in the public eye

“What disease do you fear most”



Data from YouGov survey, August 2013; US respondents over 60
Graphic from *2014 Alzheimer's Disease Facts and Figures*, Alzheimer's Association, Chicago

The Specialist Supply Problem: snapshot

- There were more players in the NBA (~450) than board-certified Behavioral Neurologists (406)
- 55 accredited fellowship slots in Behavioral Neurology
 - Only 28 fellows in training in 2020
- Projected any-specialist capacity is insufficient to handle the expected AD doubling of the case load by 2040
 - 7% growth in ALL neurologists, geriatricians, and geriatric psychiatrists

Inevitably, Primary Care Clinicians will take on larger roles in dementia diagnosis and management, or disease specific treatment will be delayed.

| Year | Neurologists | Geriatricians | Geriatric Psychiatrists |
|------|--------------|---------------|-------------------------|
| 2020 | 17,408 | 7,560 | 1,953 |
| 2030 | 18,654 | 8,363 | 1,659 |
| 2040 | 19,702 | 7,380 | 1,746 |

Aging vs. Disease

Case Study – Mr. B

- 79 year old man, concerned about his “short term memory”
 - Chronic memory changes, not clearly progressive
 - Not as fast to recall information, especially names
 - More frequently misplaces glasses, wallet, keys
 - No impact on his daily activities
 - Worried about getting dementia

PMH: Hypertension, High cholesterol

FH: Negative for dementia

SH: Married; no ETOH or tobacco use; Graduate-level education;
Continues work as a hospital chaplain

ROS:

- Tremor in his right hand: intermittent, most noticeable when eating
- Hearing impaired; doesn't like wearing hearing aids

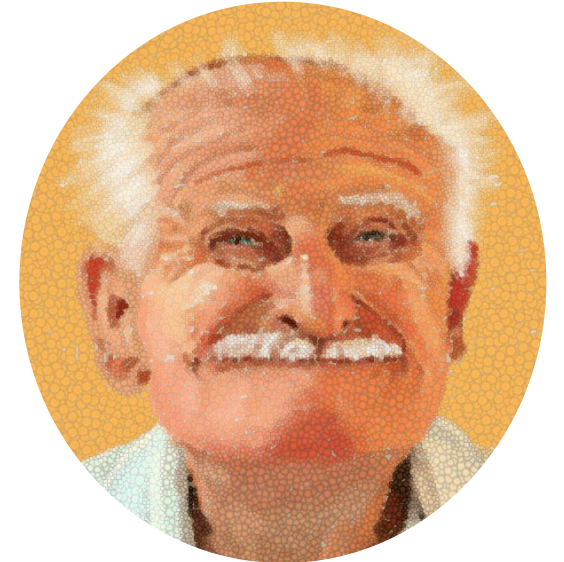
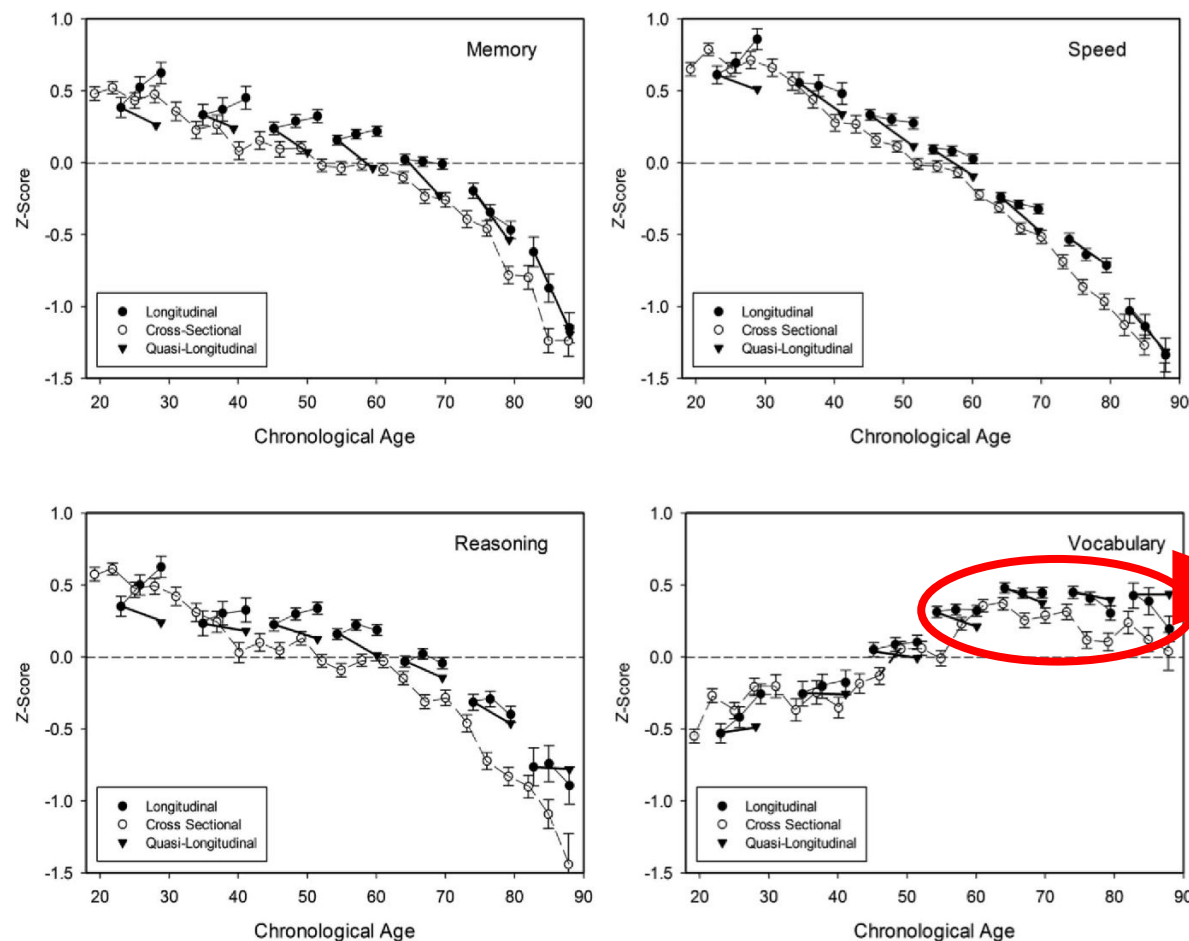


Image adapted from from: <https://arms.cgsociety.org/gb7c/old-man-smile-sketch>

Cognitive skills and psychomotor speed decline

Rapid decline after age 60



N=5,000: Cross-Sectional N=1,600 Longitudinal

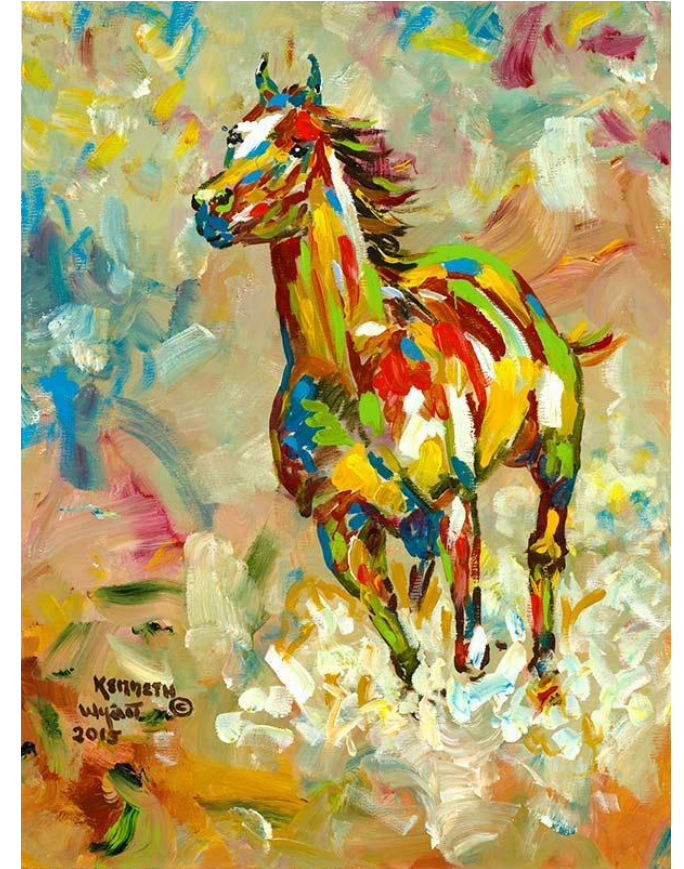
Other declines may be masked by retained verbal skills

Salthouse TA. Trajectories of normal cognitive aging. Psychol Aging. 2019 Feb;34(1):17-24

Short-term memory loss

*A horse of **many** colors*

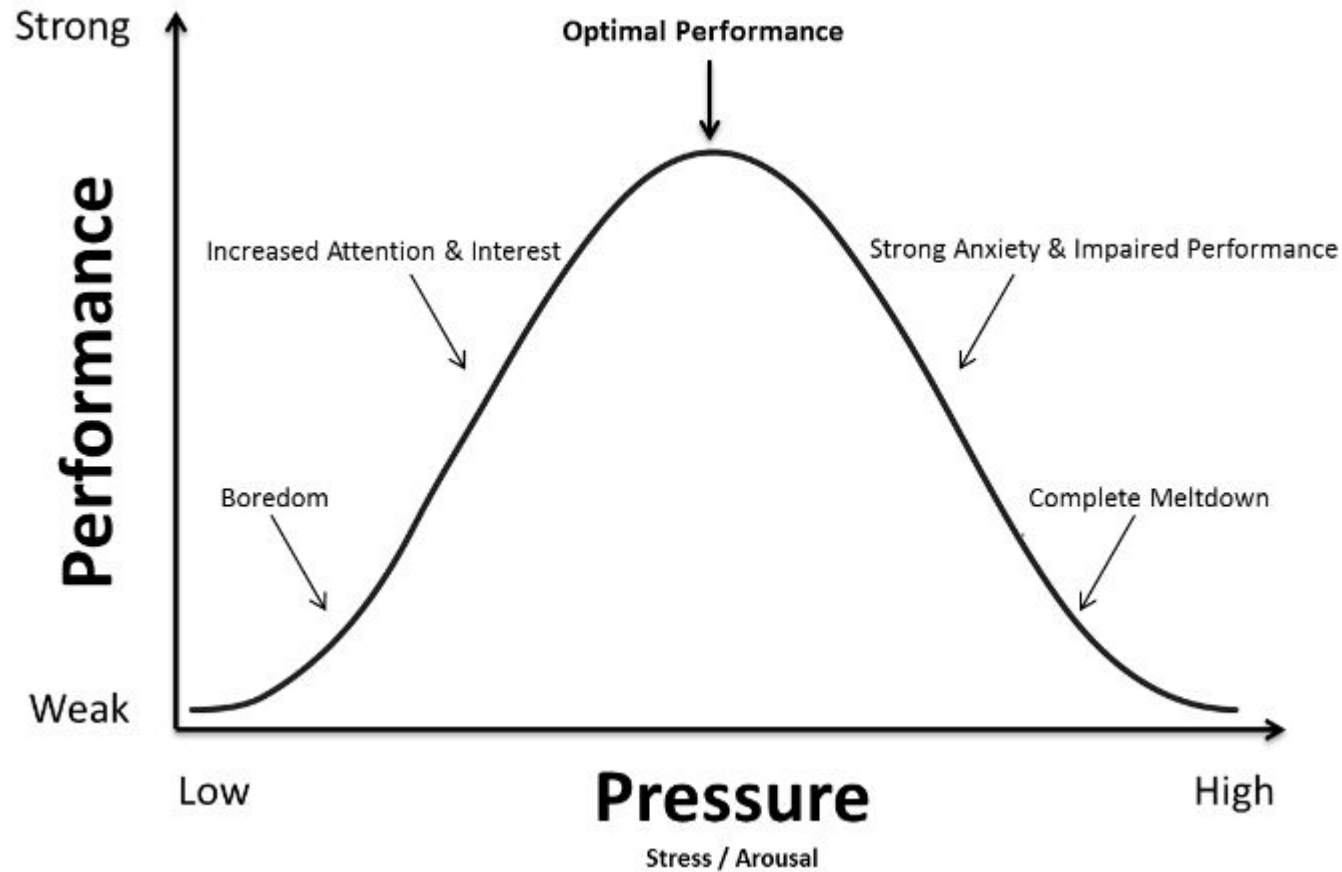
- Patients – and health care providers – often lump many problems together as “short term memory loss”
 - Distractibility
 - Slowed recall
 - Impaired word finding
 - Difficulty recalling names
 - Route finding problems
- Many of these patients do not need Memory Clinic, or even a neurologist



A horse of a different color
Kenneth Wyatt, 2015

Arousal-performance curve

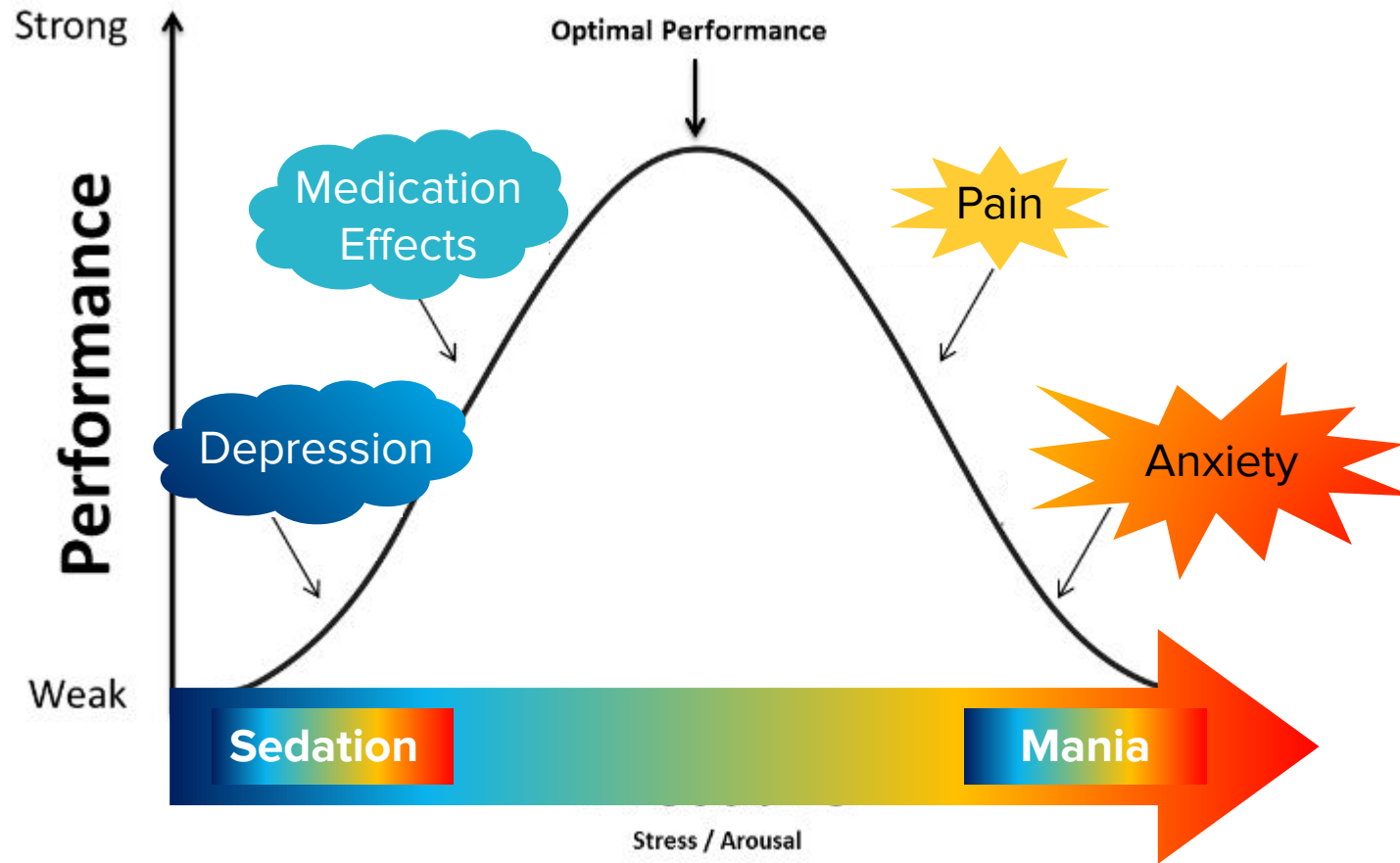
Yerkes-Dodson Law (1908)



<https://www.linkedin.com/pulse/inverted-u-model-our-daily-life-experience-ziya-ilkem-erogul>

Arousal-performance curve

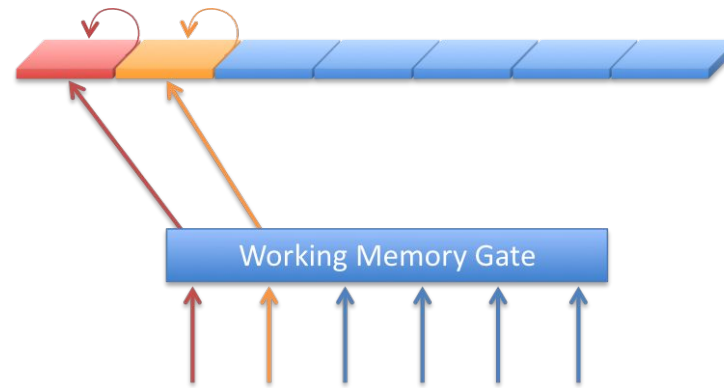
Yerkes-Dodson Law (1908)



<https://www.linkedin.com/pulse/inverted-u-model-our-daily-life-experience-ziya-ilkem-erogul>

Working Memory

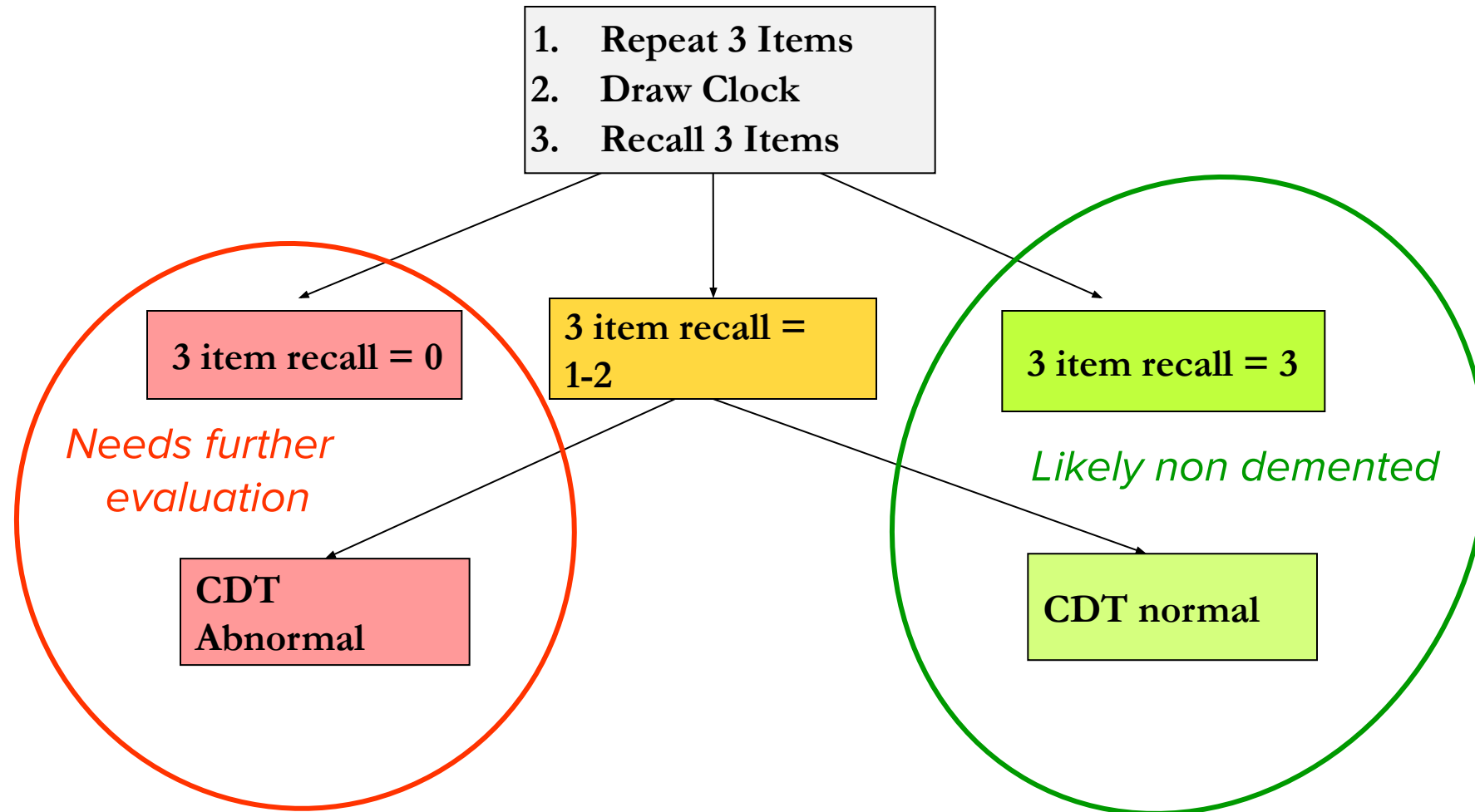
A limited capacity system



- Stimuli that occupy working memory reduce its capacity
 - Interferes with both memory formation and recall of information
- Stimuli that interrupt rehearsal reduce memory consolidation
 - e.g., Pain, Anxiety, Rumination, Sleep deprivation
- Most nonstructural causes of memory loss preferential affect working memory
 - Recall of participation is intact but details may be missing

A Practical Approach to Cognitive Assessment

Mini-Cog Screening Test



AD8 screening tool

- Informant scores of 2 or more suggest meaningful impairment
- Can be used for self-report
- More reliable with informant report
- Reliability further enhanced in combination with memory testing (e.g. Mini-cog)

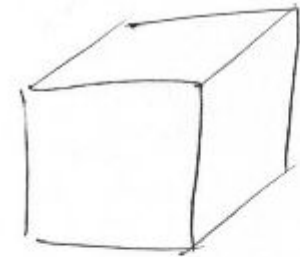
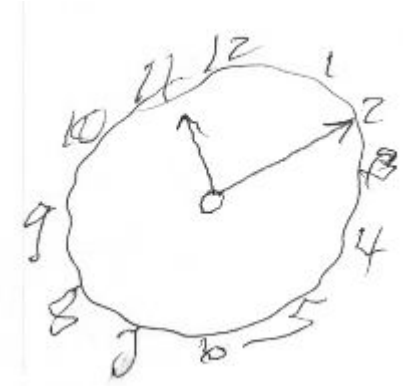
| Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems. | YES, A change | NO, No change | N/A, Don't know |
|--|------------------|------------------|--------------------|
| 1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking) | | | |
| 2. Less interest in hobbies/activities | | 1 | 0 |
| 3. Repeats the same things over and over (questions, stories, or statements) | | | |
| 4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control) | | | |
| 5. Forgets correct month or year | | | |
| 6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills) | | | |
| 7. Trouble remembering appointments | | | |
| 8. Daily problems with thinking and/or memory | | | |

Galvin JE, et al Neurology. 2005;65:559-64.

Case Study: Mr. B

UAB Memory Clinic Exam

- Mini Mental State Exam score: 29/30
 - Minor error in repetition of the phrase “no ifs, ands, or buts.”
 - Recalled 2/3 words quickly; the third was recalled slowly and effortfully.
- Rapid and accurate on test of attention, concentration, and calculation:
 - “Add up a penny, a dime, a nickel, and a quarter”
- Language:
 - Named low frequency items of clothing with 100% accuracy
 - E.g., lapel, cuff, heel
 - Easily repeated a syntactically complex two-step phrase,
 - “If she were here, I would go.”
- Intact visuospatial tests



Prompt



Patient Copy

Classifying Cognitive Impairments

Subjective Cognitive Decline (SCD)

Prevalence and relationship to disease

- 50-80% of people over age 70 have memory complaints but normal testing
- Most people don't decline, but (with 4 or more years of follow-up)
 - MCI emerges in 27%
 - Dementia occurs in 14%
- SCD precedes dementia by 10 years
- Some characteristics increase the risk for decline

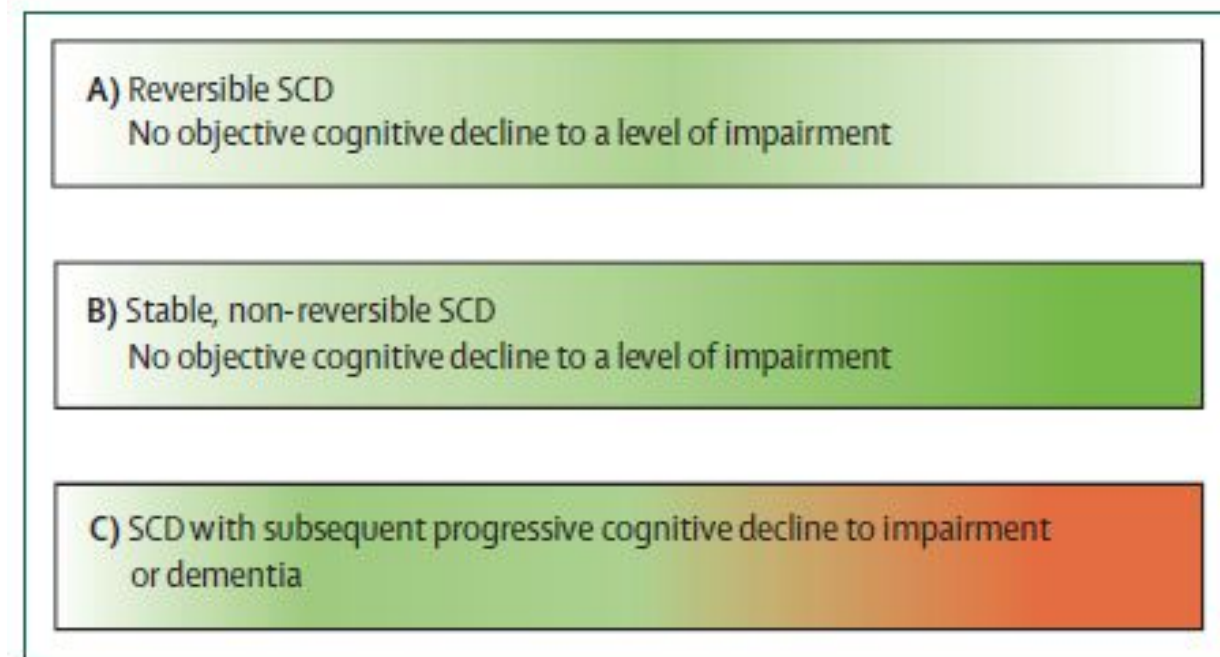


Figure 1: Schematic representation of trajectories of SCD and objective cognitive function over time

Features that increase risk for progression

Subjective Cognitive Decline to Mild Cognitive Impairment

- Subjective worsening over time
- Onset within 5 years
- Onset at age 60 or older
- Worry associated with memory symptoms
- Confirmation by an observer

Defining Subjective Cognitive Decline: Major features

- Self-experienced persistent decline in cognitive capacity unrelated to an acute event
 - Observation of decline by others is not required
- Normal performance on tests clinical testing
- Sometimes described as “*The Worried Well*”



Mild Cognitive Impairment

The front door to dementia

Clinical criteria for MCI

- Cognitive concern reflecting a change in cognition reported by patient or informant or clinician
- Objective impairment in ≥ 1 cognitive domain
 - Typically including memory
- Preservation of independence in functional abilities
 - *May have mild problems performing complex functional tasks (bill paying, meal prep, shopping)*
 - *May take more time, be less efficient, and make more errors*
- Not demented

Albert et al, Alzheimer's & Dementia 2011; 7:270-9
Morris JC , Arch Neurol 2012 Feb 6. [Epub ahead of print]

Case Study – Mr. B

- Stable on annual cognitive exams x 4 years
 - Alabama Brief Cognitive screener scores: 29, 27, 28, 28
 - Acute confusion, but no persistent cognitive losses with CABG after year 3
- No reported losses in daily function
- Missed annual follow-up at year 5 due to wife's illness
 - No make-up visit was scheduled
 - Wife died during year 6
- Family requests follow-up in year 8

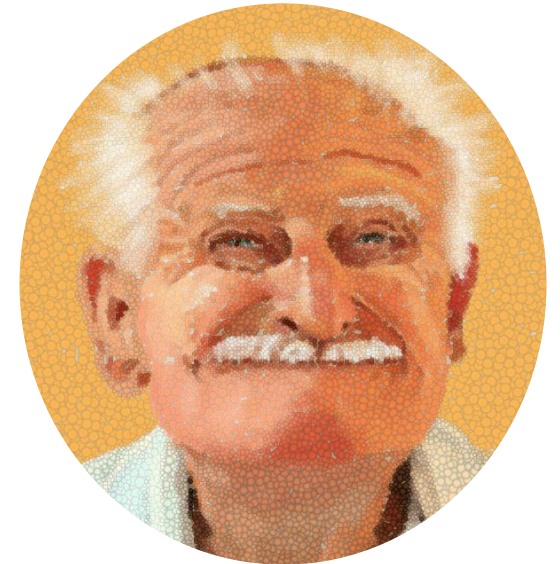
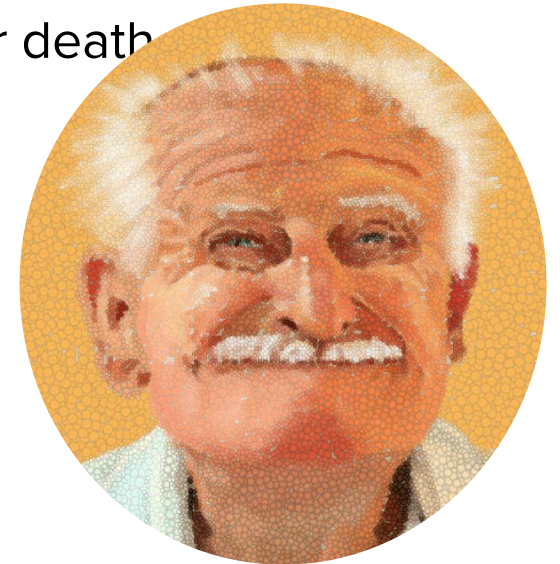


Image adapted from from: <https://arms.cgsociety.org/gb7c/old-man-smile-sketch>

Case Study – Mr. B

- Resumes follow-up at year 8
- Moved from family home to senior apartment
- Family has noticed much worse memory
 - Wife had hinted to daughters that he was struggling more prior to her death
 - Changes attributed to was stress/grief
- Decline is clearly progressive
 - Prominent word-finding difficulties
 - Has gotten lost while driving
 - Struggles with computer and smart phone
 - Now dependent for finances



Dementia

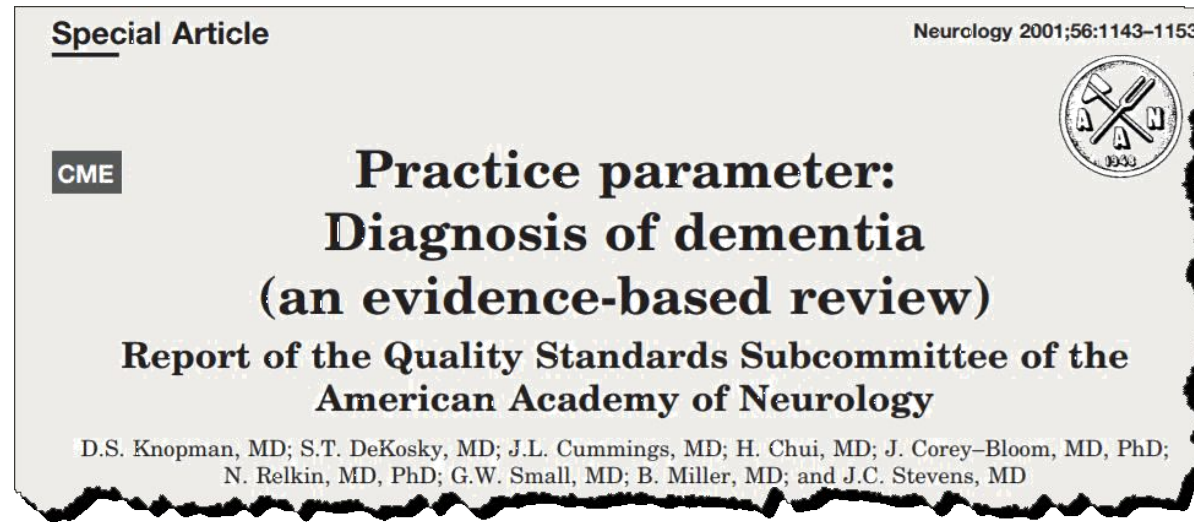
Defining Dementia

- Cognitive declines that interfere with usual activities
- Not resulting from delirium or psychiatric disorder
- Diagnosed by history and examination (not a test or score)
- Involves at least 2 cognitive domains:
 - Memory
 - Reasoning and judgment
 - Visuospatial
 - Language
 - Personality, behavior, comportment



Alzheimer's and Dementia, April 2011

Recommended Evaluation



- Screen for depression
- Cerebral Imaging
- Routine Labs
 - CBC, Chem 20, B12, Thyroid

Lab abnormalities account for fewer than 1% of dementia cases¹

1. Clarfeld AM *Arch Int Med* 2003;163:2219-29

Reversible Cognitive Impairment

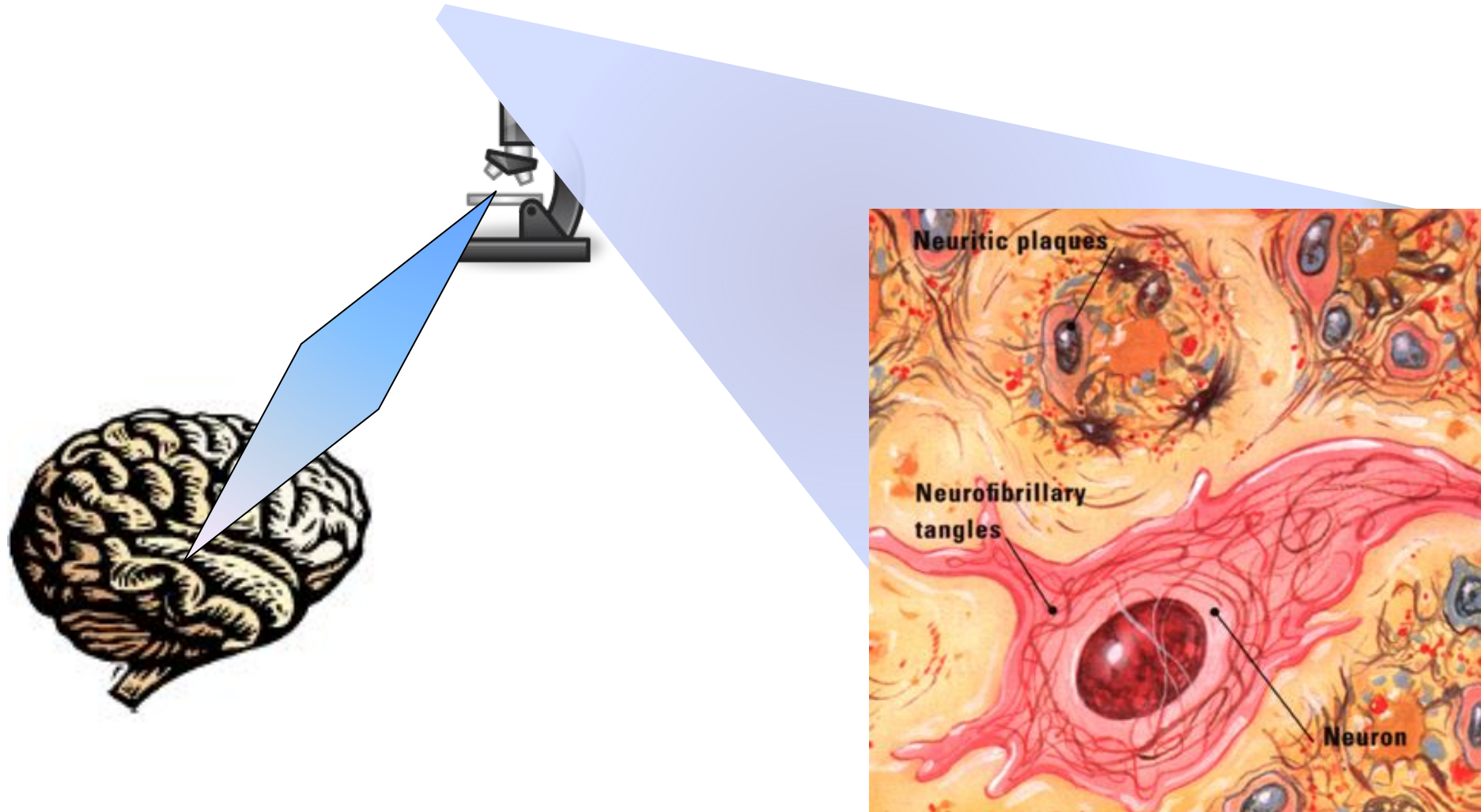
Additional Considerations

- Alcohol
- Anxiety
- Medications
 - Anticholinergics, opioids, benzodiazepines,
- Pain
- Sleep apnea and sleep disorders

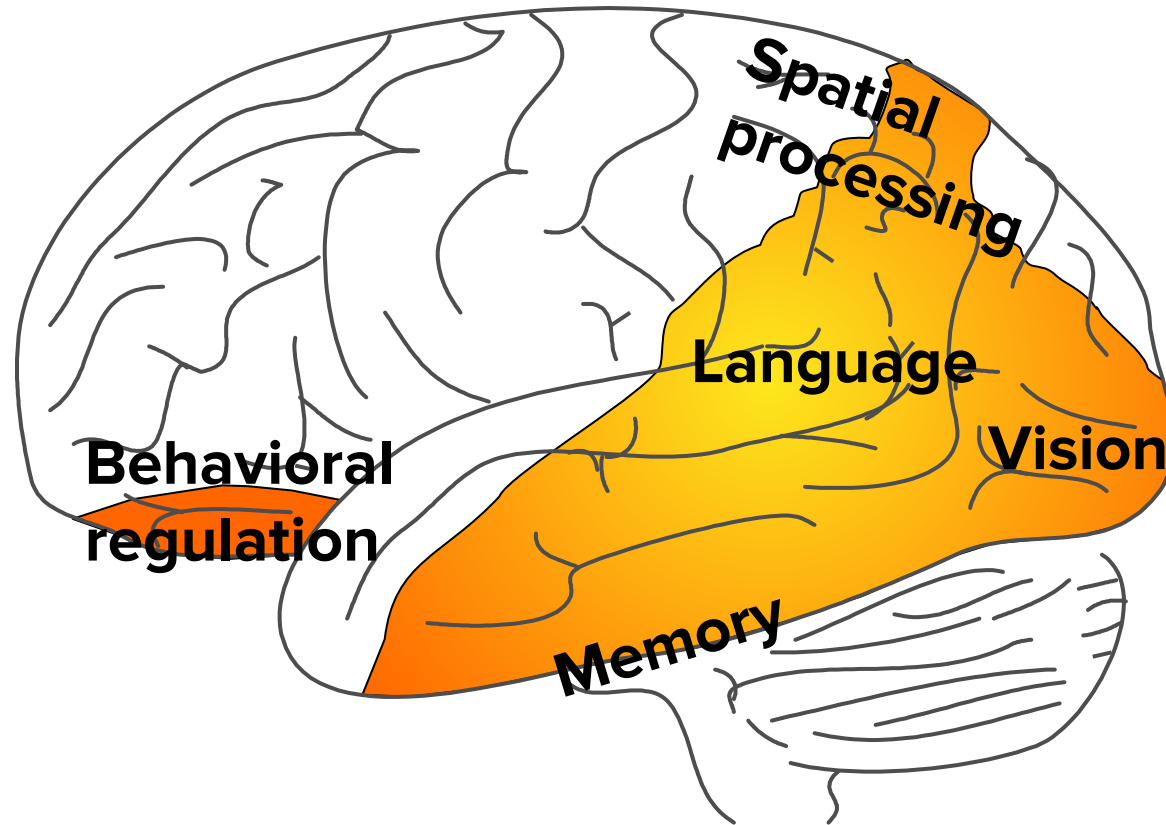
Alzheimer's disease

Alzheimer pathology

Under the microscope



AD Behavioral Pathology



■ = Regions of Highest Density Neurofibrillary Tangle Accumulation

The Straight A's of Alzheimer's disease

Recognizing AD's Core symptoms

- **Amnesia** for recent events and activities

- Supported by:

- **Anomia**
- **Apraxia**
- **Agnosia**

Not just conversations,
birthdays, and
appointments

Reduced function in
work or home roles

- Causing:

- **ADL losses**

- Masked by:

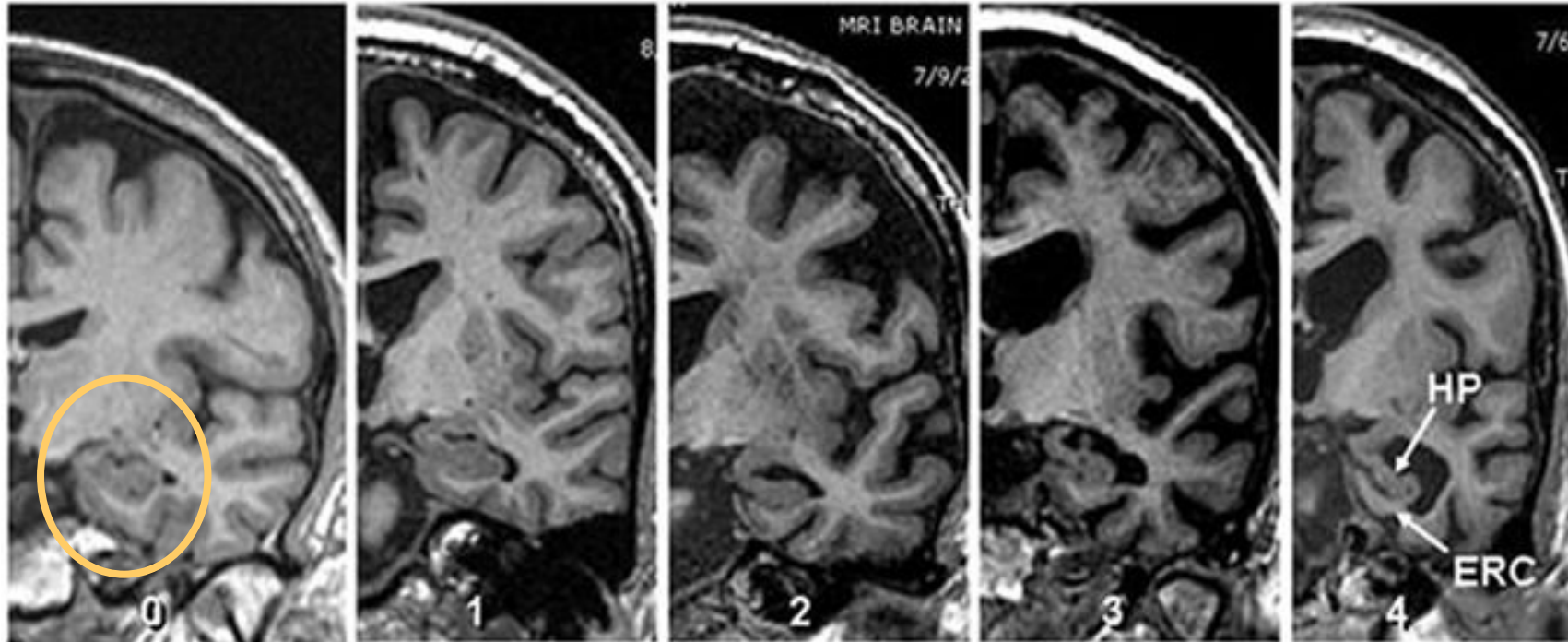
- **Anosognosia**
- **Apathy**

Low concerns or poor
insight about the
issues



Imaging characteristics of AD

Hippocampus and Entorhinal Atrophy



Duara R, et al *Front Aging Neurosci.* 2013;5:47

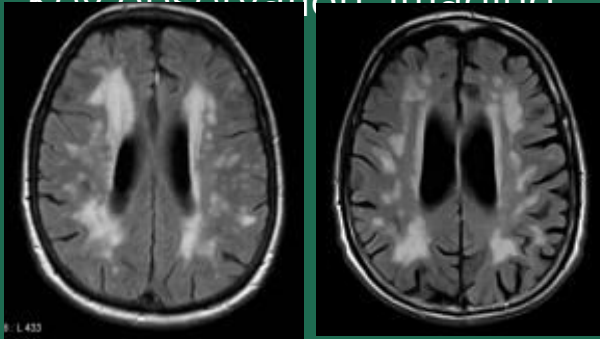
Non-Alzheimer dementia syndromes

Vascular Dementia

Related to ischemic brain changes

Both infarcts and non-infarction ischemic lesions

Key observation: Imaging

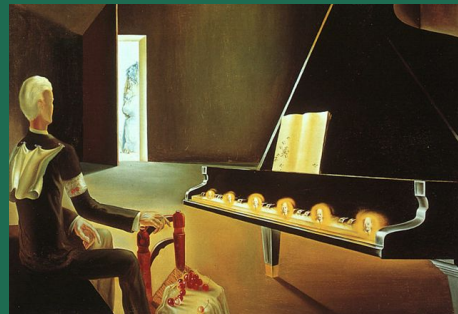


Lewy Body Dementia

Parkinson's pathology – cortical location

Prodromal REM sleep behavior disorder

Key observation: Early hallucinations

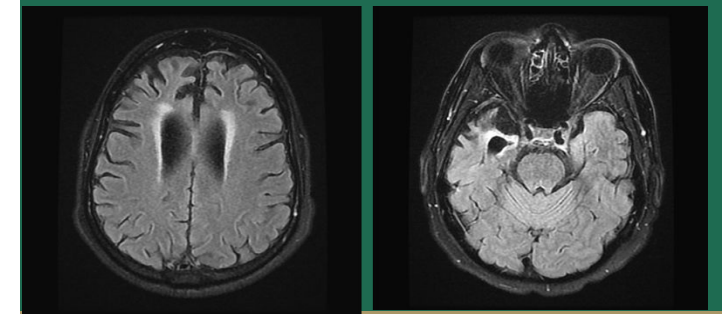


Behavior Variant Frontotemporal Dementia

Variable pathophysiology

Characterized by changes in social cognition

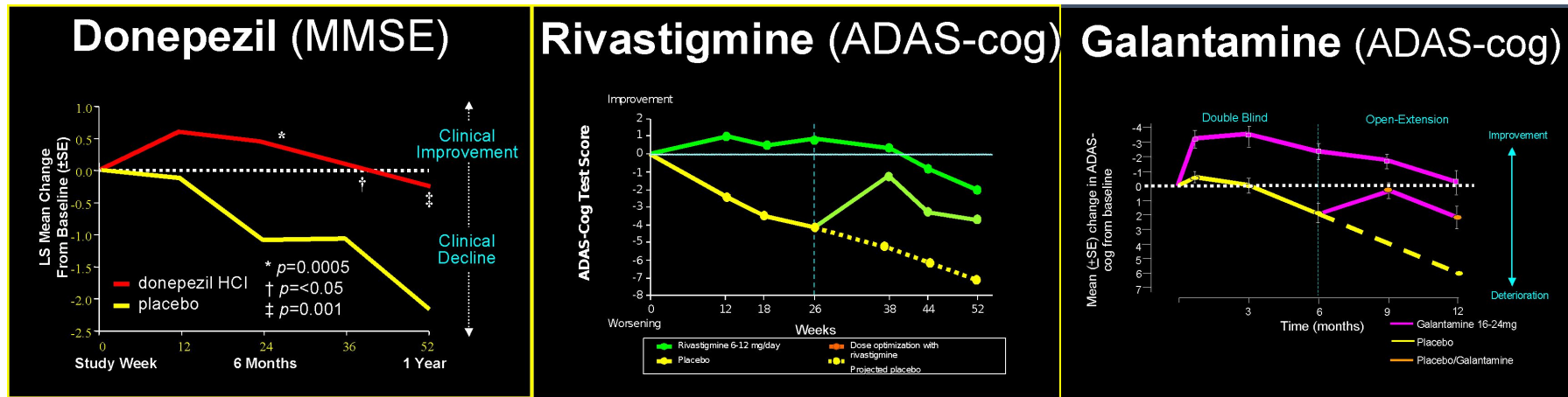
Key observation: Focal atrophy on imaging



Alzheimer Therapeutics in 2021

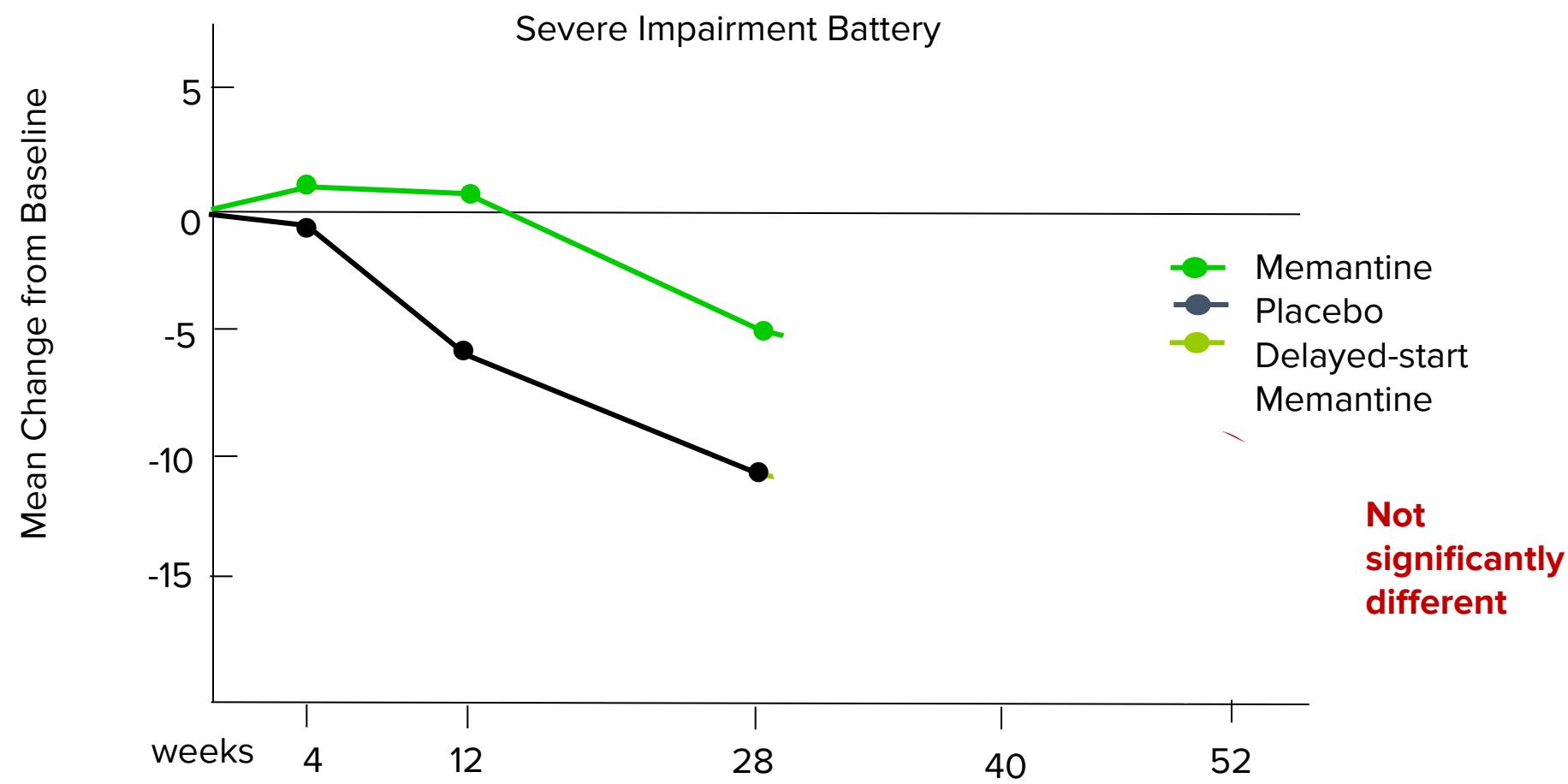
Cholinesterase Inhibitors

Stabilize cognition over one year



Among people with **mild and moderate AD**, treatment with any of the three drugs results in reduced loss of ability over one year.

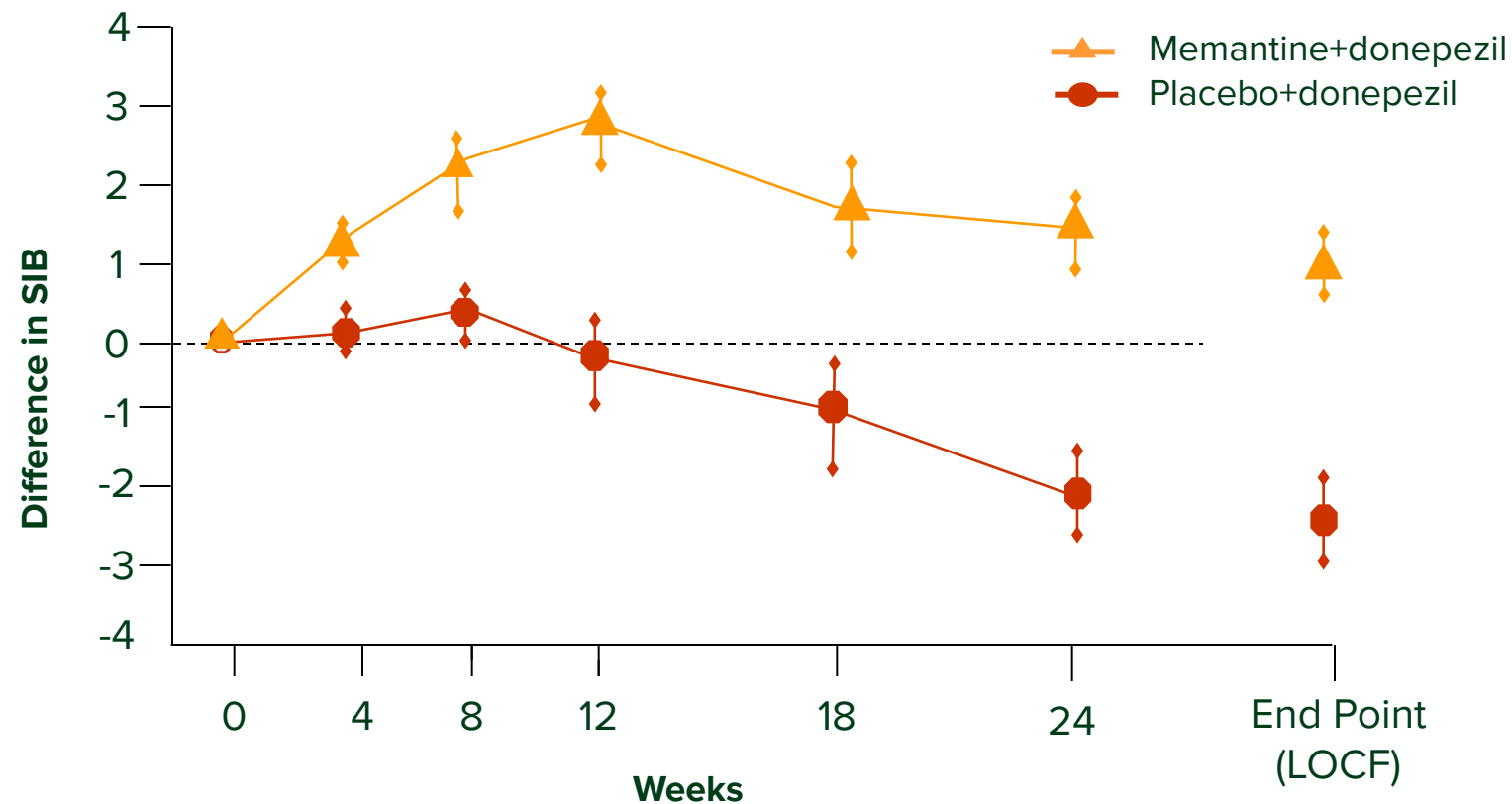
Memantine in Moderate-Severe AD



Observed Cases; Reisberg et al. *Arch Neurol.* 2006;63:49-54

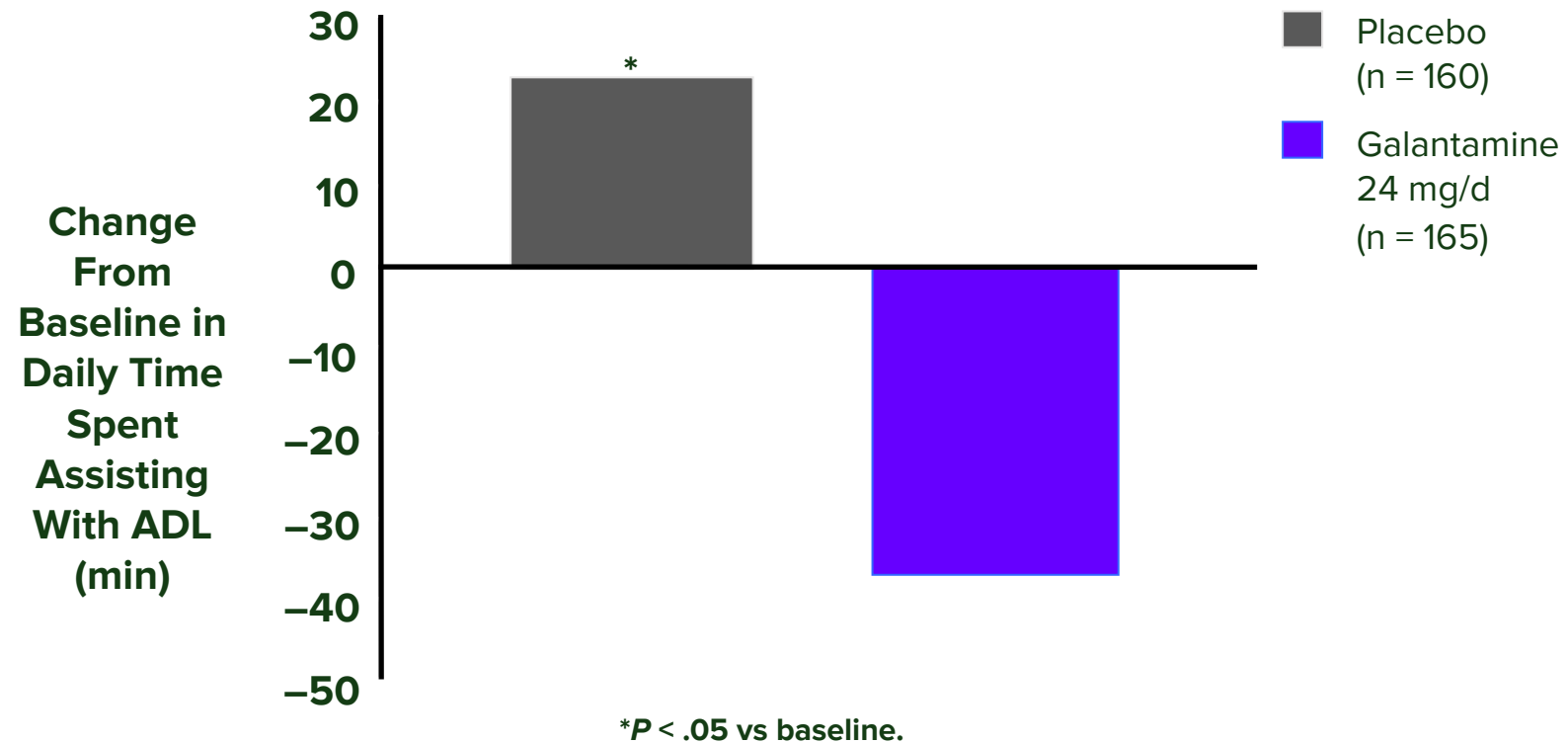
Combination Rx in Moderate-Severe AD

Memantine with Donepezil (cognitive)



Tariot et al. *JAMA*. 2004;291:317-324.

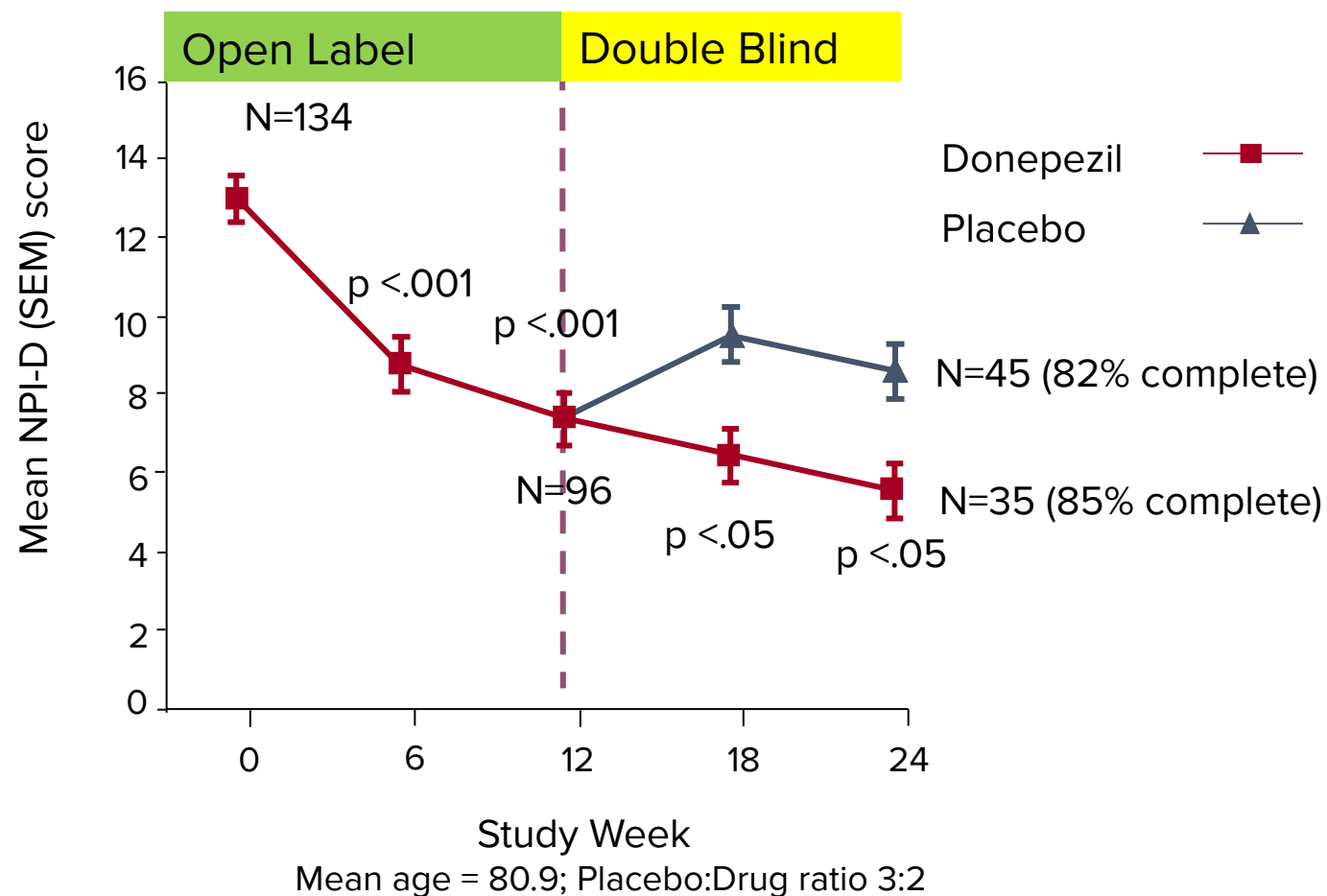
Drug Treatment Effects on Caregiver Time



Sano et al. *Int J Geriatr Psychiatry*. 2003;18:842-850

Drug Treatments and Caregiver Distress

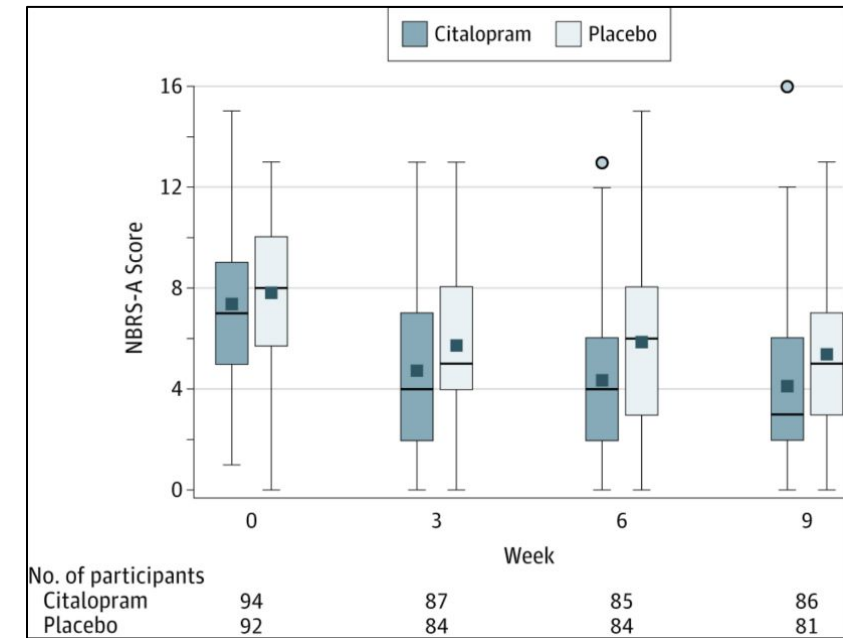
Behavioral Symptoms



Holmes et al. *Neurology*. 2004;63:214-219

Pharmacologic Treatment of Behavioral Symptoms

- For nonpsychotic agitation:
 - Citalopram is best supported by clinical trial data ¹
 - Reduction – not elimination – is typical
 - Arrhythmia concerns (\square QT_c) emerge over 30mg daily
- For psychosis
 - Treat distress, not the symptoms
 - Antipsychotics have limited overall efficacy for agitation ²
 - Antipsychotic use increases risk of death 1.6-1.7x (black box warning)

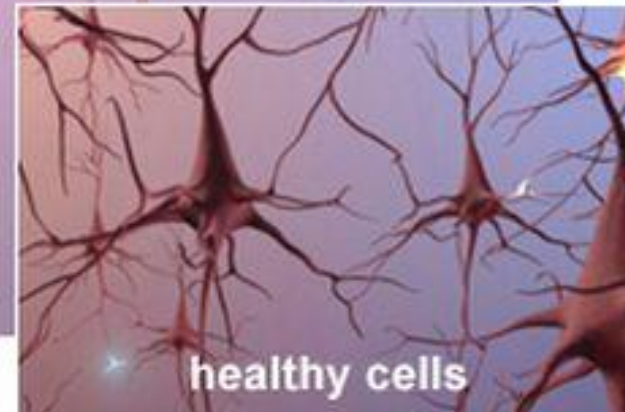
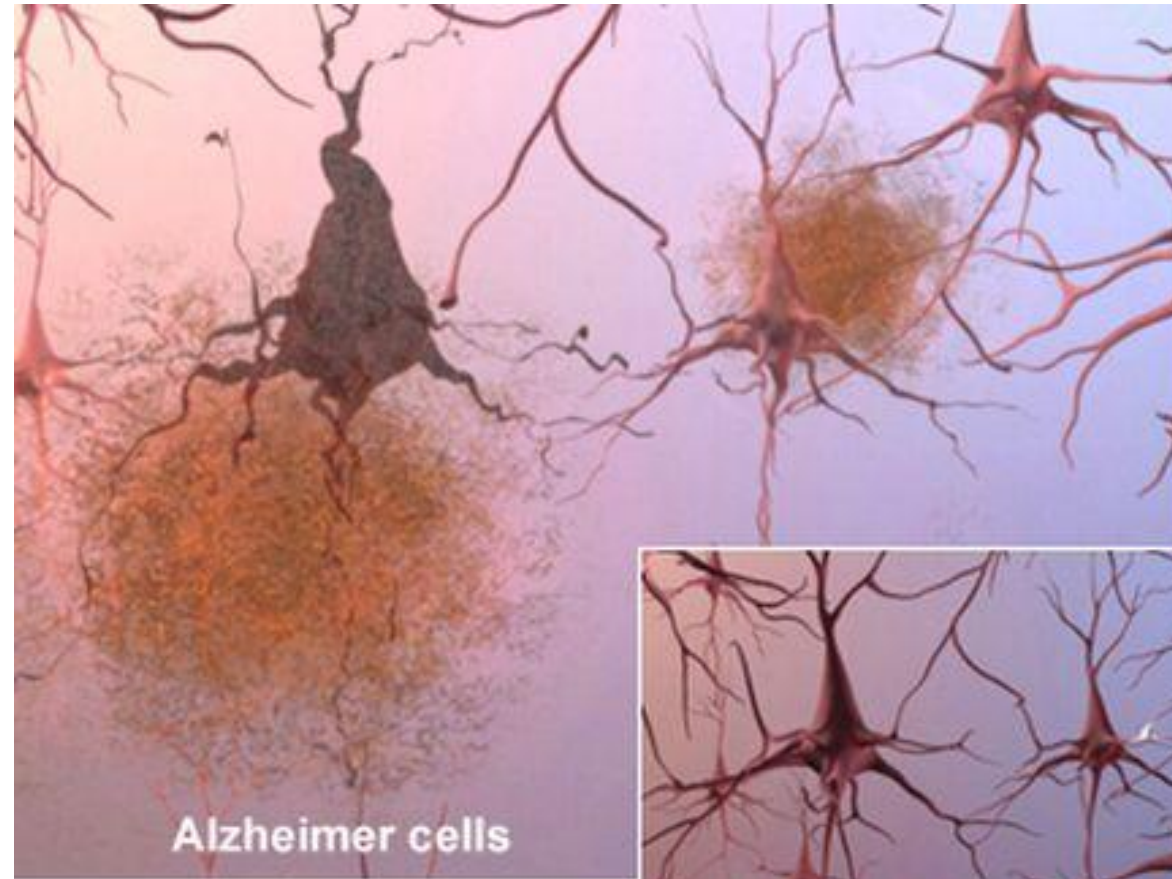
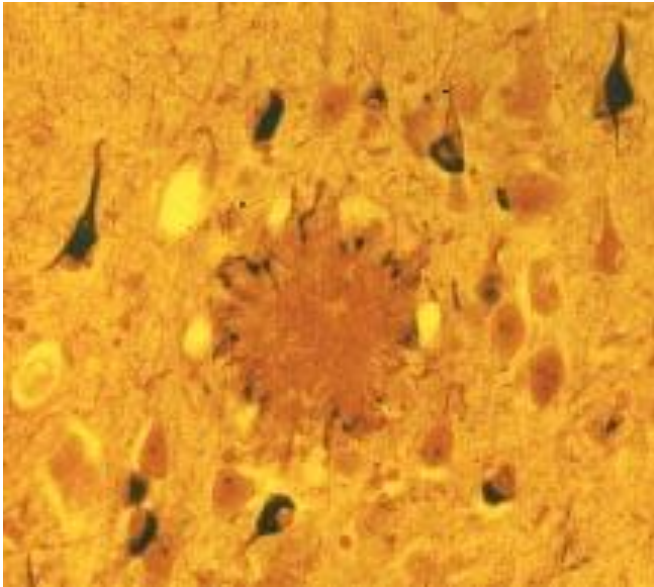


1. Porsteinsson A, et al *JAMA*. 2014;311(7):682-691. 2. Schneider LS, et al. *N Eng J Med*. 2006;355:1525-1538. 3. Schneider LS, et al. *JAMA* 2005;294:1934-43

The emergence of disease modifying therapies

Traditional view

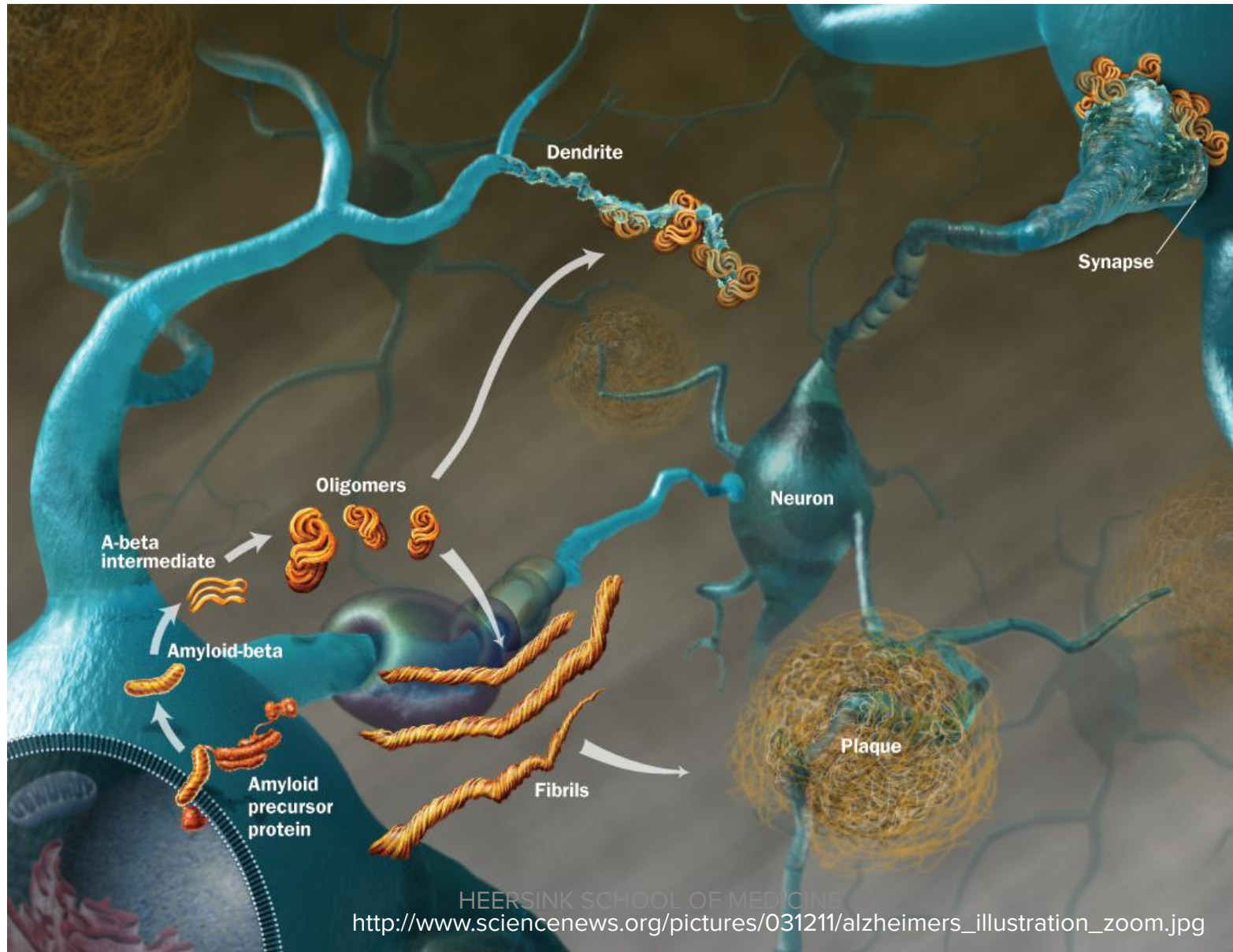
Amyloid plaque damages brain cells



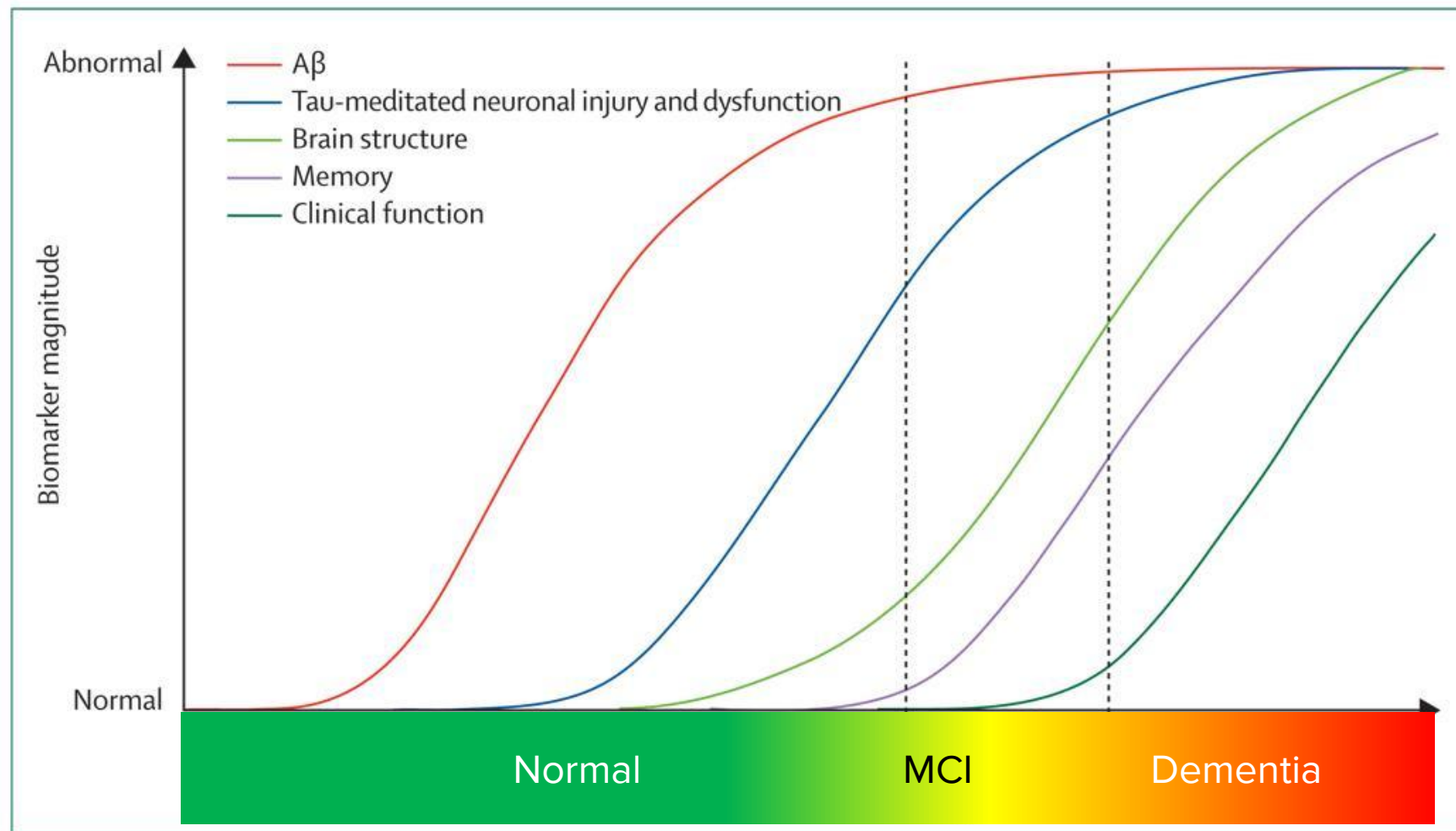
http://flippies.com/adflipoff/wp-content/plugins/RSSPoster_PRO/cache/5ccdd_cells.jpg

Newer view:

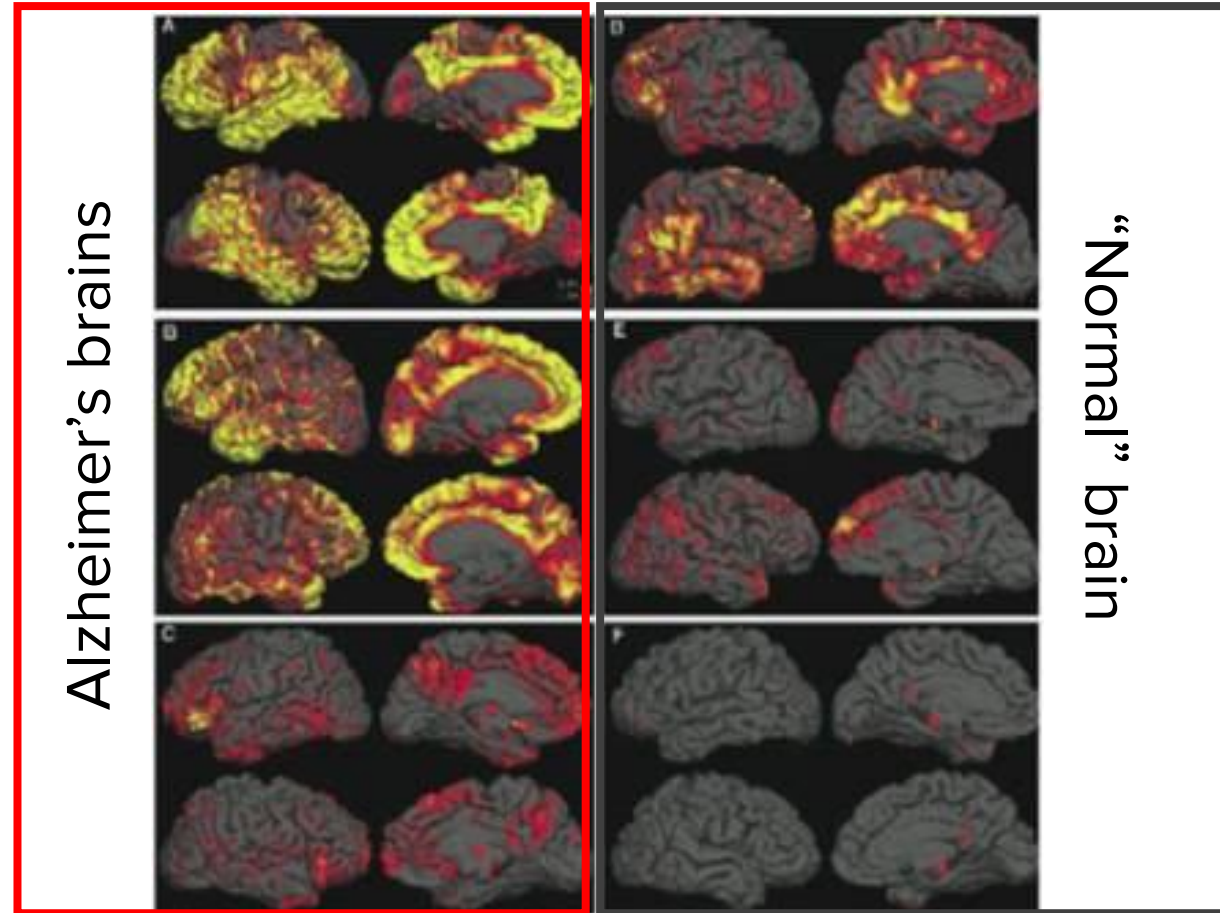
Amyloid damage begins **before** the plaque forms



Timing of Amyloid and Tau Pathology in AD



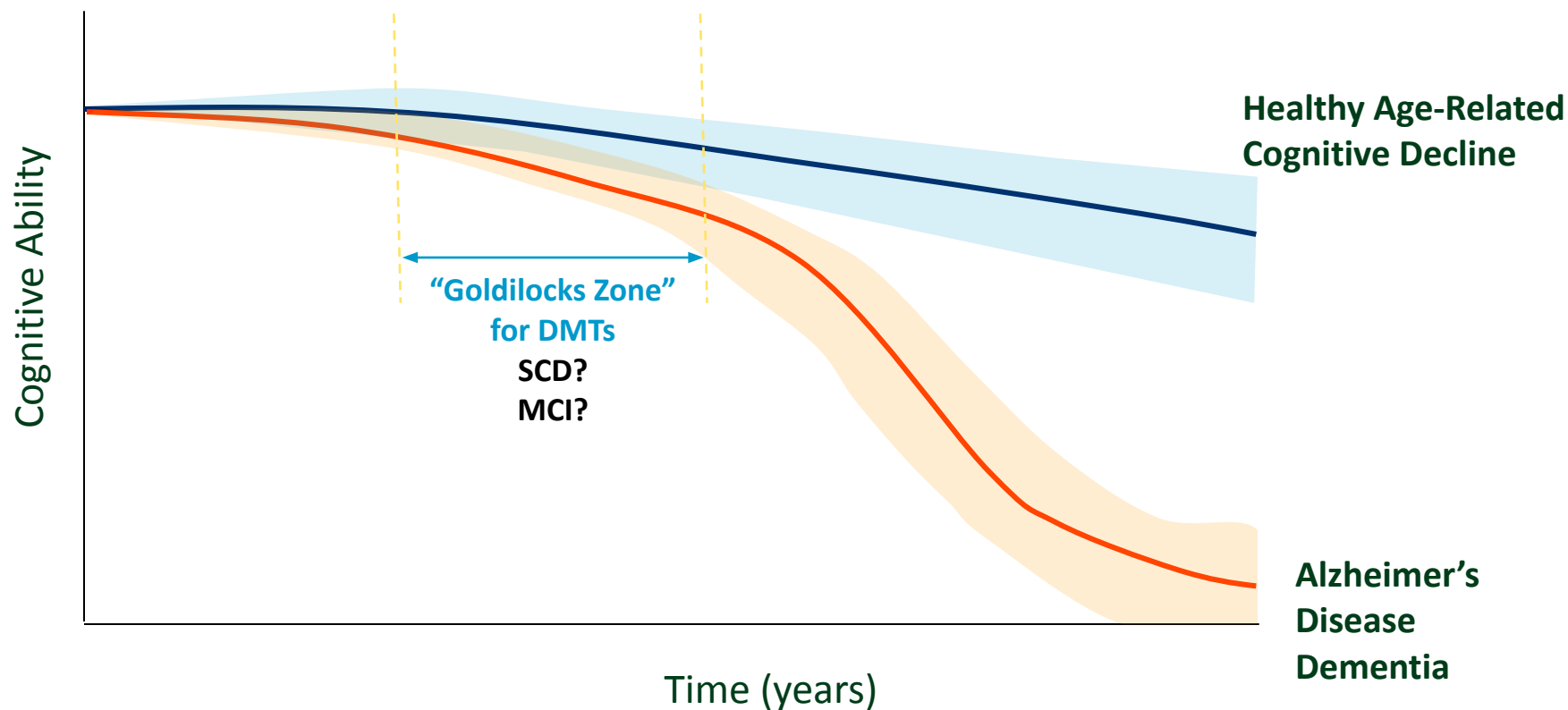
Evidence for A β pathology before symptoms



Sensitivity and specificity of new A β and tau PET agents remain unclear

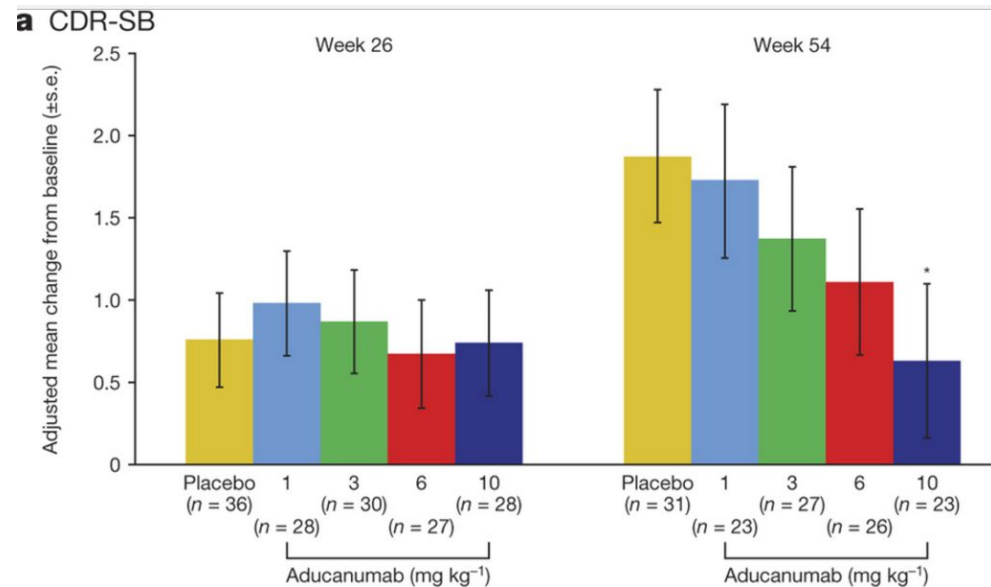
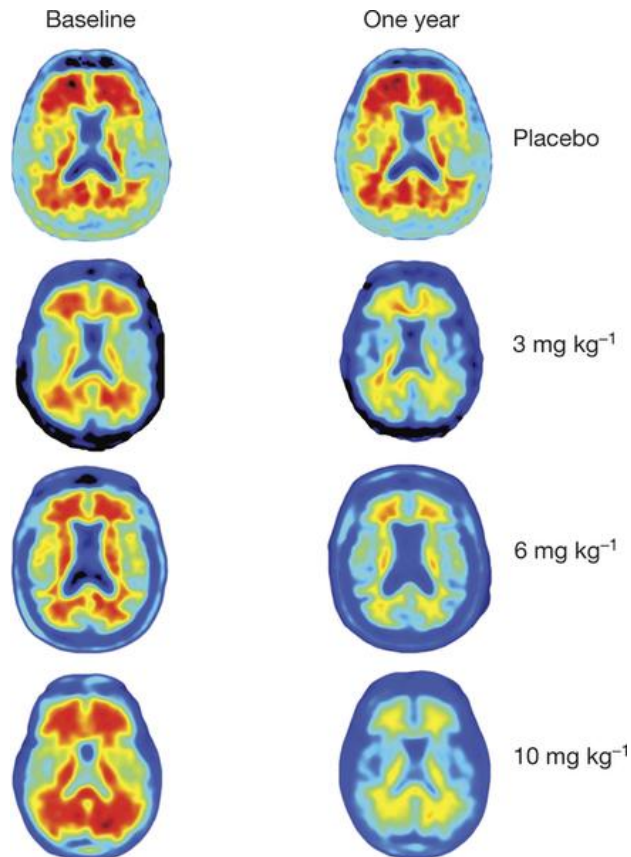
The challenge of early diagnosis

Subtly diverging clinical paths



Aducanumab Phase II data

Dose-response over time



Dose-response $P < 0.05$ at week 54 based on a linear contrast test

Dose-related response in early AD

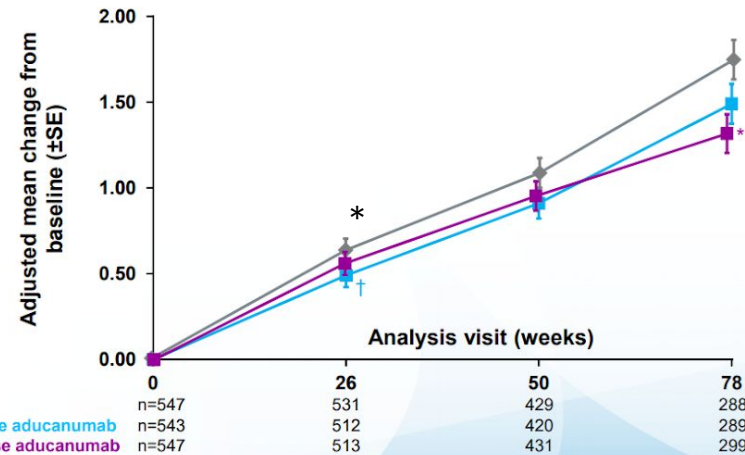


September 1, 2016

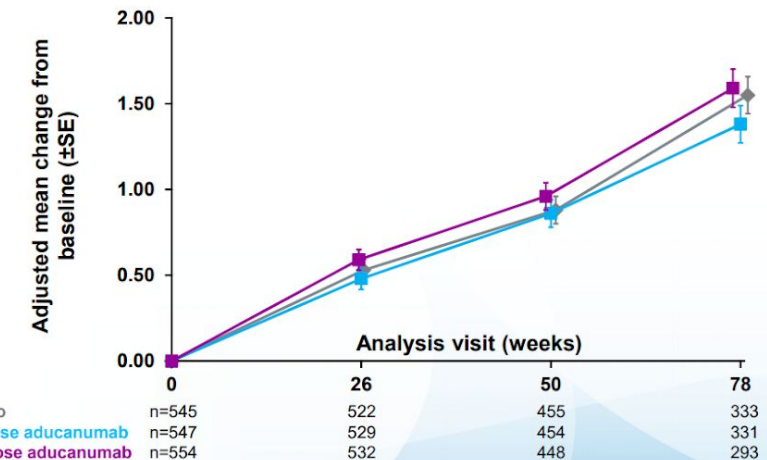
Aducanumab Phase III – primary data*

Overall Results (Global Function)

EMERGE: Longitudinal change from baseline in CDR-SB



ENGAGE: Longitudinal change from baseline in CDR-SB



ITT population. *p < 0.05, †p < 0.1 and ‡p < 0.05 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status. ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating-Sum of Boxes; ITT, intent to treat; MMRM, mixed model for repeated measure; MMSE, Mini Mental State Examination; SE, standard error.

ITT population. Values at each time point were based on an MMRM model, with change from baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status. ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating-Sum of Boxes; ITT, intent to treat; MMRM, mixed model for repeated measure; MMSE, Mini Mental State Examination; SE, standard error.

<https://www.evaluate.com/vantage/articles/news/trial-results/biogen-stacks-deck-path-forward-no-clearer-alzheimers>

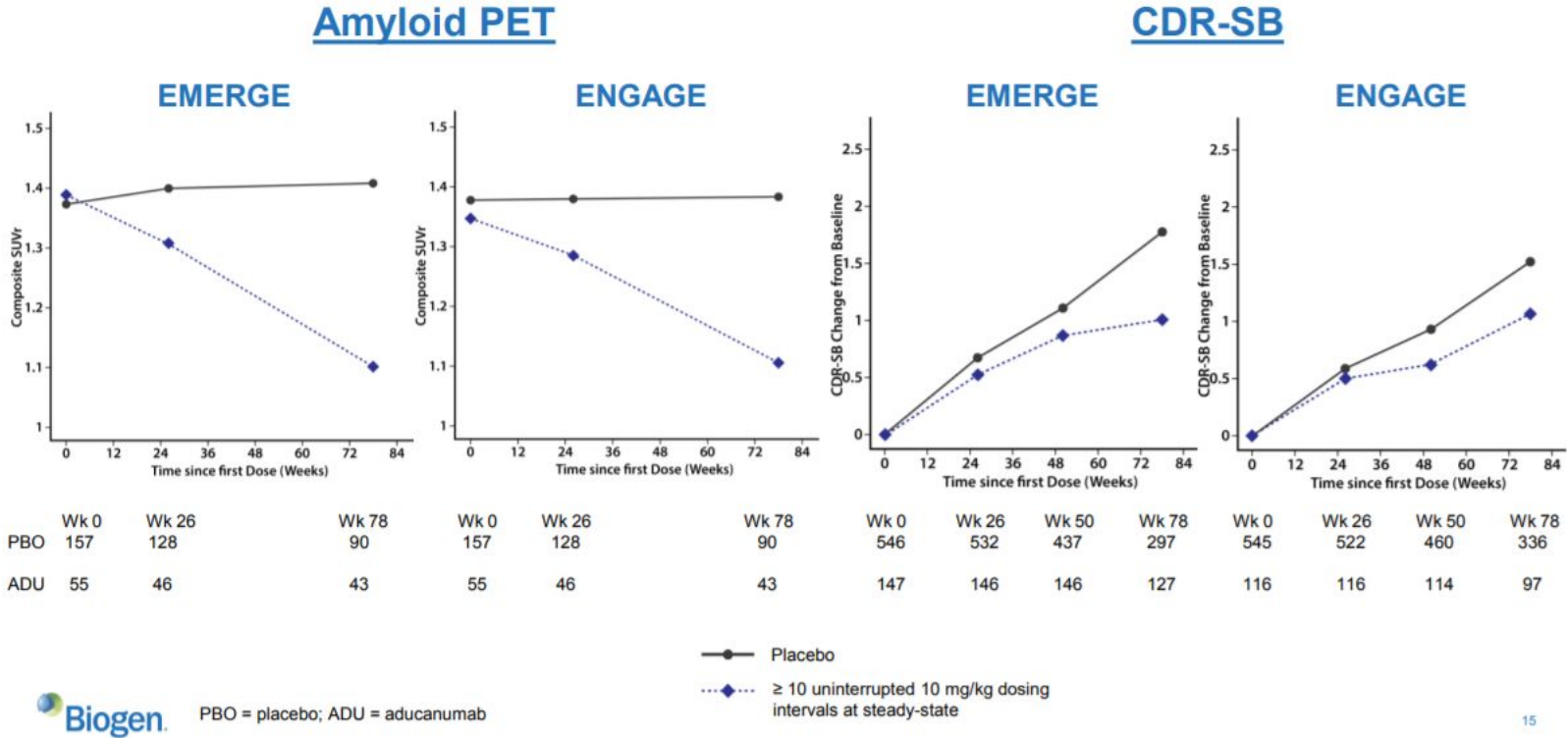
* Biogen proprietary data obtained from public sources; reproduced under Fair Use doctrine

Aducanumab Phase III post hoc analysis*

Efficacy suggested by high-dose exposure

ENGAGE consistent with EMERGE in subset of patients with sufficient exposure to 10 mg/kg aducanumab

High Dose Group



15

* Biogen proprietary data obtained from public sources; reproduced under Fair Use doctrine

Treatment landscape

Aducanumab (*Aduhelm*)

- CMS has started the NCD process for “*Aduhelm*,” final decision in March 2022
- Some payers have indicated willingness to pay under new label (including Cigna)¹
- “Appropriate Use” paper has been published (Cummings JL et al, 2021)
 - Other guidance statements in process
- “On behalf of those impacted by Alzheimer's disease, the *Alzheimer's Association* enthusiastically welcomes today's historic FDA approval of aducanumab (Biogen/Eisai) for treatment of Alzheimer's disease”
- Four anti-amyloid antibodies have been granted “Breakthrough Therapy” status
 - Allows “Accelerated Approval”

Summary

- Cognitive impairments frequently emerge in aging
 - Memory lapses are often related to “software issues”
 - Meds, Mood, Pain Sleep
- “Dementia” is a statement of severity not cause
- Alzheimer’s disease is a frequent cause of MCI and dementia
- Commonly used medications typically delay decline
 - Benefits from cholinesterase inhibitors appear more prolonged than memantine
 - Treatments have positive impacts on caregivers
- Alzheimer pathology predates cognitive symptoms
 - Disease modifying therapies are becoming available

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