

Cognitive Decline: Memory Loss, Alzheimer's, & Dementia - Update 2017



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Disclosures

- Royalties from Publishing for
 - Memory Loss, Alzheimer's Disease, and Dementia: A Practical Guide for Clinicians, 2016 (Elsevier)
 - Seven Steps to Managing Your Memory: What's Normal, What's Not, and What to Do About It, 2017 (Oxford University Press)
- Consultant/speaker for General Electric, Lilly, Axovant
- Clinical trial investigator for Biogen, Lilly, vTv therapeutics, Axovant

Learning Objectives

- Using the NIA-AA &/or DSM-5 Criteria, diagnose
 - Alzheimer's disease (AD) &
 - Mild Cognitive Impairment (MCI) due to AD
- Obtain biomarkers when helpful
- Treat Alzheimer's disease
- Diagnose Chronic Traumatic Encephalopathy
- Diagnose & treat other common dementias
- Use Dextromethorphan / Quinidine sulfate
- Manage issues of driving and agitation

Dementia: Prevalence

- Increases geometrically with age
- 5-10% of individuals > age 65
- 50% of those > age 85
- Alzheimer's disease most common—about 7/10 patients

Patient 1

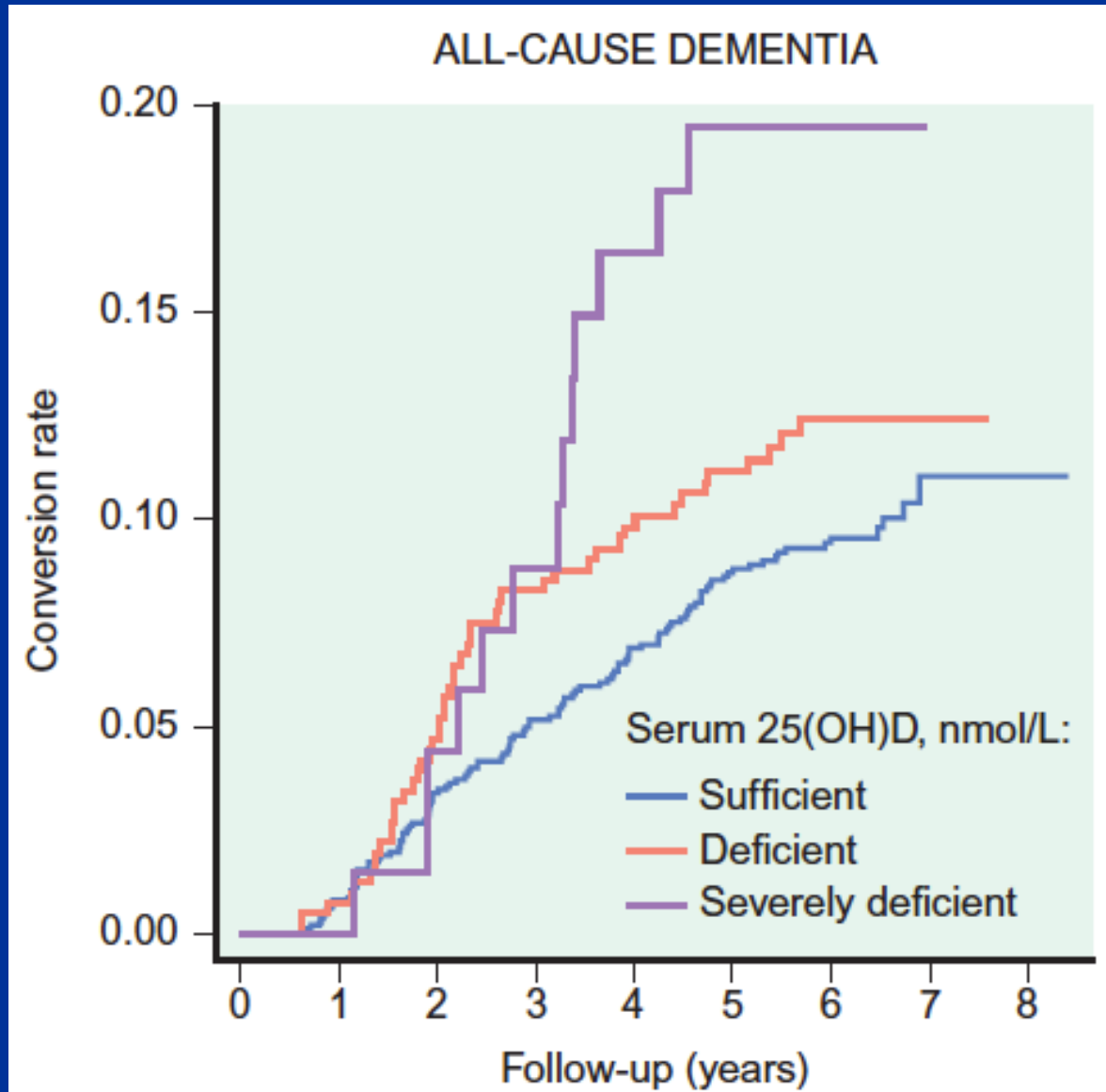
- 81 M with memory difficulties.
- 8 years ago got lost, asked the same questions repeatedly.
- Gradual worsening, last 6-12 mos unable to learn new information
- Prominent word finding difficulties
- Remembers everything about his days during WWII

Alzheimer's disease

Diagnosis: What's new?

- New NIA-AA & DSM-5 Diagnostic Criteria:
 - Dementia / Major Neurocognitive Disorder
 - Alzheimer's disease (AD)
 - Mild Cognitive Impairment due to AD / Mild Neurocognitive Disorder due to AD
- Biomarkers more available & increase level of certainty when present
- Amyloid PET scans detect β -amyloid in brain!
- Pathophysiology starts decades prior to clinical disease
- Check Vitamin D

Check Vitamin D

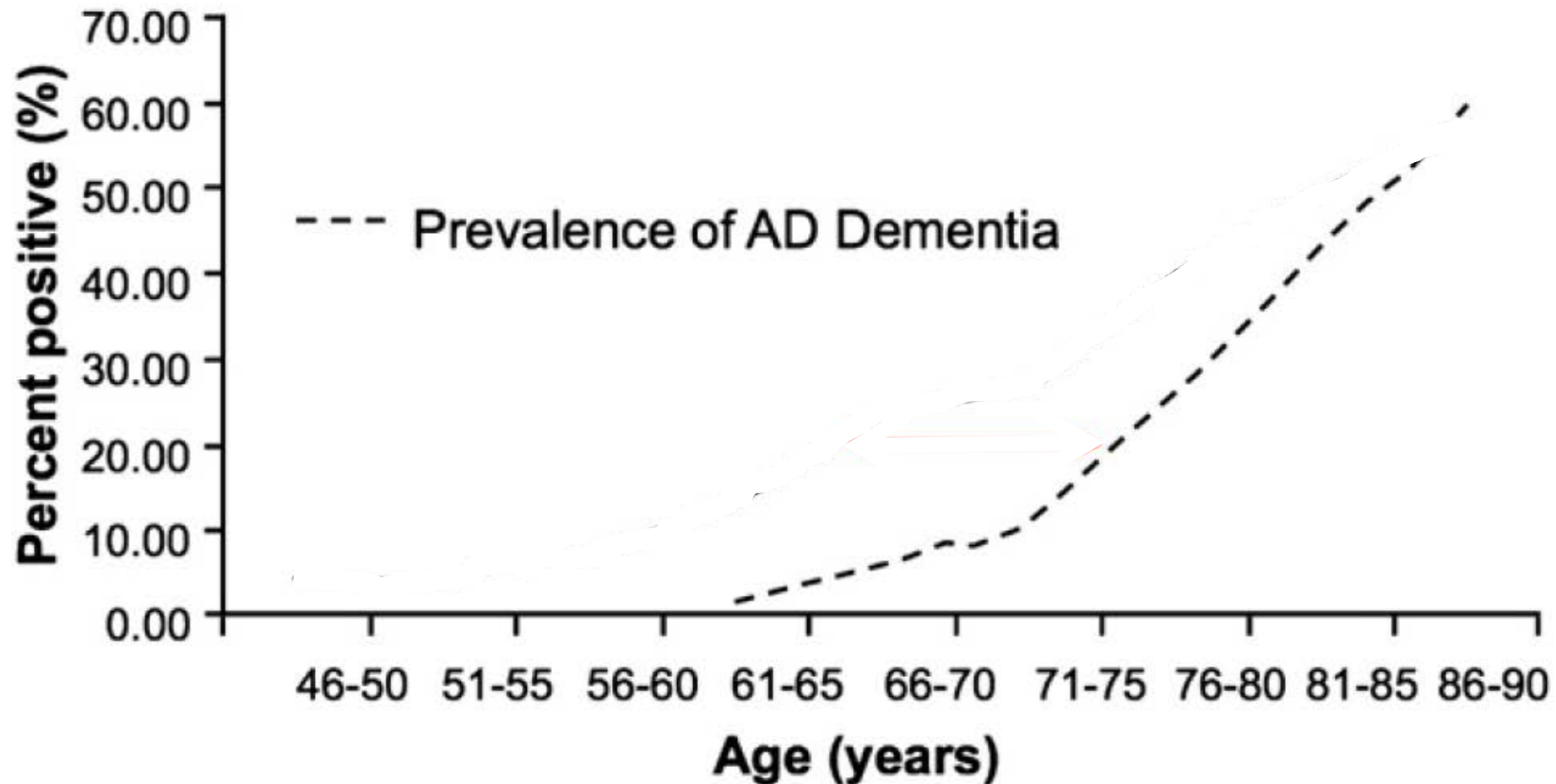


- In addition to B12 & TSH
- Relationship between Vitamin D & dementia being evaluated

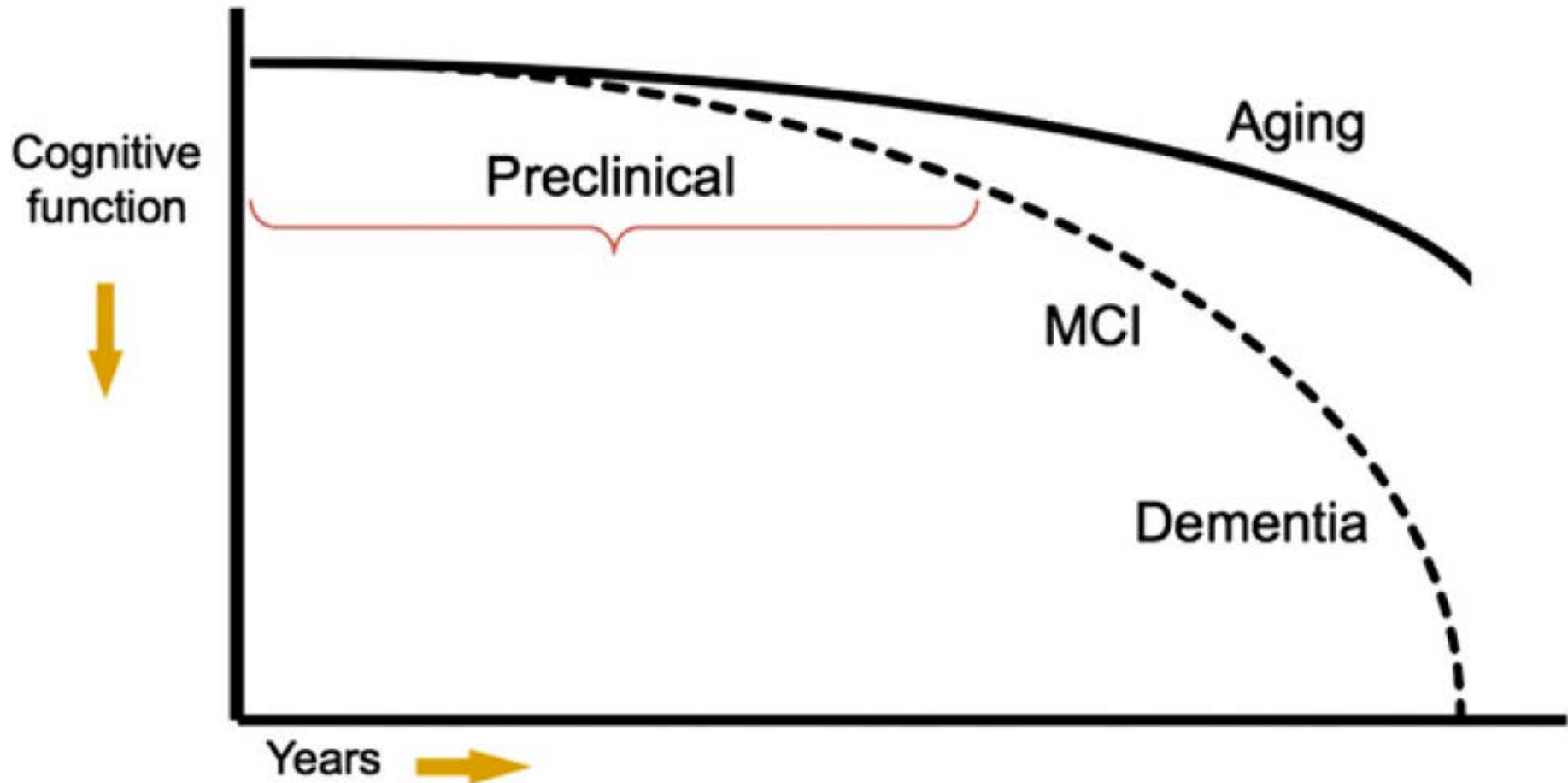
From Budson & Solomon, 2016, adapted from Neurology 2014;83:920-928

Pathophysiology starts decades prior to clinical disease

Appearance of Plaques vs. Dementia



The continuum of Alzheimer's disease



NIA-AA Criteria: All-Cause Dementia

- Decline from prior level of function
 - function at work or usual activities impaired
- Cognitive impairment
 - History from patient & informant
 - Objective cognitive testing (office or formal)
- 2 or more cognitive domains impaired:
 - Memory
 - Reasoning & judgment
 - Visuospatial ability
 - Language
 - Personality, behavior, comportment

DSM-5 Criteria:

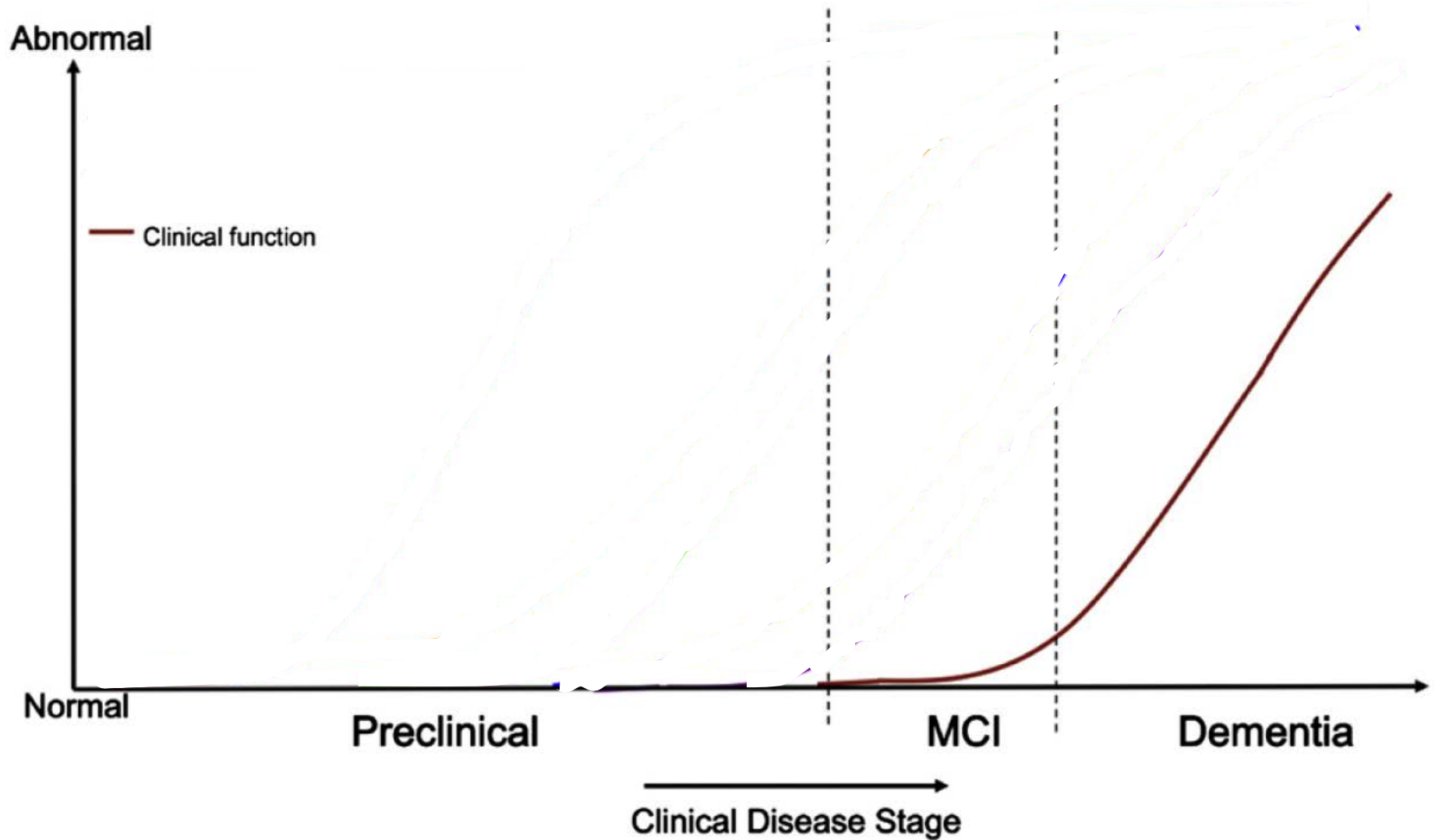
Major Neurocognitive Disorder

- A. Decline from prior level of function in 1 or more cognitive domains based on:
 - 1. Concern of individual, informant, or clinician, and
 - 2. Impairment in cognitive performance
- B. Deficits interfere with independence in everyday activities.
- C. Deficits do not occur exclusively in delirium
- D. Not better explained by another mental disorder
 - Specify whether due to AD, FTD, LBD, VaD, etc.
 - Specify w/ or w/o behavioral disturbance
 - Specify mild (IADL), moderate (BADL), Severe

NIA-AA Criteria: Alzheimer's disease

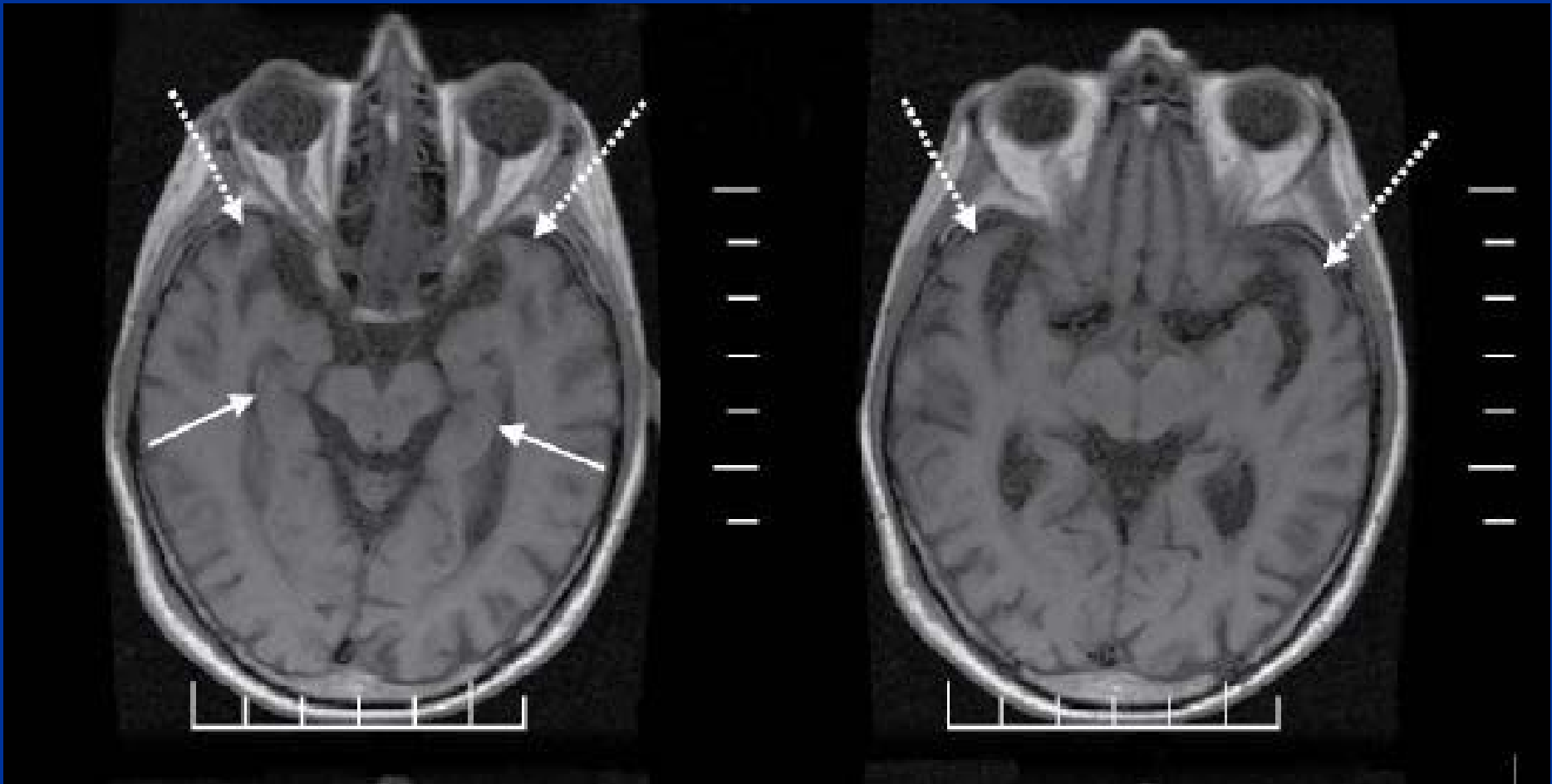
- Dementia present using All-Cause Dementia criteria
- Insidious onset over months to years
- Progressive cognitive impairment
 - Amnestic presentation
 - Non-amnestic presentation
 - Language: word finding
 - Visuospatial: getting lost, impaired face recognition
 - Executive dysfunction: reasoning, judgment, problem solving
- Exclusionary criteria
 - Other dementia or disorder affecting cognition: vascular, dementia with Lewy bodies, frontal temporal dementia, other

Biomarkers



Biomarkers: what to look for / when to use them

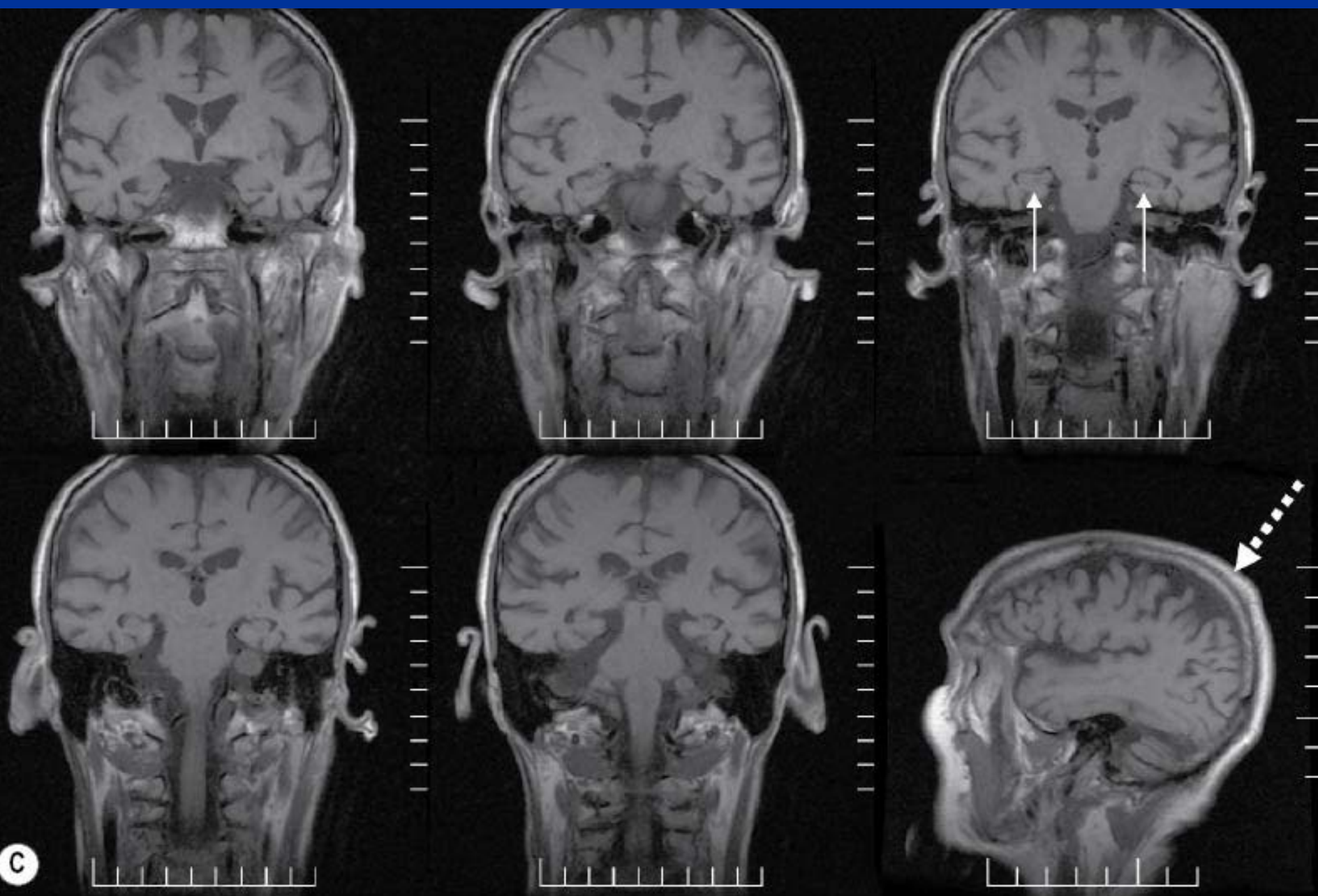
- Structural MRI/CT
 - Qualitative atrophy of medial temporal, anterior temporal, & parietal cortex
 - Always look for on scan (cannot depend on radiology)



From Budson
& Solomon,
2016

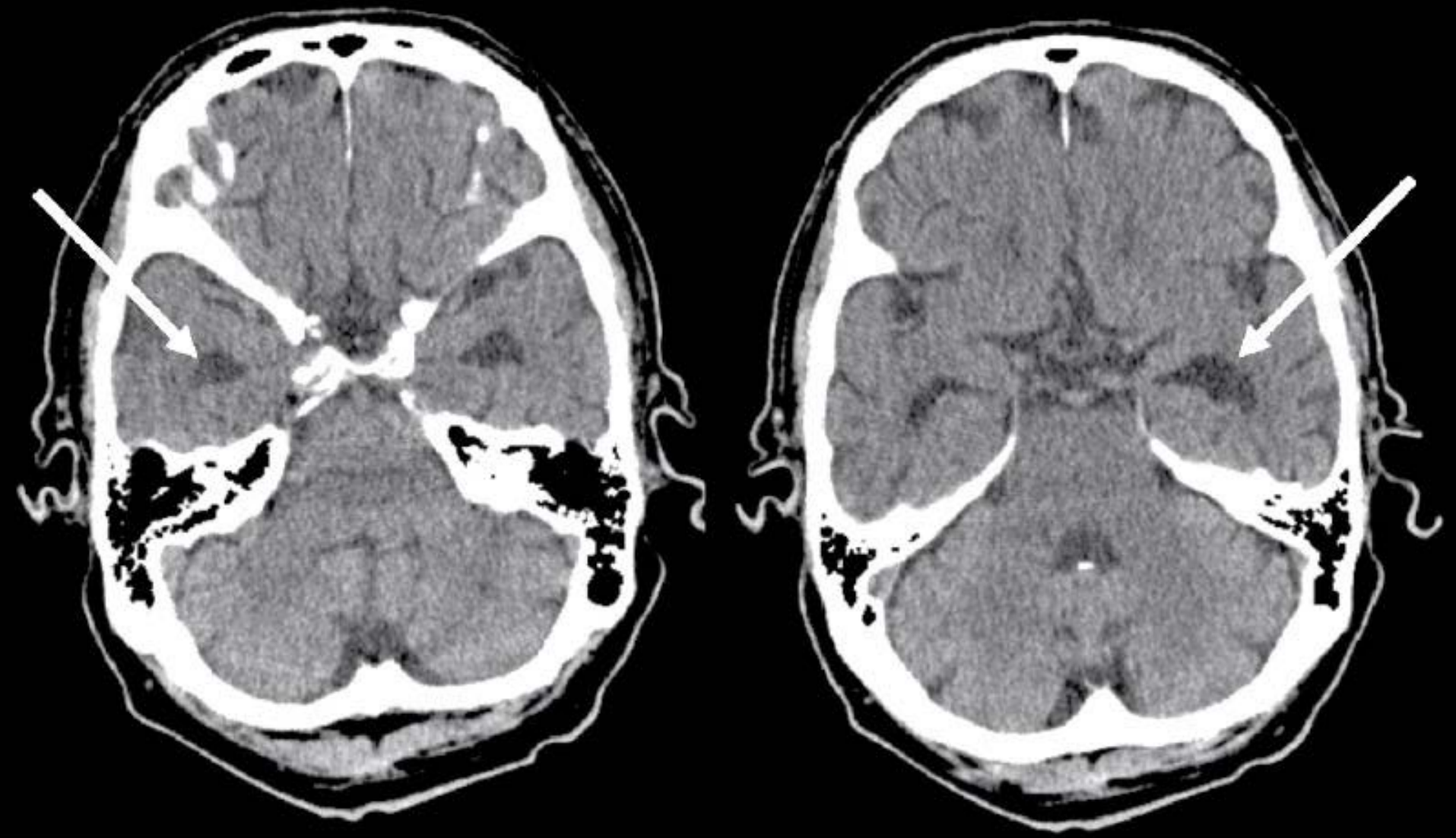


From
Budson
&
Solomon,
2016



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From Budson & Solomon, 2016



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From Budson & Solomon, 2016

Biomarkers: what to look for / when to use them

- Structural MRI/CT
 - Qualitative atrophy of medial temporal, anterior temporal, & parietal cortex
 - Always look for on scan (cannot depend on radiology)
- CSF A β , phospho tau (p-tau), & total tau
 - ↻ ↓A β & ↑ p-tau, total tau (www.athenadiagnostics.com)
 - Pt clearly demented, unclear if AD, & knowing would change management or prognosis, e.g., young patient
- FDG-PET
 - ↻ ↓ metabolism in temporal and parietal cortex
 - Pt clearly demented, unclear if AD, Lewy body, FTD, & knowing would change management or prognosis

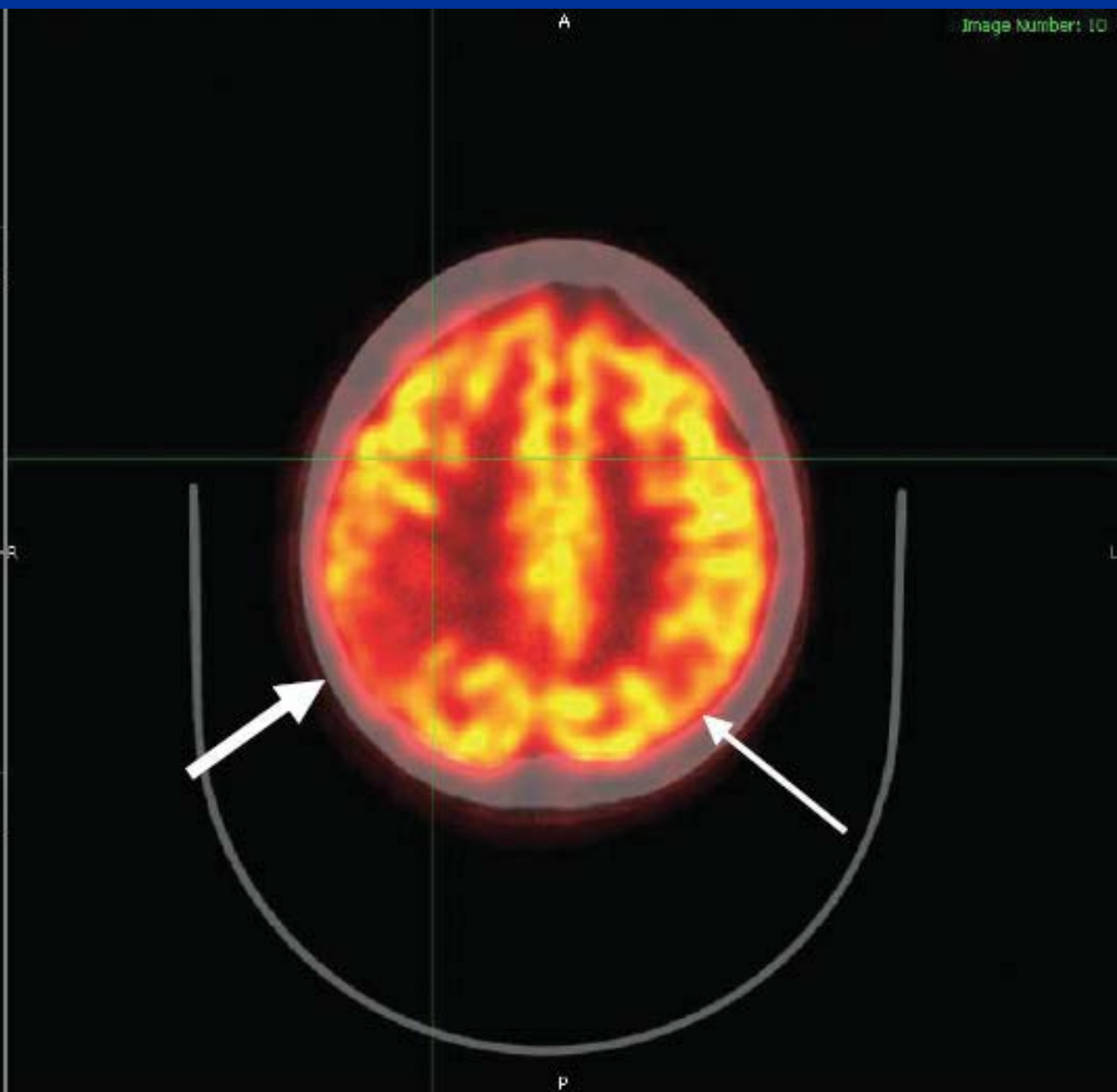
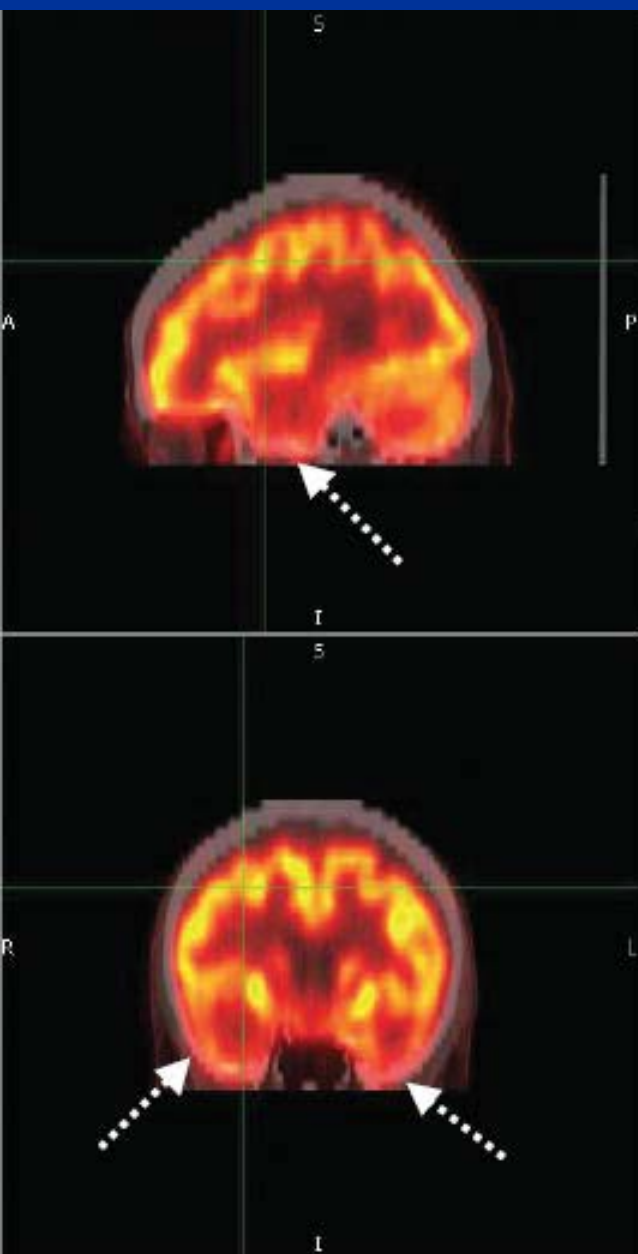


Image Number: 10

A β PET Scans FDA Approved!

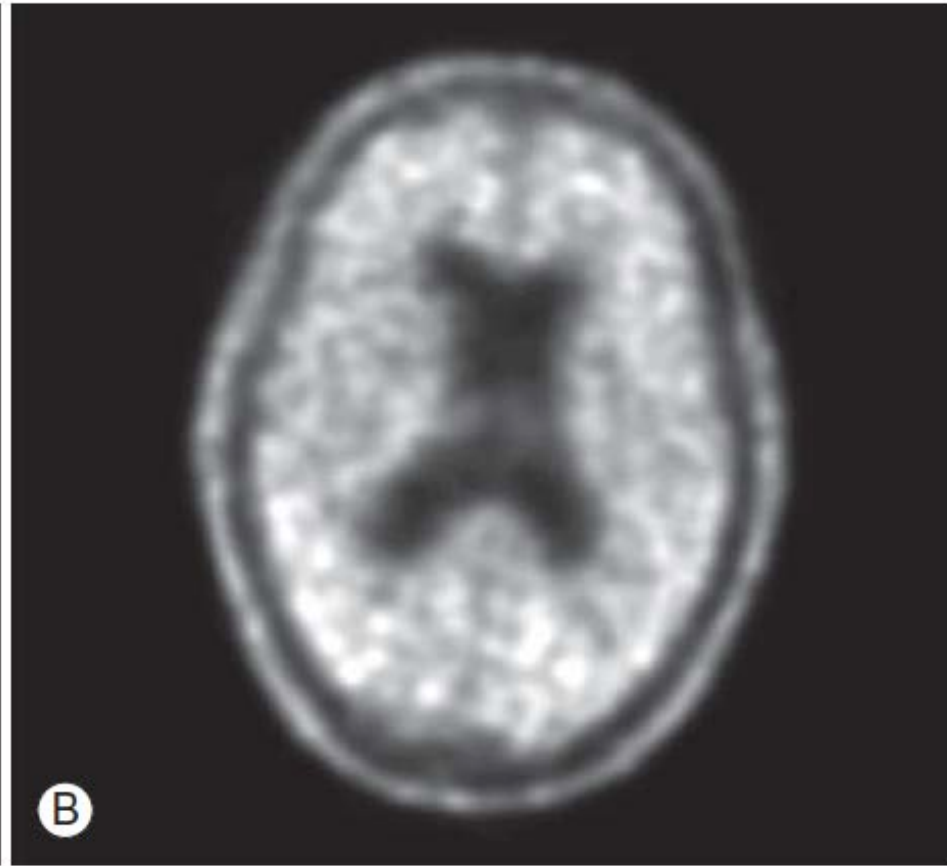
(but payment?)

- April 2012: Florbetapir Avid Radiopharmaceuticals
- October 2013: Flutemetamol GE Healthcare
- March 2014: Florbetaben Piramal Imaging
- ¹⁸F-fluorine based compounds (can be sent by Fedx)
 - Will detect Alzheimer's disease (AD) pathophysiology
 - Use when knowing that AD pathology is present in symptomatic patient would change management.
 - **WARNING: will detect AD pathology in asymptomatic patients who may not develop disease for 10-15+ years**
 - Will have broader use when disease modifying therapies are available.

Amyloid Imaging with florbetapir



Non-AD dementia



Alzheimer's Disease

65 year old

MoCA 21

From Budson & Solomon, 2016

Treatment: What's new?

- New symptomatic medications being developed which modulate neurotransmitters.
- New disease modifying therapies also being developed
 - Monoclonal antibodies directed against β -amyloid
 - Enzyme inhibitors that stop the formation of β -amyloid
 - Trials on-going in patients with mild AD, MCI due to AD, *and* healthy individuals with memory complaints & + amyloid PET scan.

Treatment: currently available for AD

- D/c or change anticholinergic agents, sedatives, etc.
- To enhance cognition:
 - Cholinesterase Inhibitors:
 - donepezil (Aricept, *available oral dissolving tablet, now generic*)
 - rivastigmine (Exelon, *available QD patch*)
 - galantamine (formerly Razadyne, *now generic*)
 - huperzine A (Cerebra). Nutritional product.
 - Memantine:
 - Namenda

Current treatments for AD:

Big picture

- Do we need better medications?
 - Yes
- Are the current medications just symptomatic?
 - Yes
- Do they actually work? Do they actually help patients in any meaningful way?
 - Yes
- Here is the data

Cholinesterase inhibitors

- Improved cognition, participation in activities of daily living, & global function in mild to moderate patients.
 - Neurology 1998;50:136
 - BMJ: 1999;318:633
 - Neurology 2000;54:2261
- Improves cognition & behavior in mild to moderate and moderate to severe disease
 - Neurology 2000;54:2269
 - Neurology 2001;57:613
- Reduces emergent behavioral disturbances in mild to moderate patients.
 - Am J Psychiatry 2004;161:532

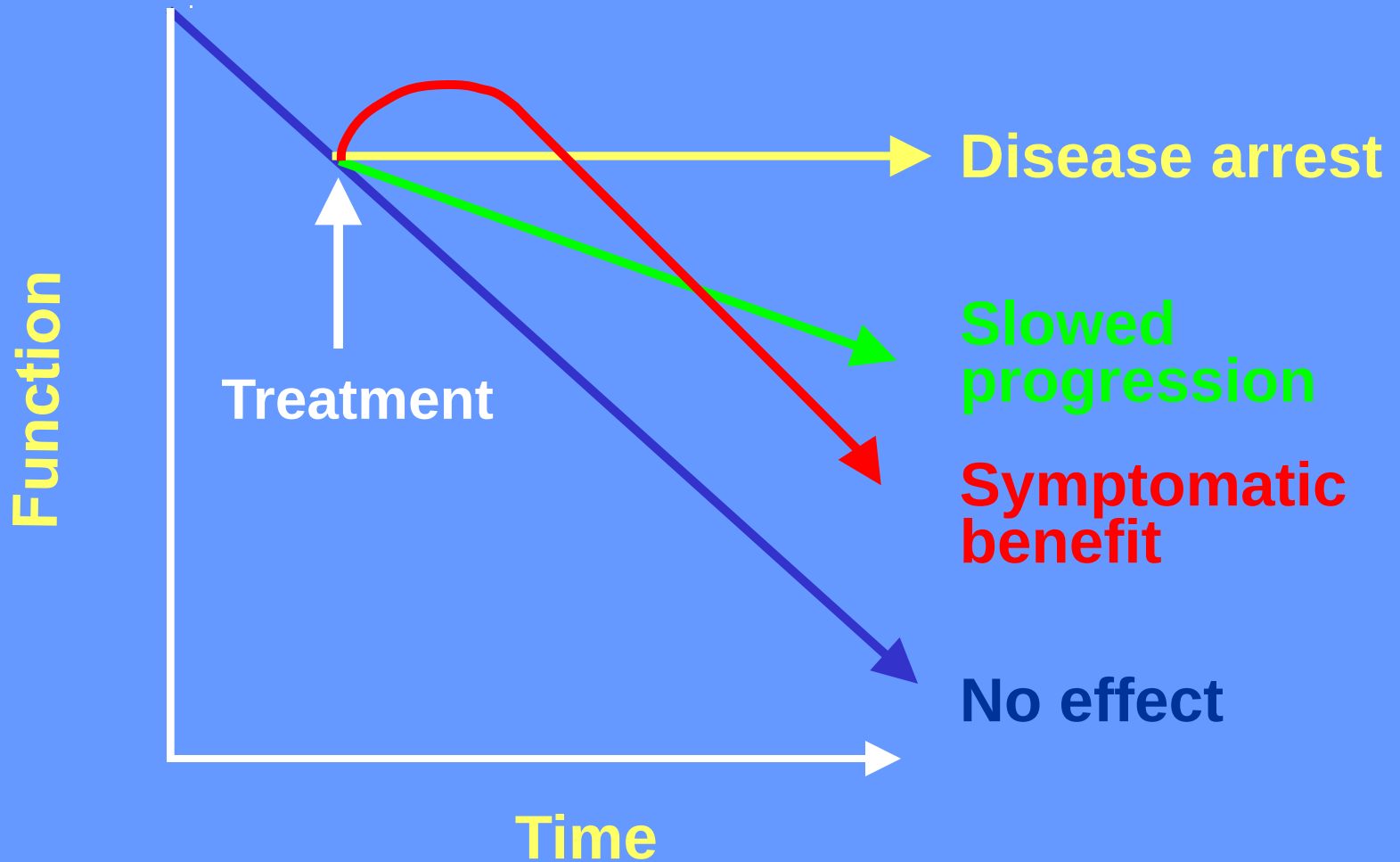
Treatment expectations

- Small but noticeable improvements:
 - Less time spent looking for keys, glasses, etc.
 - Repeats self less often
 - Dwells in past less
 - Easier time keeping track of conversation
 - More engaged, outgoing

Cholinesterase inhibitor side-effects

- Gastrointestinal effects
 - anorexia
 - nausea/vomiting
 - diarrhea
- Vivid dreams
 - take in AM or earlier PM dose
- Other cholinergic symptoms
 - Increased salivation
 - Increased rhinorrhea
 - Muscle cramps
 - rarely slows heart rate

Treatment Outcomes



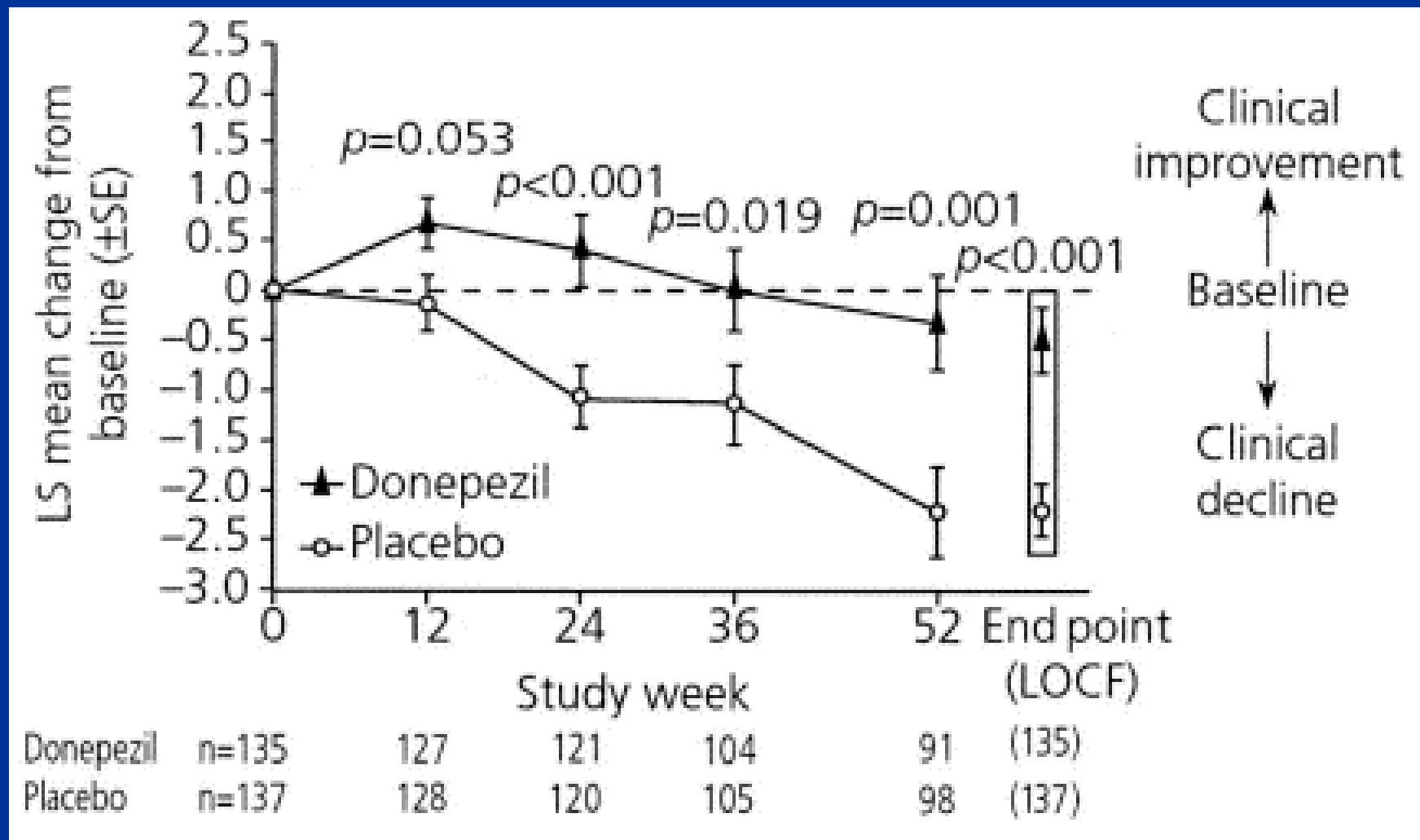
Turning back the clock

- About 25-30% show an improvement equivalent to a 1-year reversal of symptoms
- About 50-60% show an improvement equivalent to a 6-month reversal
- About 10-15% show either an improvement equivalent to less than a 6-month reversal or no improvement

NEJM 2004 351:56-67

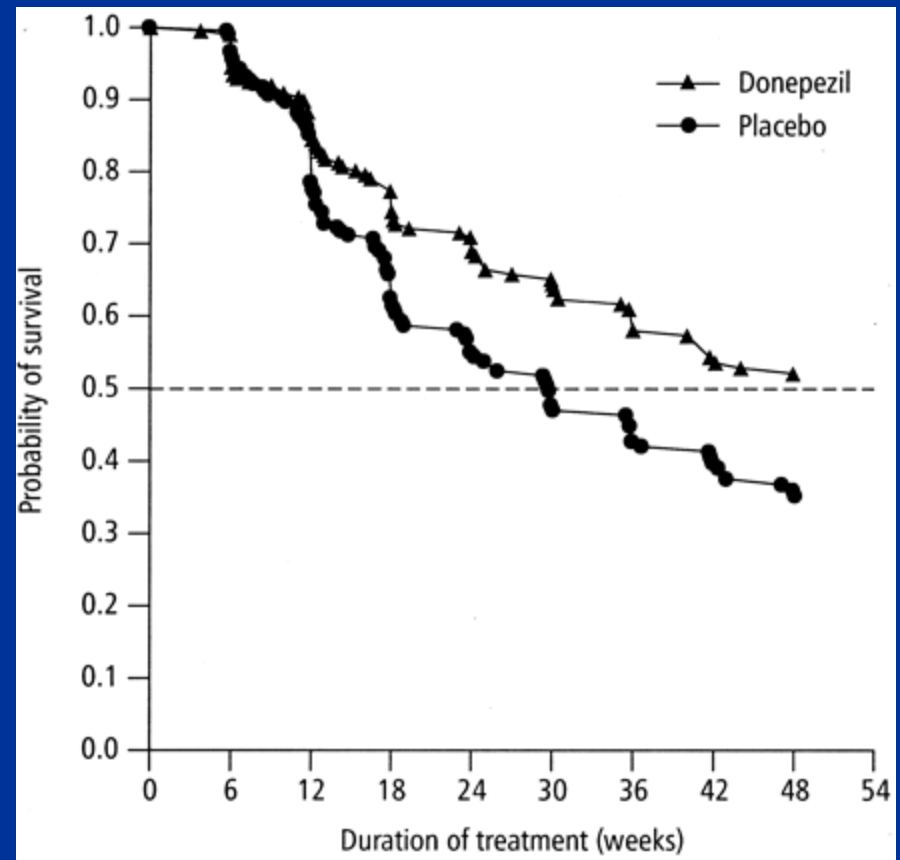
- My recommendation: Give a trial, measure response
 - ask patient, ask caregiver, test patient

Change in MMSE in mild to moderate Alzheimer's disease



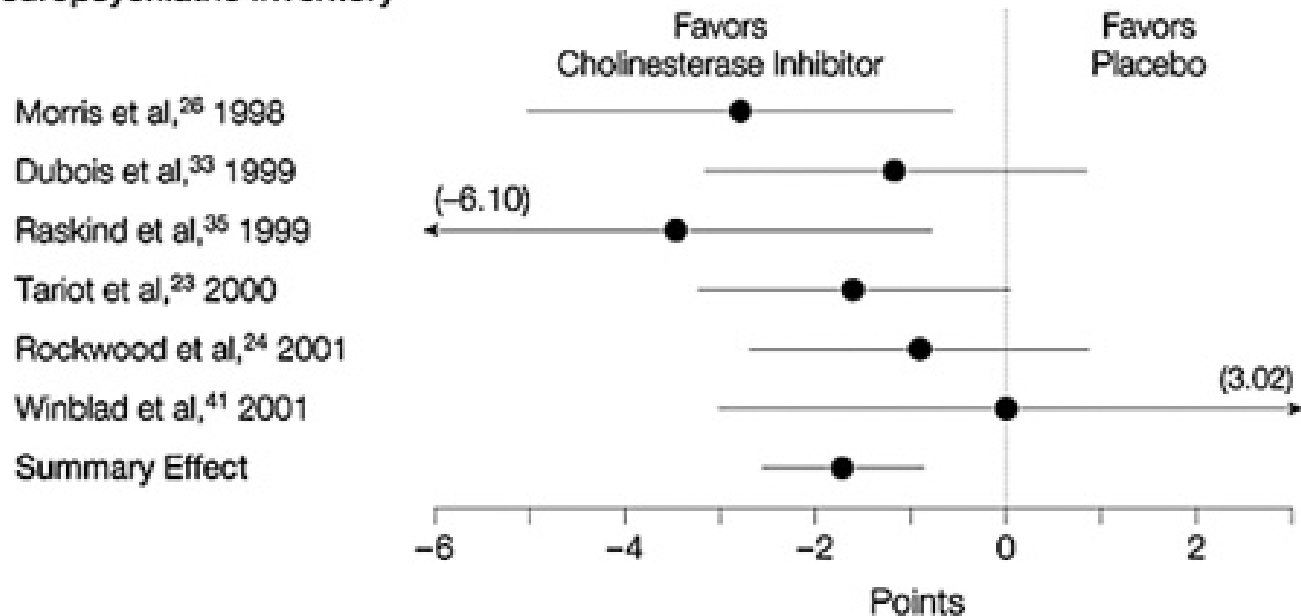
Time to clinically evident functional decline

- 431 patients
- mild to moderate AD
- double-blind placebo controlled trial



Meta analysis: neuropsychiatric symptoms in AD

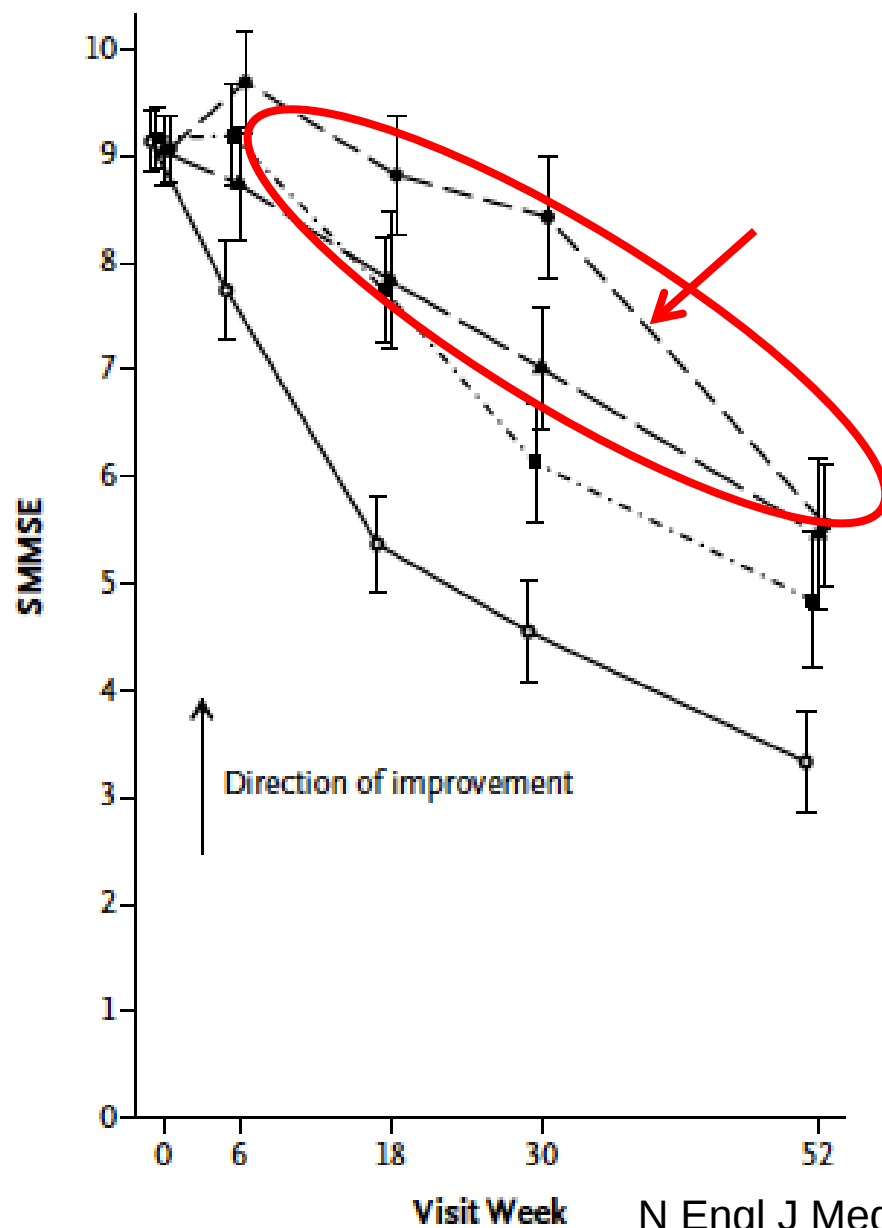
A Neuropsychiatric Inventory



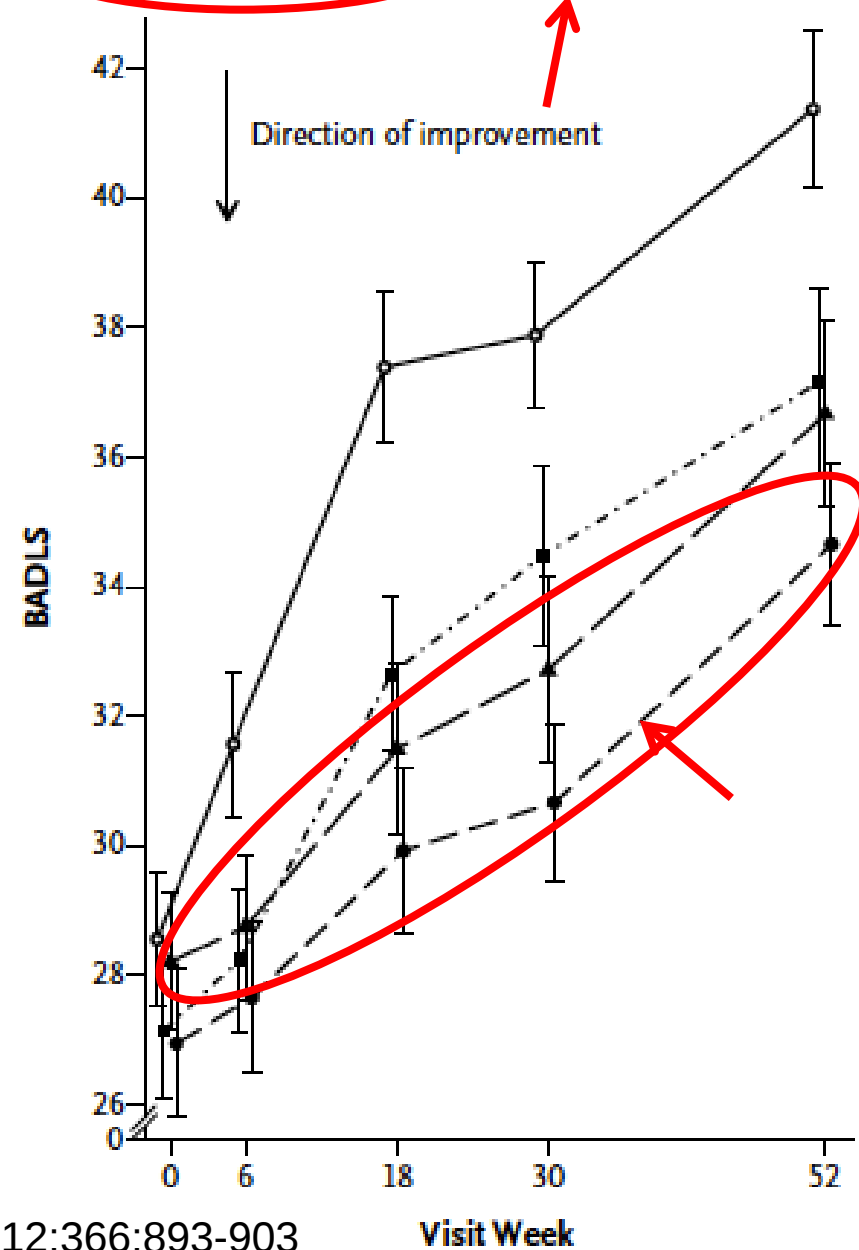
Cholinesterase inhibitors: How long to use them?

- A double-blind placebo controlled study found continued efficacy for 4 years.
- Retrospective & prospective studies suggest beneficial effects last for at least 5 years.
 - CNS Drugs 2004 18:757-68.
- Should we stop treatment in moderate or severe disease?

—○— Placebo donepezil and placebo memantine
 - -■- - Placebo donepezil and active memantine



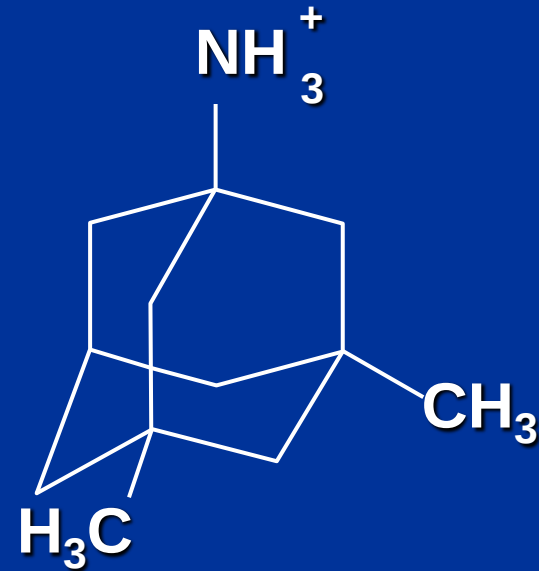
—▲— Active donepezil and placebo memantine
 - -●- - Active donepezil and active memantine



- “In patients with moderate or severe Alzheimer’s disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months.” (NEJM 2012; 366: 893-903)
- My recommendation: continue cholinesterase inhibitors as long as there is quality of life to preserve

Memantine (Namenda)

- Approved for use in patients with moderate to severe Alzheimer's disease, with or without cholinesterase inhibitors
- Uncompetitive NMDA-receptor antagonist
- Enhances dopamine activity
- Does not alter AChE activity in the presence or absence of AChEIs



Amantadine Derivative
1-amino-3,5-dimethyladamantane

Memantine in patients with moderate to severe AD

- Improvement or less decline in cognition, activities of daily living, and global change, as well as reduced care dependence
 - N Engl J Med 2003;348:1333
 - Int J Geriatr Psychiatry 1999;14:135
- Cognitive, functional, global, and behavioral outcome measures are better with memantine + donepezil versus donepezil alone
 - JAMA 2004;291:317

Treatment expectations

- Small but noticeable improvements:
 - More alert
 - More talkative
 - More engaged
 - More outgoing
 - Brighter overall
 - Less agitated
 - *Note: Memory not improved*

Memantine Side-effects

- None statistically more than placebo
- Agitation less than in placebo group
- “Dizziness”
- Drowsiness and confusion, dose related, sometimes transient, worse in milder patients

Memantine uses

- FDA: moderate to severe AD (MMSE <16)
- Patients with AD or vascular dementia at any stage who are a bit Parkinsonian, or who are not depressed but appear withdrawn, not taking initiative, not talking much
- Patients with Lewy Body Dementia
- Try in patients with Frontotemporal Dementia

Patient 2

- 72M with mild memory complaints. CEO of a large company.
- Trouble remembering his schedule—secretary has to remind him.
- Trouble remembering the content of meetings; needs to take more notes.
- Gradual worsening over the last 2 years.
- Never forgot anything critically important
- No trouble with words or other things.
- Isolated problems with memory on testing

Mild cognitive impairment

NIA-AA Criteria: MCI due to AD

- Establish clinical & cognitive criteria
 - Concern of change in cognition by patient, informant, or clinician
 - Testing shows impairment in one or more cognitive domains, typically including memory
 - Preservation of independence in functional abilities
 - Not demented
- Examine etiology: MCI due to AD
 - R/o vascular, traumatic, medical causes
 - Provide evidence of longitudinal decline in cognition
 - Report history consistent with AD genetic factors

DSM-5 Criteria:

Mild Neurocognitive Disorder

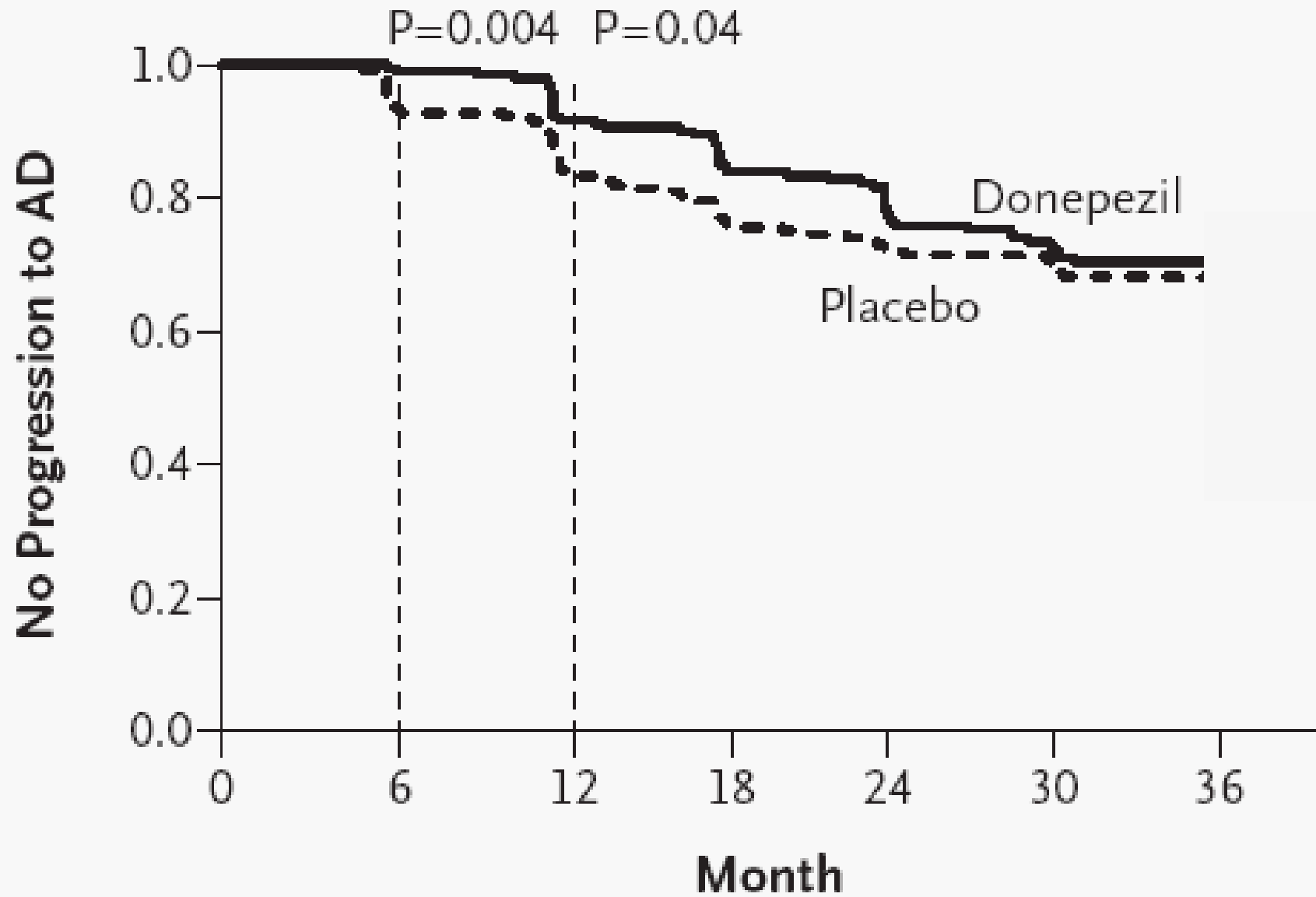
- A. Modest decline from prior level of function in 1 or more cognitive domains based on:
 - 1. Concern of individual, informant, or clinician, and
 - 2. Modest impairment in cognitive performance
- B. Deficits *do not* interfere with capacity for independence in everyday activities.
- C. Deficits do not occur exclusively in delirium
- D. Not better explained by another mental disorder
 - Specify whether due to AD, FTD, LBD, VaD, TBI, Substance/medication use, HIV, Prion, PD, HD, medical condition, multiple etiologies, etc.
 - Specify w/ or w/o behavioral disturbance

MCI: Prognosis & Treatment

- 70% progress to AD at a rate of 15% per year
- 30% stable or improve
- No FDA approved medications
- Should we use cholinesterase inhibitors?

- 769 patients with MCI studied for 3 years
- Vit E 2000 IU, donepezil 10 mg, or placebo
- Conclusion : no differences in the probability of progression to AD over the three years for either treatment
- Donepezil treatment associated with a lower rate of progression to AD over one year
- Vit E showed no effect

B



MCI: Prognosis & Treatment

- 70% progress to AD at a rate of 15% per year
- 30% stable or improve
- No FDA approved medications
- My recommendation: try cholinesterase inhibitor if patient wants to improve his or her memory to improve their lives

Vit E does nothing in MCI; what about in mild to moderate AD?

- JAMA 2014;311:33-44
- Vit E 2000 IU, memantine 20 mg, both, placebo
- ADL scores declined 6.2 mo less in Vit E group
- No difference in memantine alone or memantine plus Vit E
- Unclear whether Vit E is helpful in AD.

Patient 3

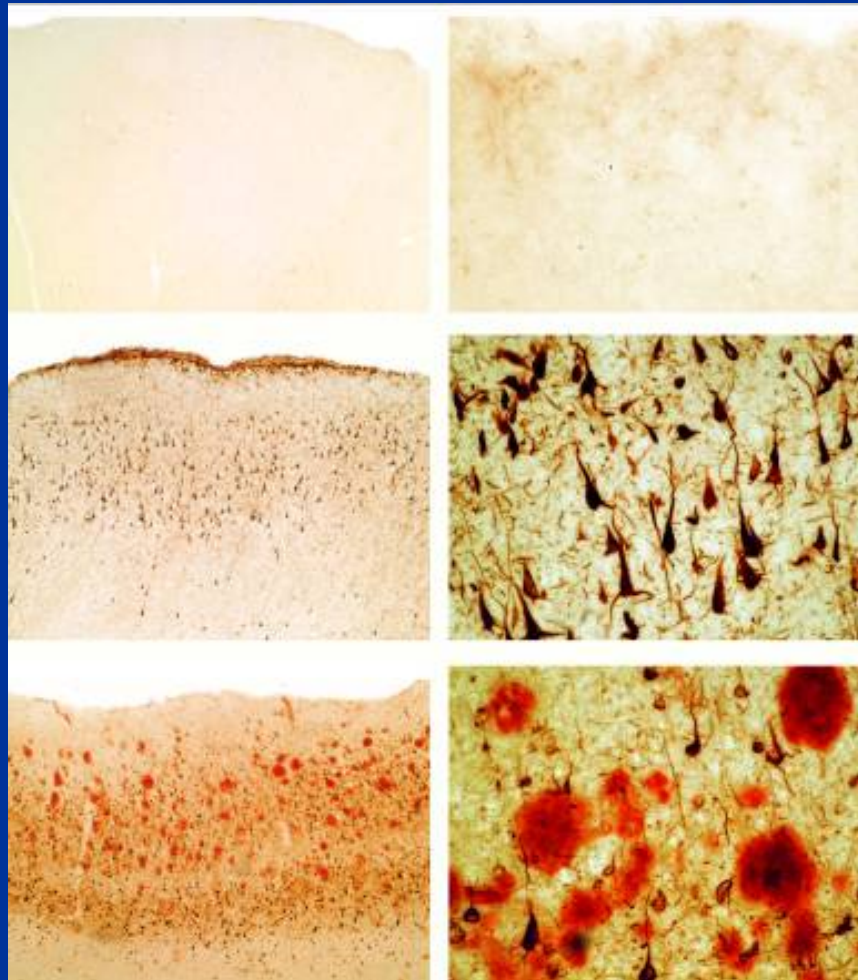
- 59 F w/ forgetfulness
- Long history of domestic abuse with frequent blows to the head and “occasional” concussions
- Tearfulness & emotional blunting
- Language deficits including anomia, frequent paraphasic, phonemic, & neologistic errors
- Put plastic Tupperware into the oven, was cooking with incorrect ingredients.
- Exam: masked facial expression, bilateral resting tremor, glabellar tap sign, brisk reflexes
- Over time, became more aphasic, apraxic, and frontal

Chronic Traumatic Encephalopathy



Chronic Traumatic Encephalopathy (CTE) vs. Alzheimer's Disease

control



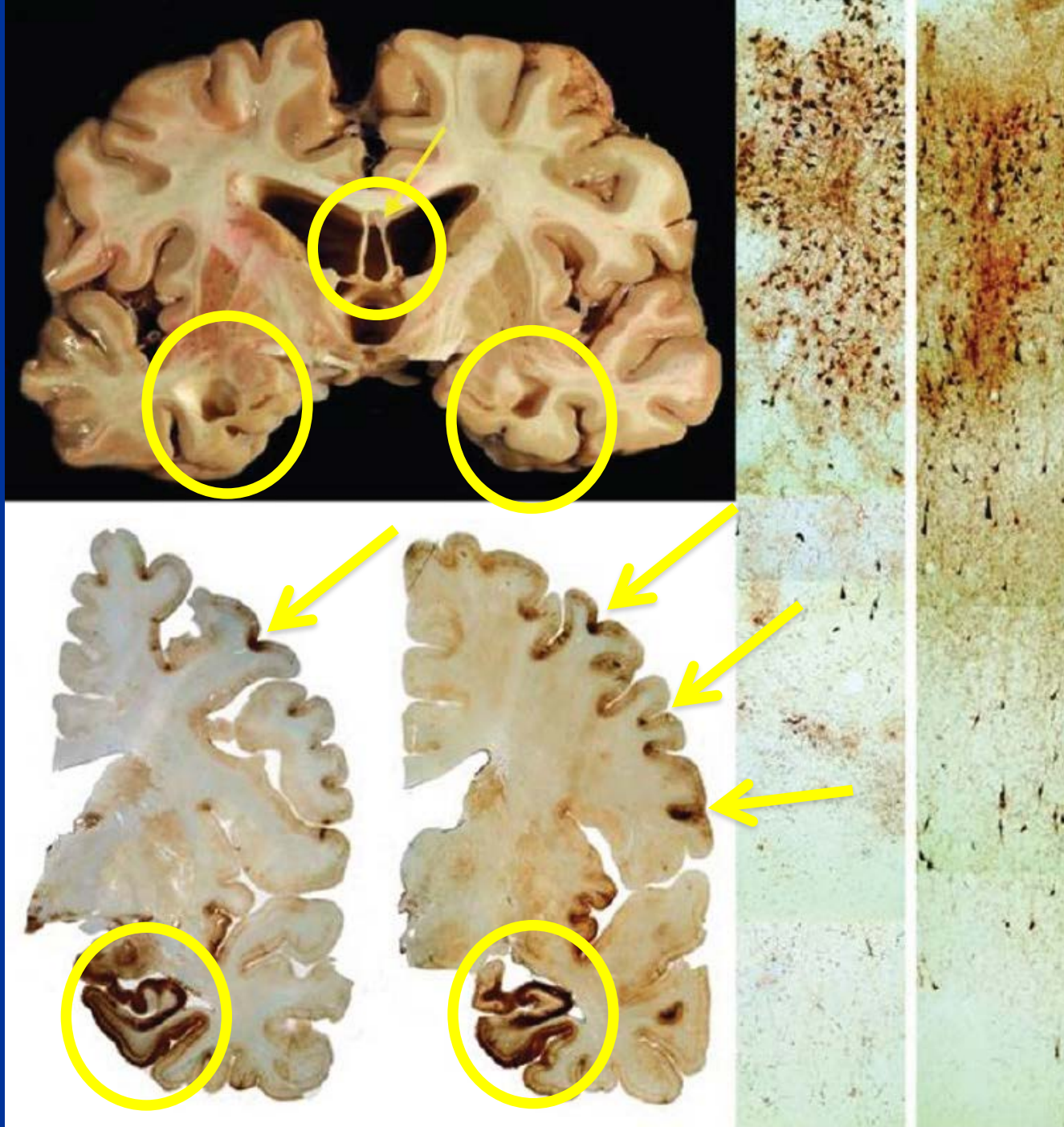
no tau,
no A β

CTE

tau, no A β

AD

tau & A β



From
Budson
&
Solomon,
2016

REVIEW

Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome

Philip H Montenigro¹, Christine M Baugh², Daniel H Daneshvar³, Jesse Mez⁴, Andrew E Budson^{4,5}, Rhoda Au^{2,6}, Douglas I Katz^{2,7}, Robert C Cantu^{8,9} and Robert A Stern^{1,4,2,8*}

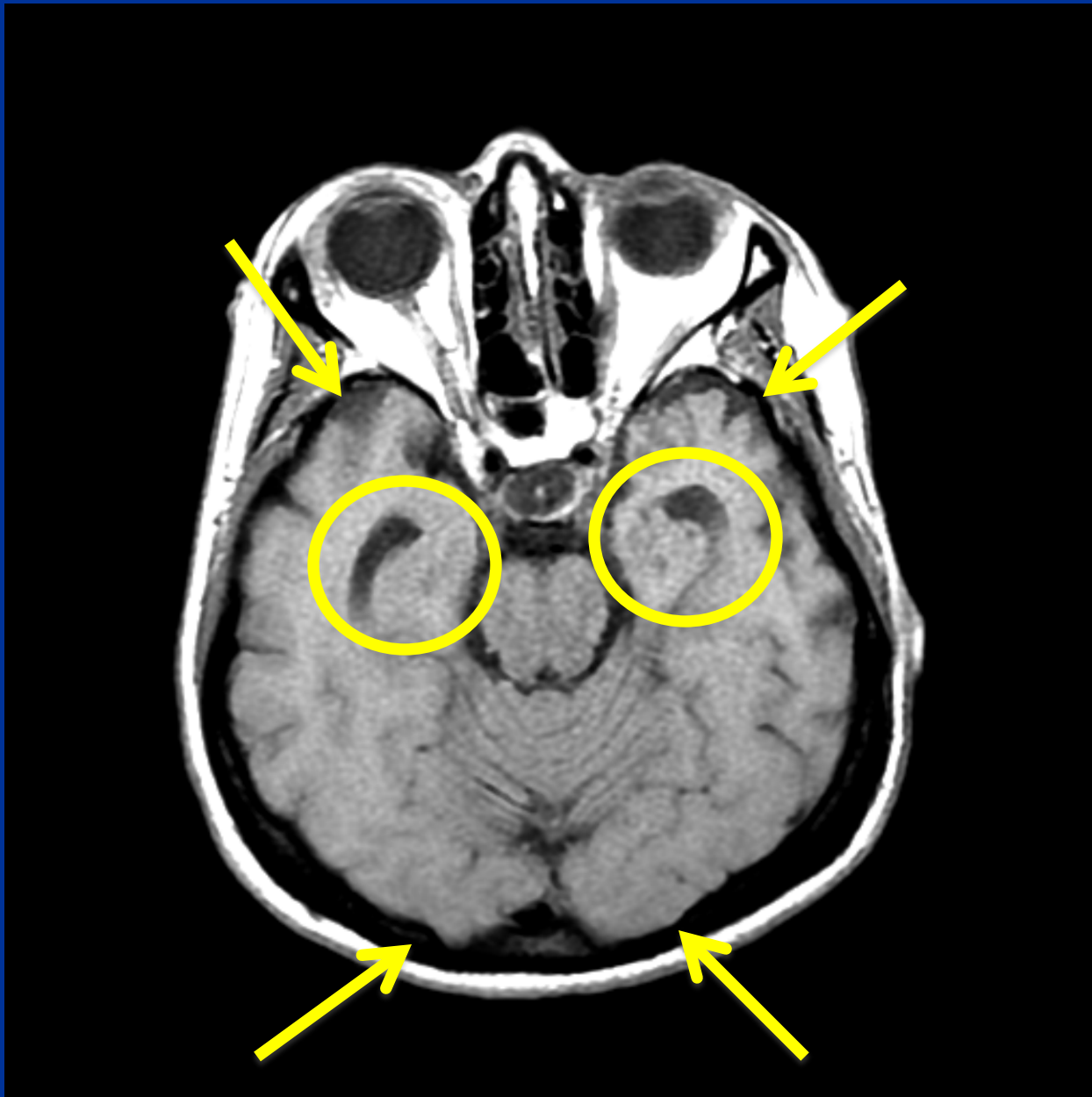
- Very preliminary, designed for research
- Can still give us some guideposts
- Are complicated. (All in your syllabus!)

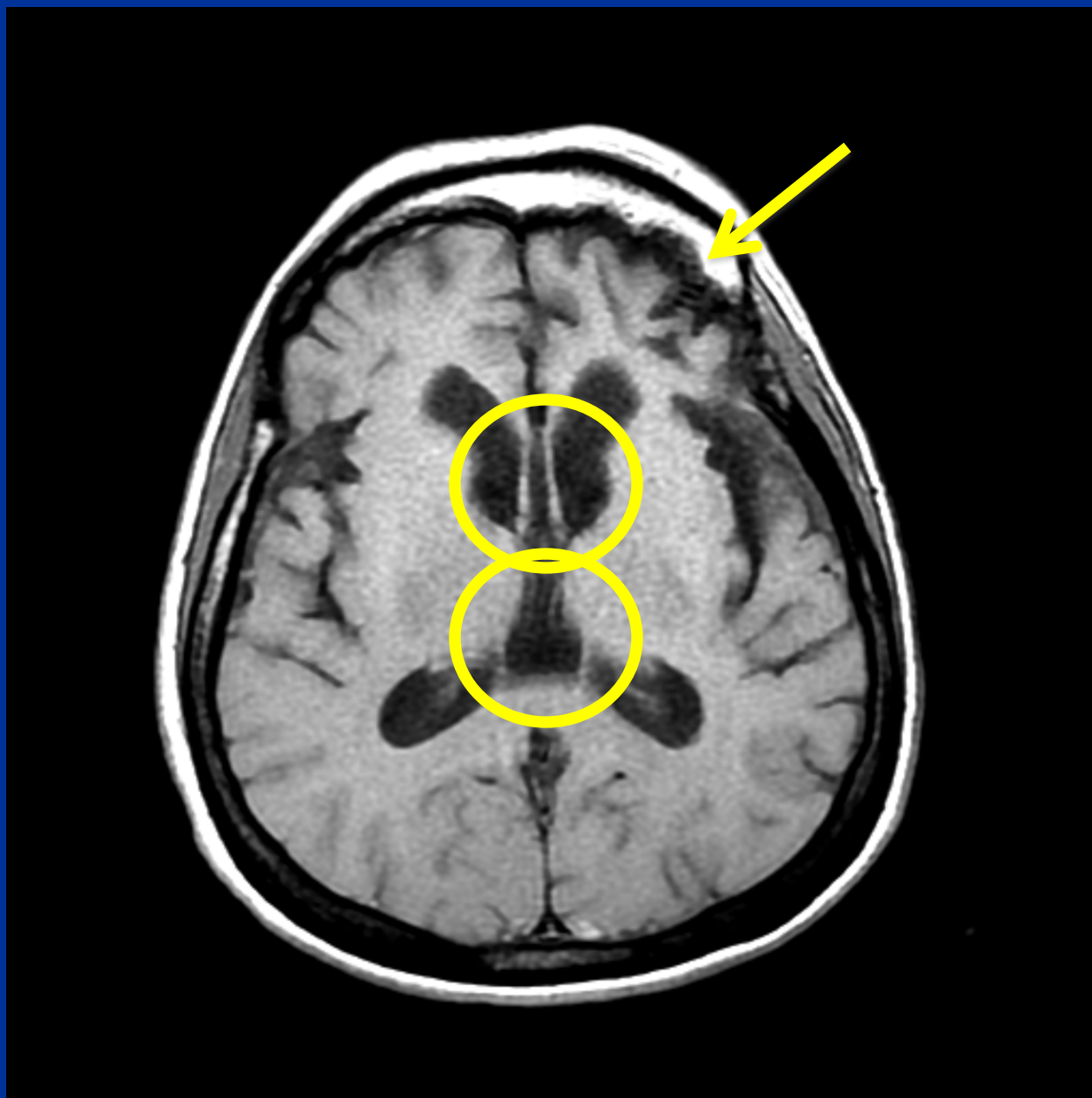


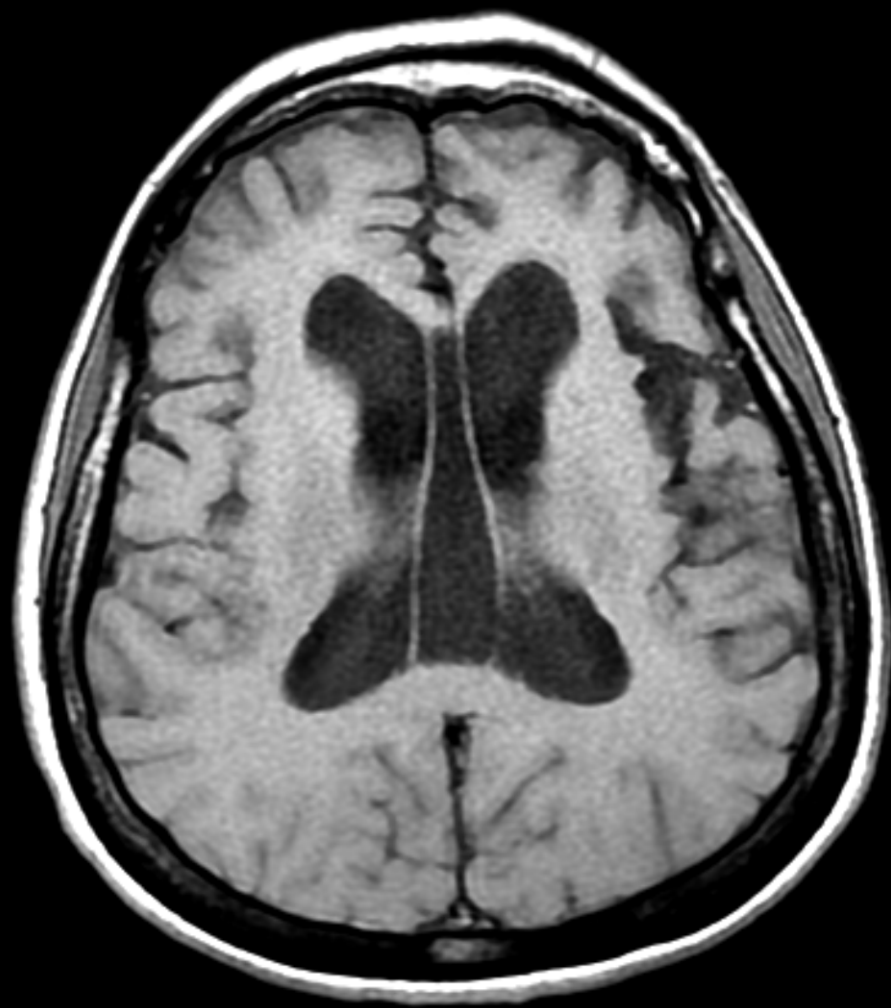
CTE Brief Summary

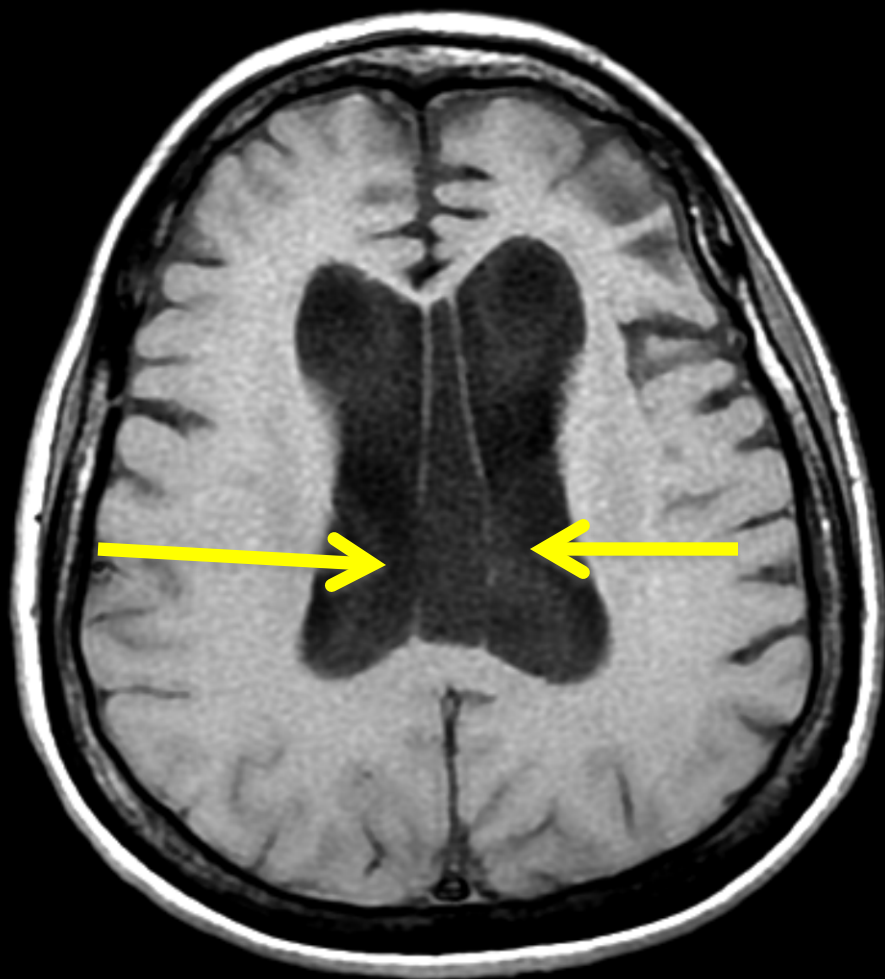
- Caused by multiple impacts to the head
- Characterized by perivascular accumulation of tau irregularly in the depths of cortical sulci
- Two main syndromes (also mixed & dementia):
 - Behavioral/Mood Variant (younger, m=35 yrs)
 - Cognitive Variant (older, m=59 yrs)
- Commonly initial features include:
 - Impairment in memory, executive func, attention, visuospatial, & language.
 - Depression, hoplessness, explosivity, out of control, violent

T1
MRI
scan

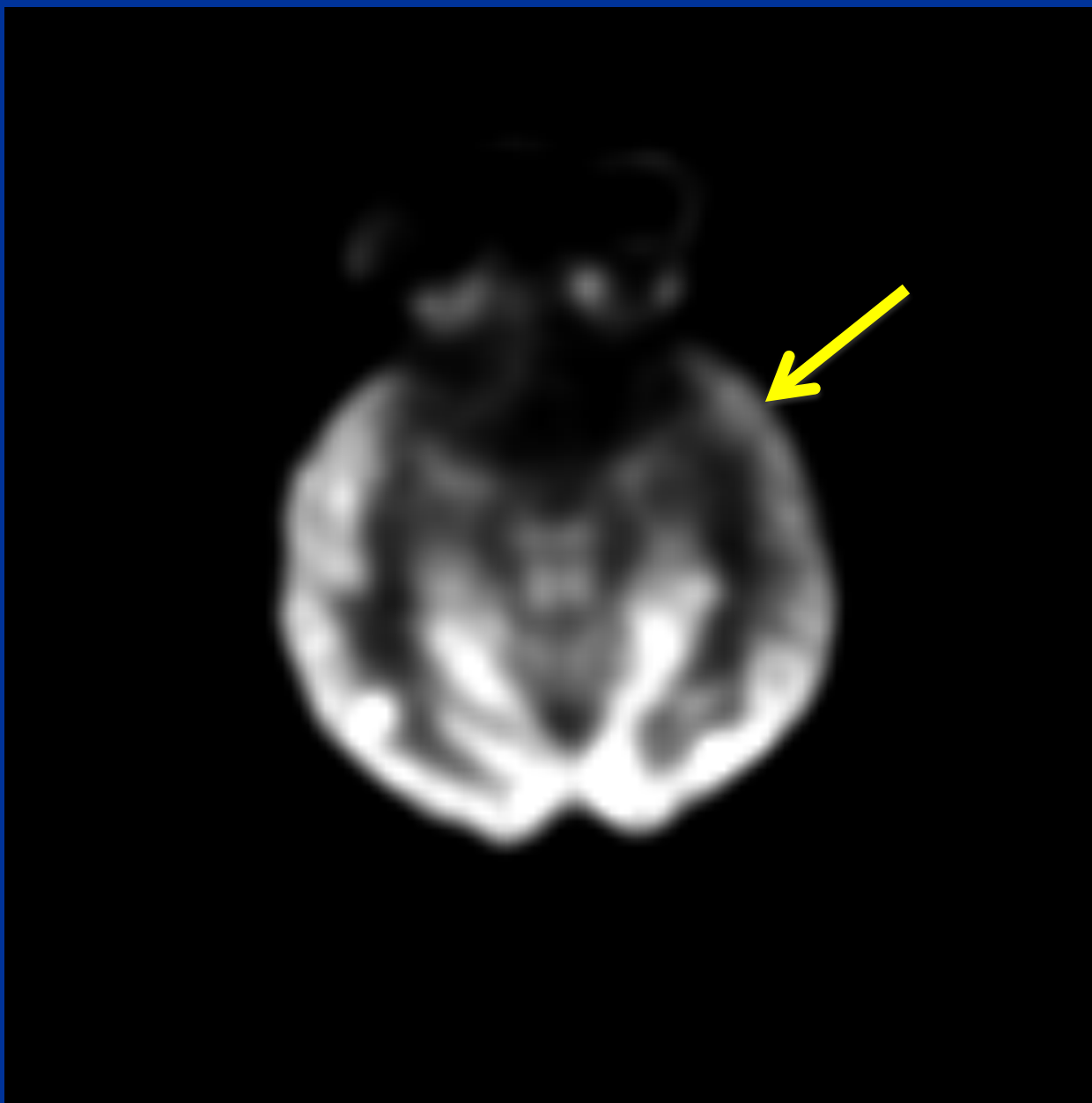


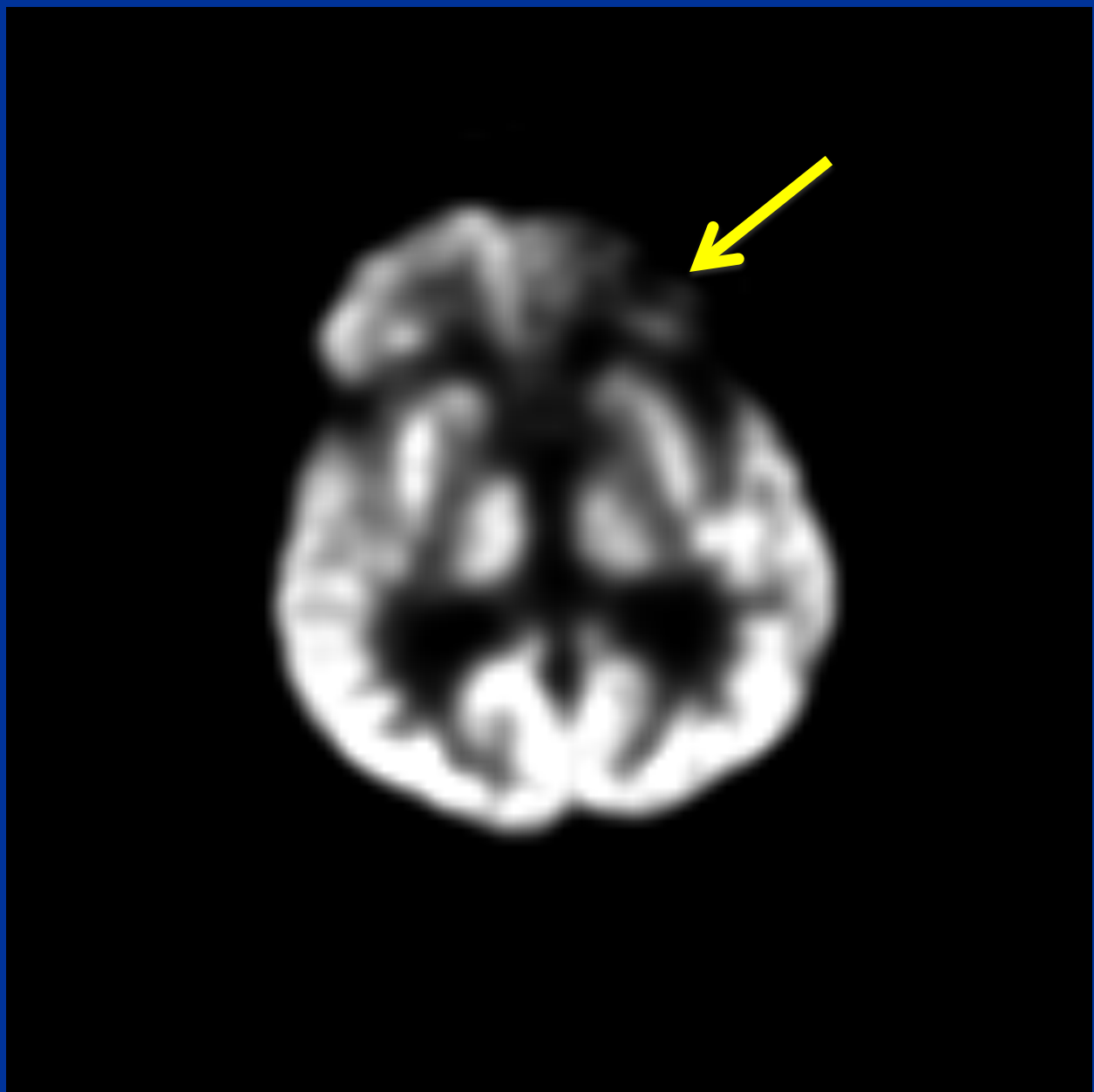


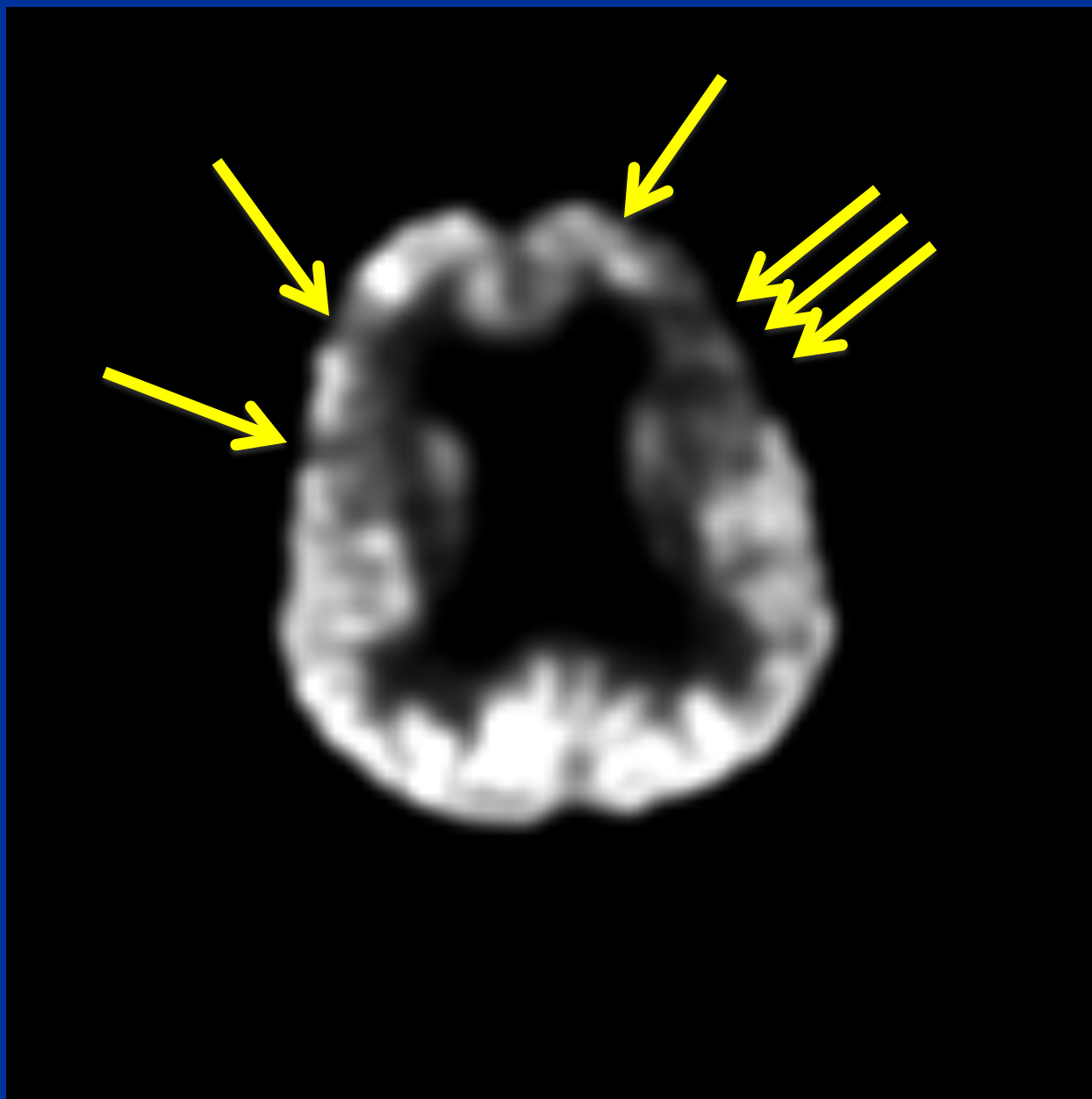


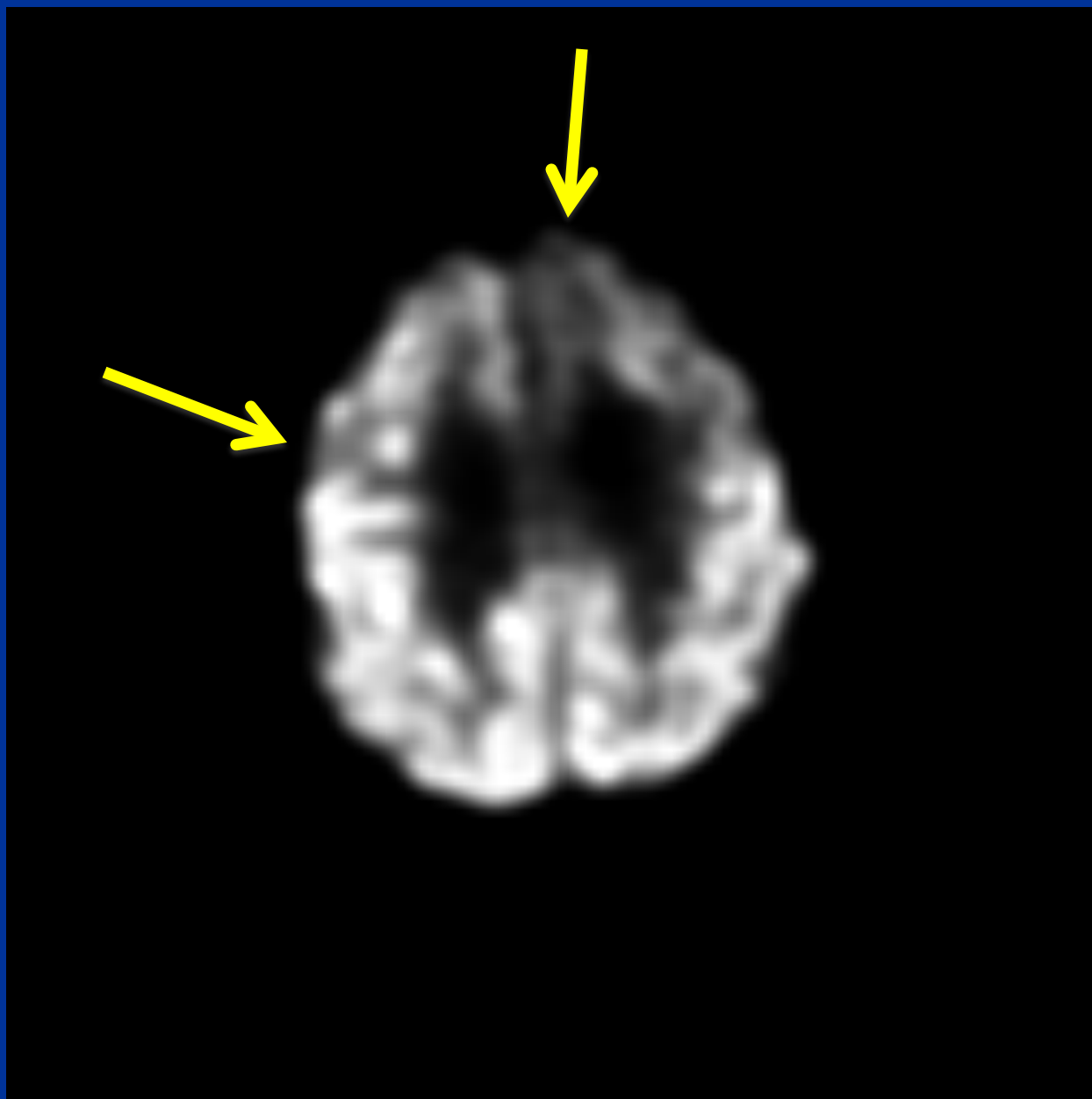


FDG
PET
scan









clinical exam

ELSEVIER

Chronic Traumatic Encephalopathy

Andrew E. Budson, Paul R. Solomon

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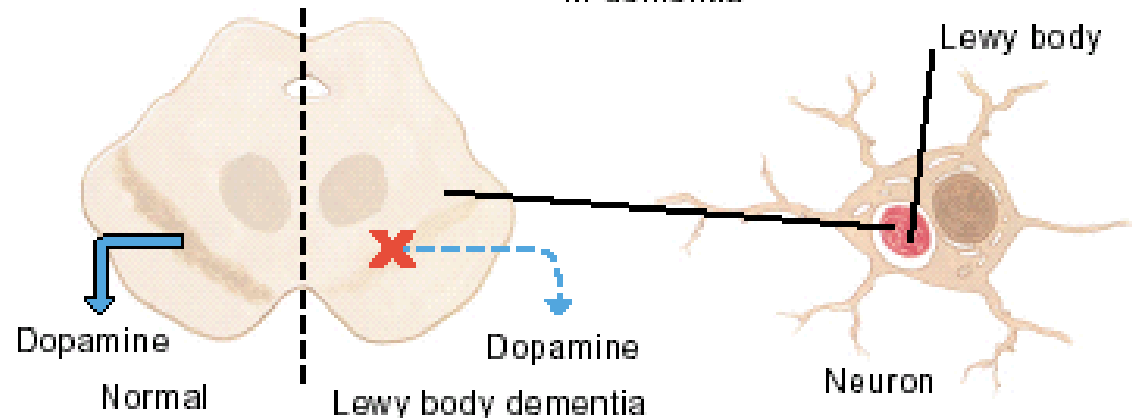
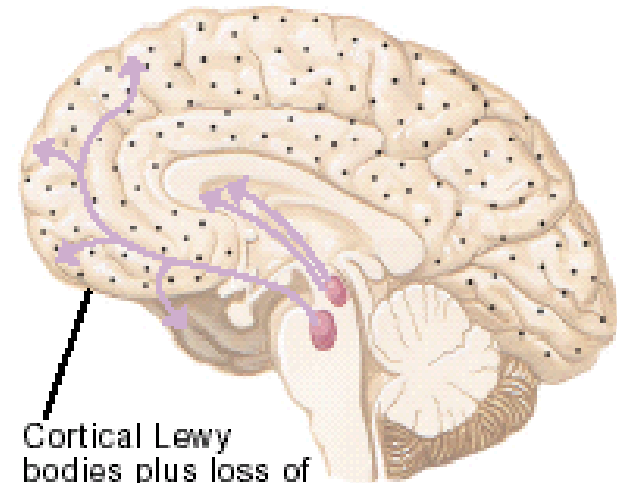
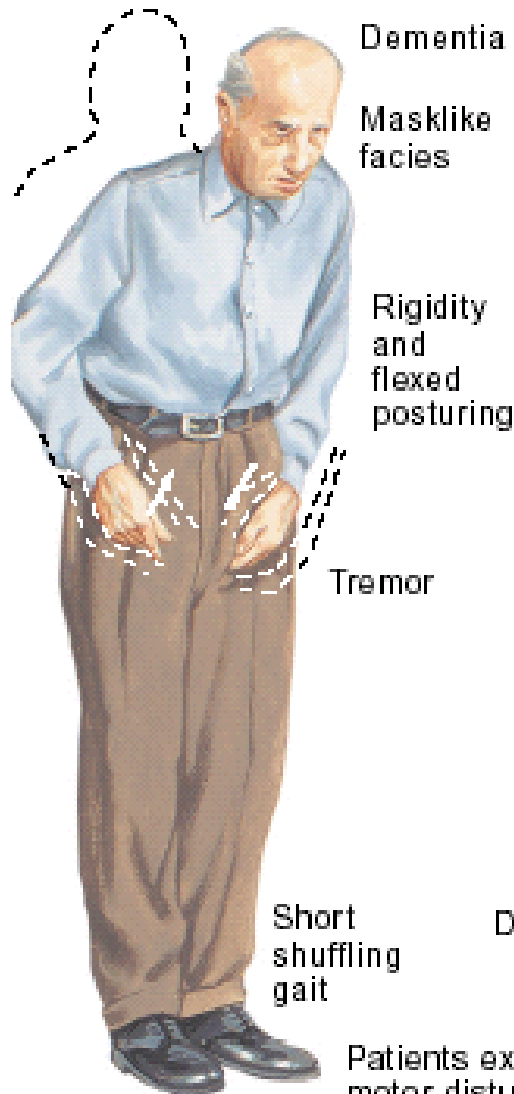
Patient 4

- 65M with memory problems.
- Also Parkinsonism
 - Masked faces, shuffling gait, cogwheeling
- Visual hallucinations of people and animals
- Visual perceptual defects
- Wife complains he is waking her up moving & kicking her in his sleep

Dementia with Lewy Bodies /
Parkinson's Disease Dementia

Dementia with Lewy Bodies

Dementia with Lewy bodies



Lewy bodies found in substantia nigra as well as other brainstem nuclei and cortex

10

15

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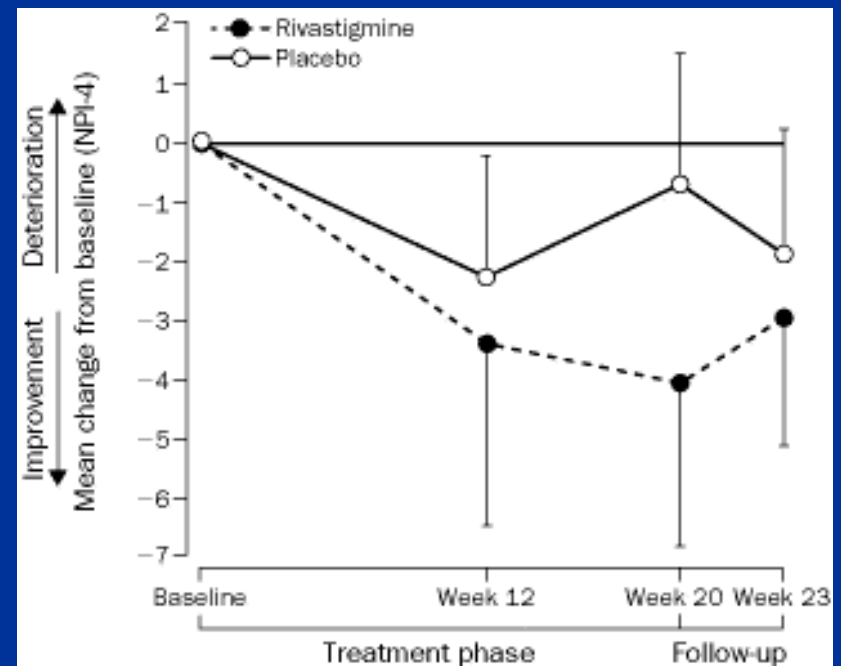
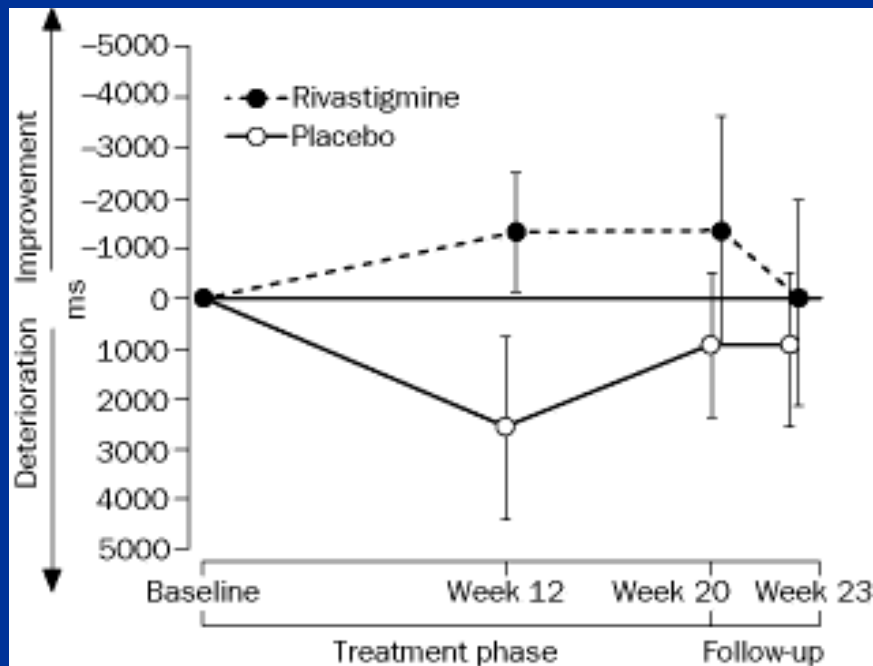
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20

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& Solomon,
2016

Rivastigmine in Dementia with Lewy Bodies



Rivastigmine patch is FDA approved
for Parkinson's Disease Dementia

Lancet 2000 356:2031-6

Patient 5

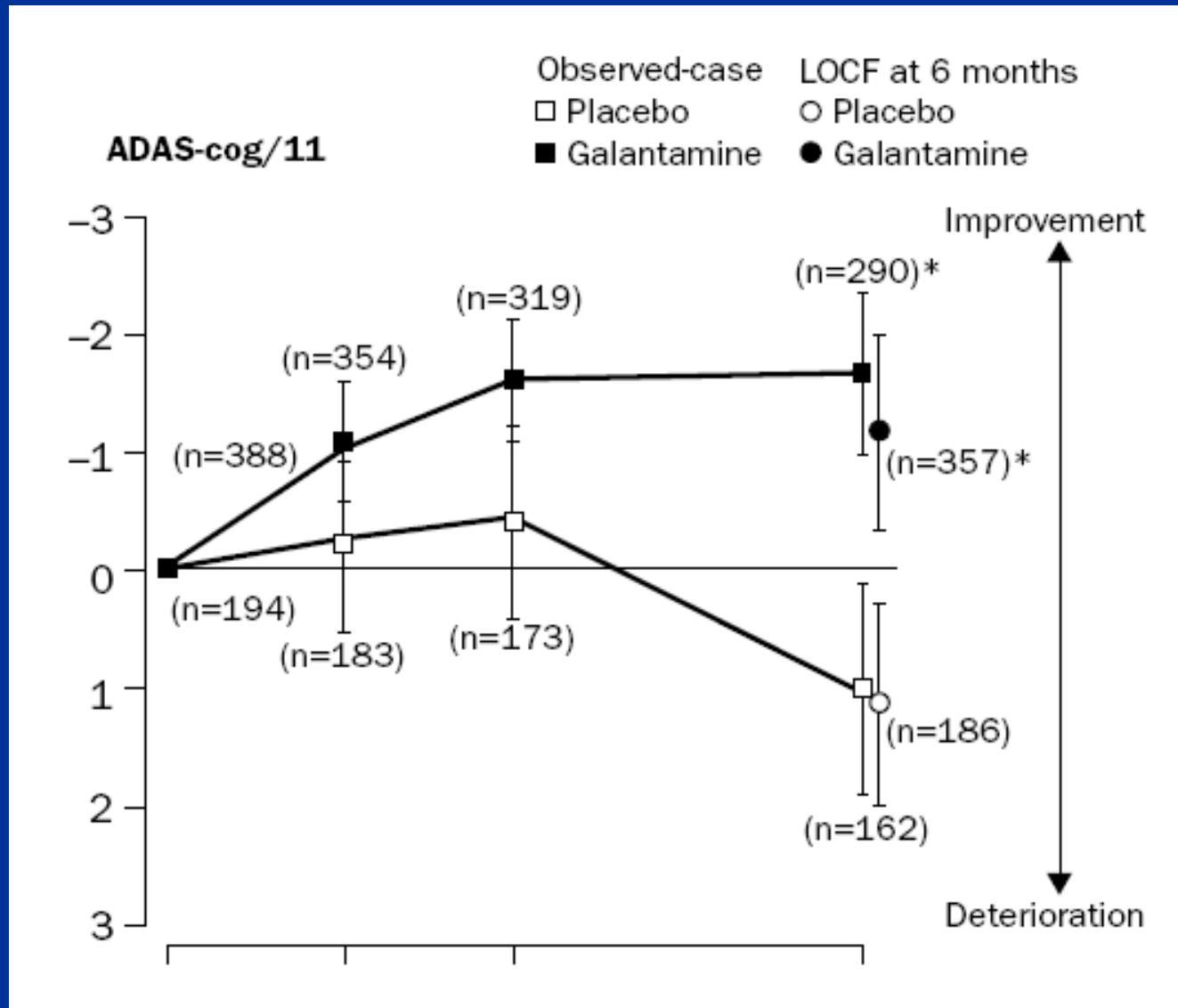
- 74M 6 yr history of “Small TIAs.”
- Family complains of memory problems, but patient remembered the last Red Sox game well
- Has trouble recalling specific things, but is generally oriented to time, place & what is going on
- Poor walking
- Early incontinence

Vascular Dementia





Galantamine in vascular dementia



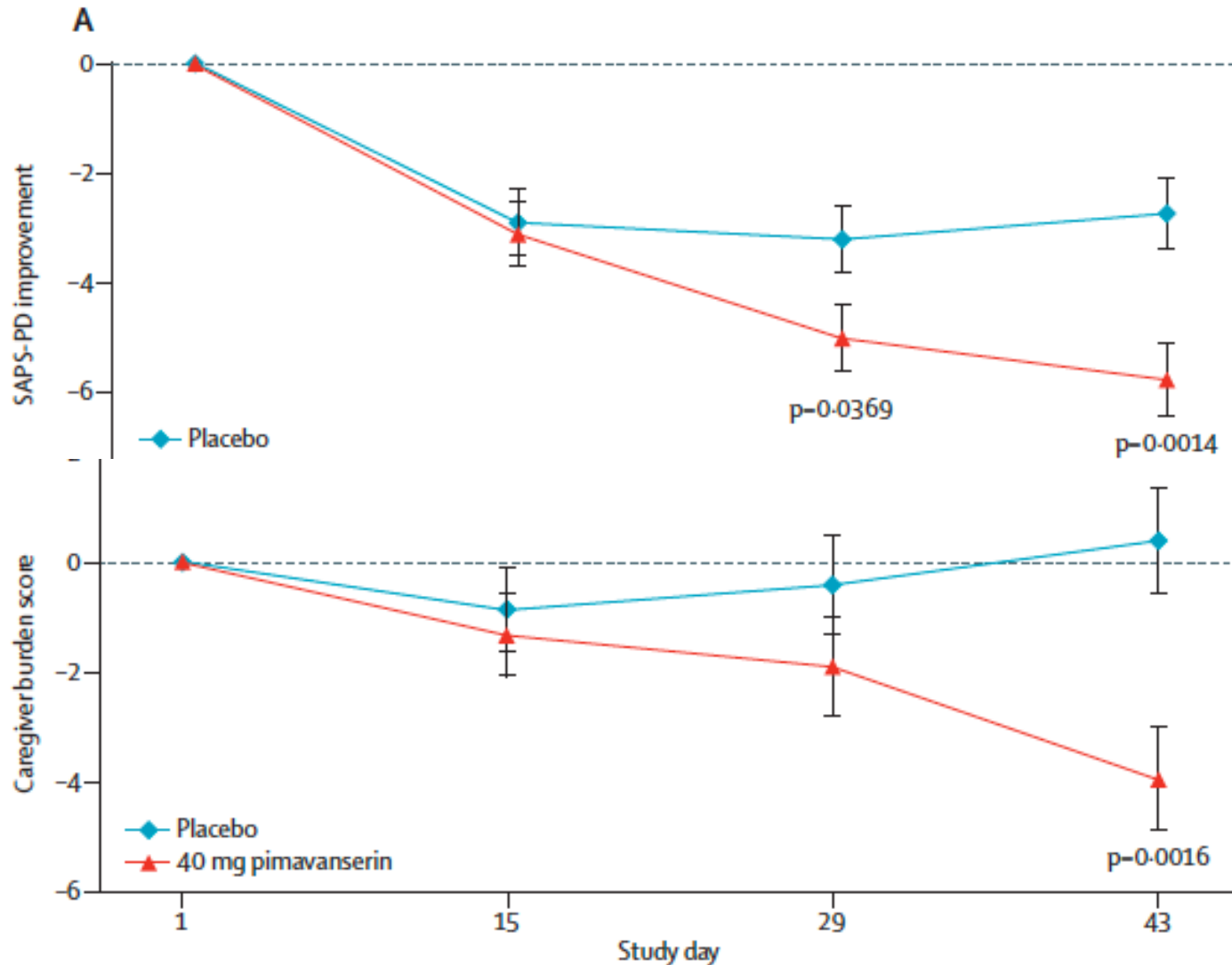
Managing agitation

- Try to determine the underlying cause of agitation
- Non-pharmacological: reassure, reconsider, redirect
- Agitation is often due to anxiety
 - Start with sertraline/Zoloft 50 to 100 mg or escitalopram/Lexapro 10-20 mg (others not as good)
- Manage sleep cycle disturbances
 - Limit naps, Ritalin SR 20 mg or provigil in AM if nec.
- Daytime agitation
 - risperidone/Risperdal: start 0.25 mg QD
- Nighttime agitation
 - trazodone: start 50 mg QHS
 - quetiapine/Seroquel: start 25 mg QHS
 - **NEW!** pimavanserin (Nuplazid) 40 mg QD for PDD
 - **NEW!** 20 mg Dextromethorphan HBr / 10 mg Quinidine sulfate (Nuedexta)

Pimavanserin for psychosis in PDD

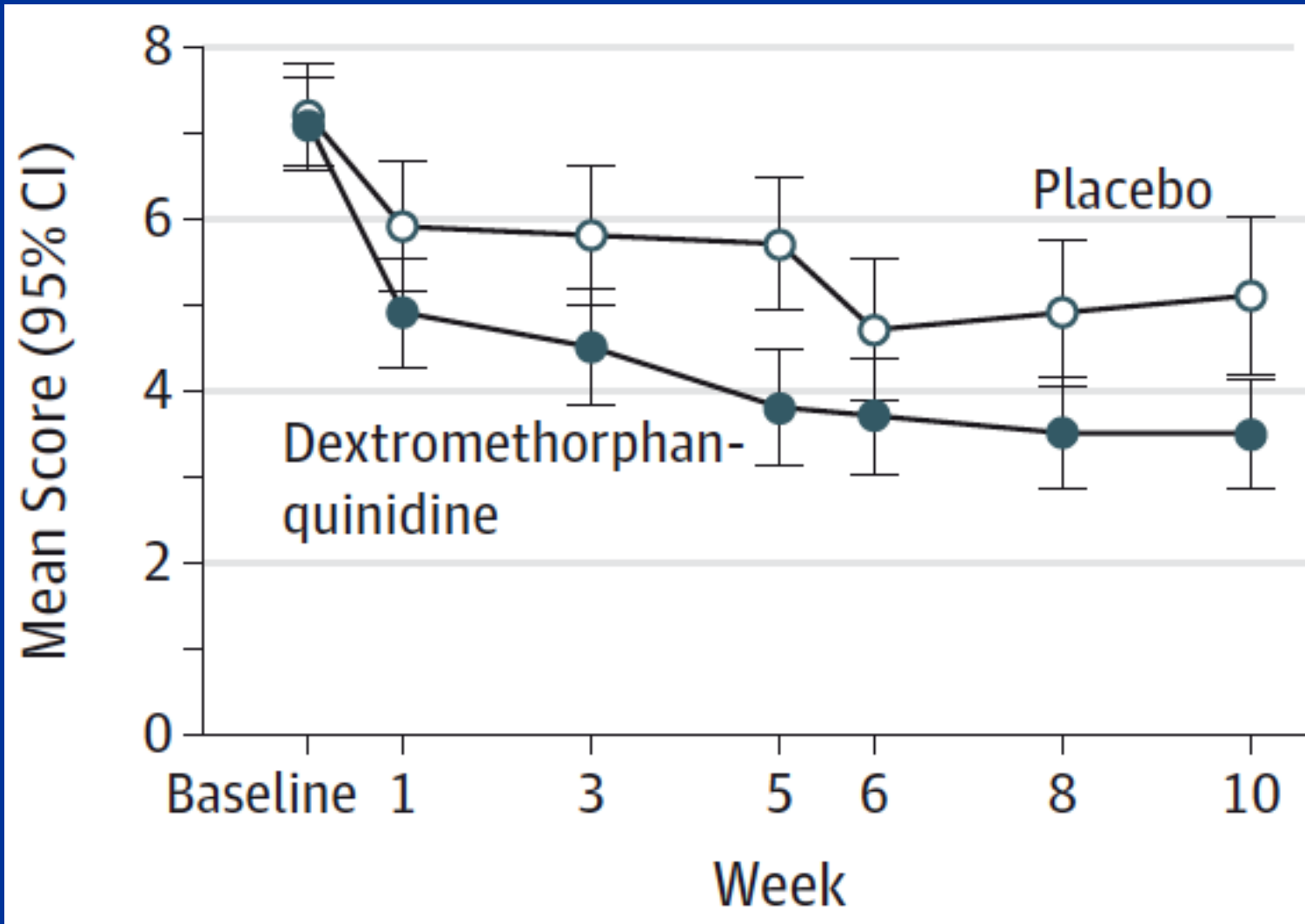
selective serotonin 5-HT_{2A} inverse agonist

Trials on-
going in
Alzheimer's
disease



Cummings et al., Lancet. 2014 383(9916):533-40

NPI Aggression Domain Scores



Weeks 1: 20/10 QD, 2-3: 20/10 BID, 4+: 30/10 BID

JAMA. 2015;314:1242-54

Pseudobulbar Affect (PBA)

- Crying or laughing for little or no reason.
- Very common in AD, VaD, & other dementias
- New medication FDA approved to reduce PBA:
 - 20 mg Dextromethorphan HBr / 10 mg Quinidine sulfate (Nuedexta)
 - 1 capsule daily x 7 days, then 1 capsule Q12H
 - Common adverse reactions: falls, diarrhea, UTI, dizziness, cough, vomiting, asthenia, peripheral edema, influenza, ↑GGT, & flatulence
 - Serious side-effects/contraindications from quinidine
 - More DM? add 10 mg/5 ml BID to Nuedexta BID

Driving

- Patients with very mild AD have accident rates similar to 16-19 year old drivers.
 - (Neurology 2010 74:1316)
- Have family member ride as passenger.
 - If family members are comfortable riding with patient driving, then patient is probably OK to drive
 - Need to ride with them monthly
- Driving evaluation at local registry of motor vehicles or rehabilitation hospital if controversy.

Non-pharmacologic approaches

- Aerobic Exercise
- Social activities
- Mediterranean diet
- “Should I do crossword puzzles, doc?”
 - If you want to get better at them...
 - Better than TV...

Take Home Points

- New Criteria allow diagnosis of AD & MCI due to AD with greater accuracy
- 70+% of dementias are Alzheimer's disease
- Check Vitamin D
- Think about dementia w/Lewy bodies, Vascular, & Chronic Traumatic Encephalopathy
- Cholinesterase inhibitors treat memory loss
- Consider Dextromethorphan / Quinidine (Nuedexta) for pseudobulbar affect & agitation
- Consider pimavanserin (Nuplazid) for psychosis
- Alzheimer's Association is a great resource for families
www.alz.org

End