Alzheimer's Disease:
future of clinical care?

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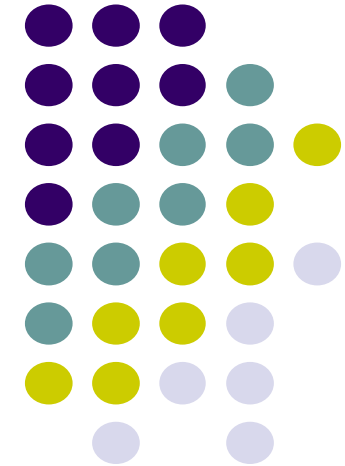
May 2, 2024



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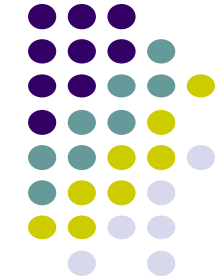
Disclosures & Acknowledgments



- No financial disclosures
- The views and opinions in this presentation are those of the presenters and they do not necessarily reflect, and should not be taken as, official policy of the U.S. Department of Veterans Affairs or the University of Washington.

Dementia Is . . .

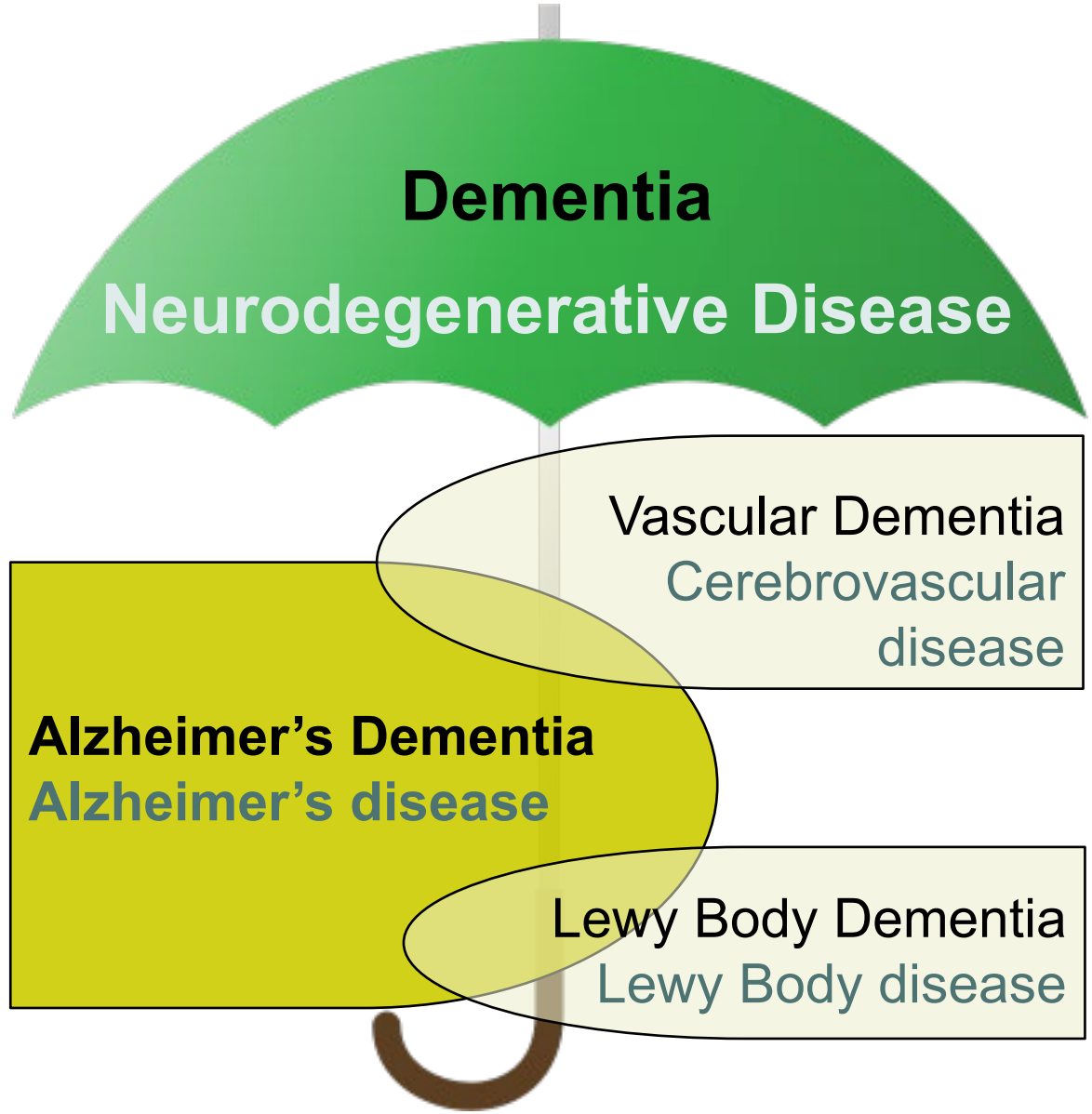
A decline in some aspect of cognitive function and/or behavior

A diagnosis of EXCLUSION

Daily Living Skills

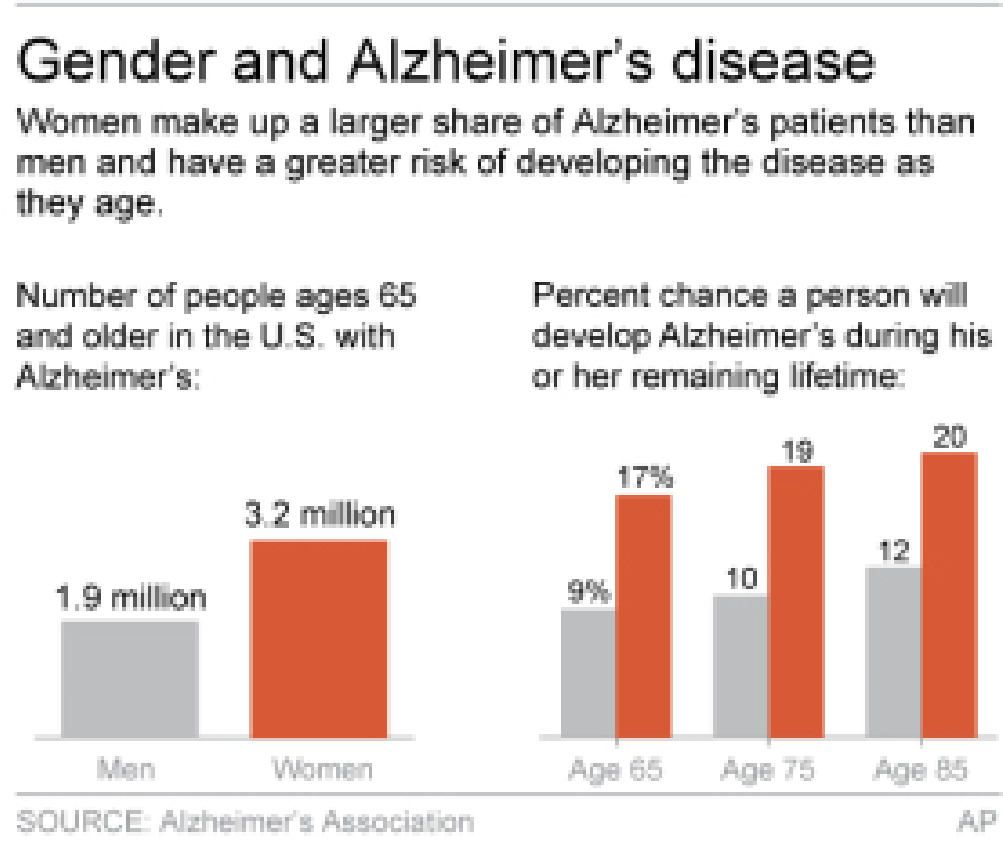
- ✓Significant
  - functional consequences
- ✓Chronic
  - insidious onset and progressive course
- ✓Loss
  - new impairments (not lifelong)
- ✓Structural Damage
  - neurons die

Top 3 Causes of Dementia in Older Adults

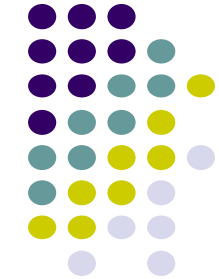


Late-Onset Alzheimer's Dementia

- Prevalence estimate 2019:
  5.6 million age 65+
- Lifetime risk
- Gender differences
- Race differences
- Risk factors
- Protective factors



Genetics of Alzheimer's disease



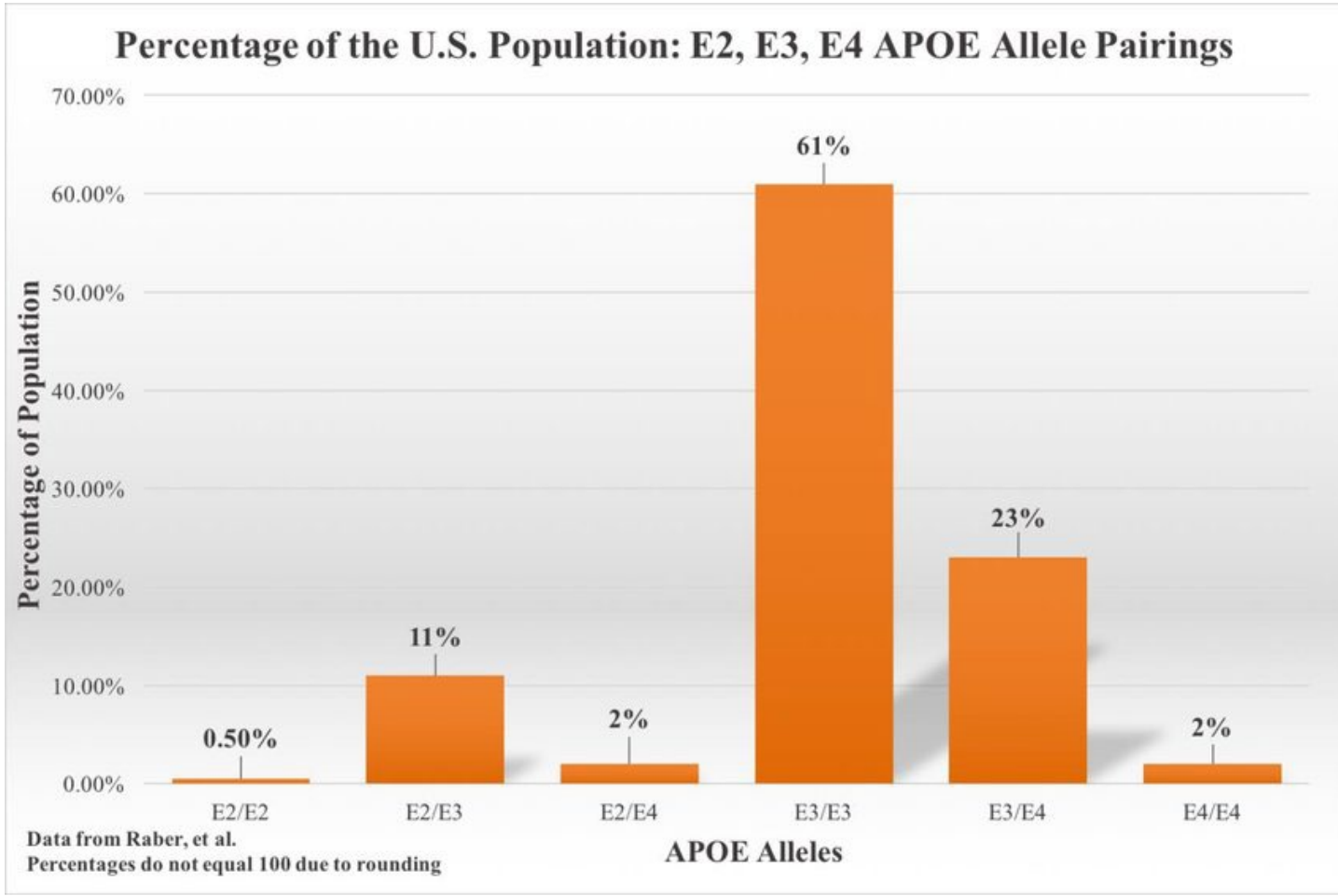
- Autosomal dominant mutations: rare, <5% of all cases, "early-onset" or "familial" AD
  - APP gene is mapped to chromosome 21
    - Trisomy 21 – Down Syndrome and AD by age 30
  - PSEN1 maps to ch 14, helps process/cleave APP
  - PSEN2 maps to ch 1, helps process/cleave APP
  - https://rarediseases.info.nih.gov/diseases
- Only one consistent association for "sporadic", "late-onset" AD
  - E4 allele of APOE (gene found on ch19)
    - Betram, et al., Nature Genetics, 2007

Genetic risk factor for AD

- Apolipoprotein E (APOE) comes in 3 different versions and we each have 2 alleles
  - E2 is a protective factor
  - E4 is a risk factor

Genotype	E2/E2	E2/E3	E2/E4	E3/E3	E3/E4	E4/E4
Disease Risk	40% less likely	40% less likely	2.6 times more likely	Average risk	3.2 times more likely	14.9 times more likely

Should I get tested for Alzheimer's risk?
www.theconversation.com



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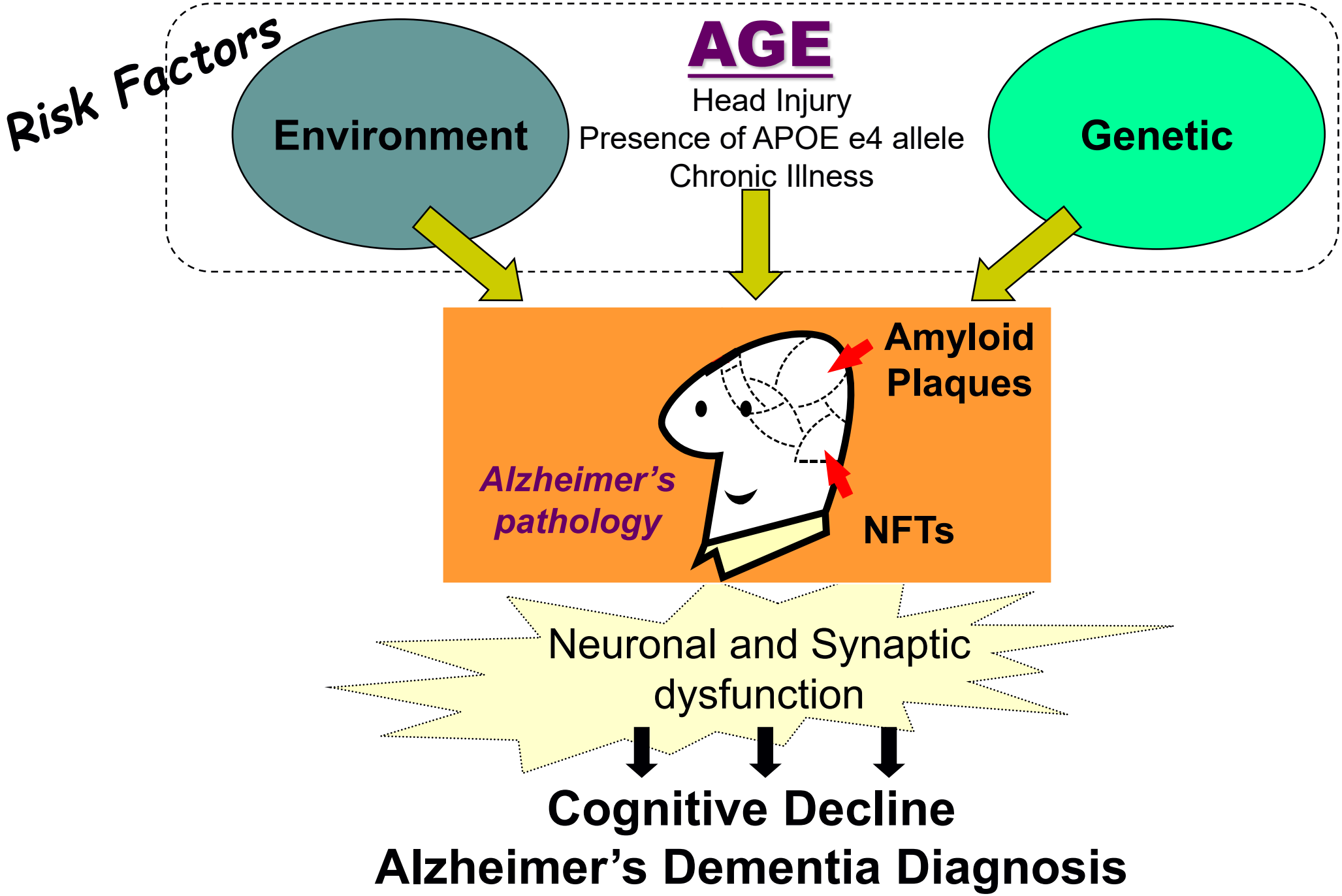
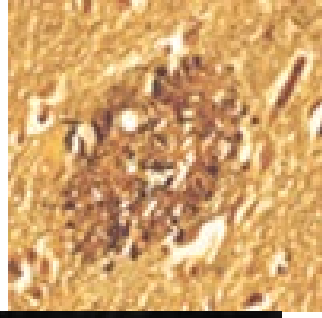
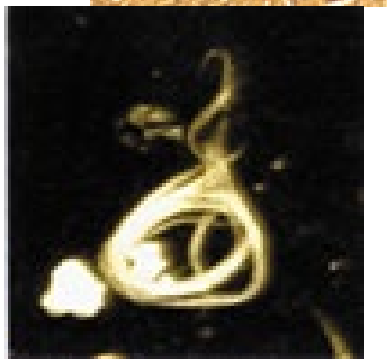

Risk Factors
Environment
AGE
Head Injury
Presence of APOE e4 allele
Chronic Illness
Genetic
Amyloid Plaques
Alzheimer's pathology
NFTs
Neuronal and Synaptic dysfunction
Cognitive Decline
Alzheimer's Dementia Diagnosis

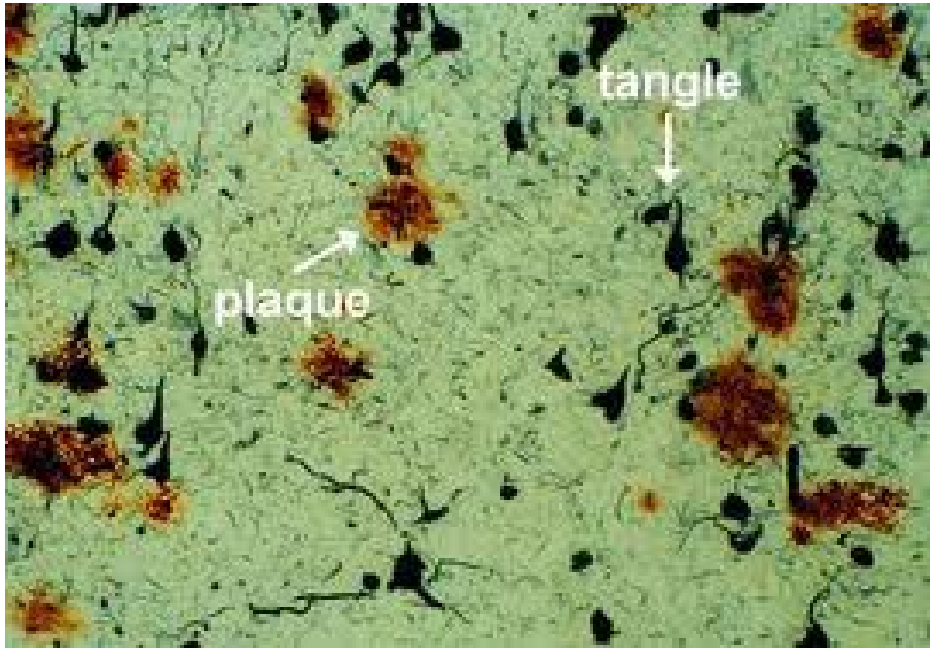
Definite Alzheimer's Disease

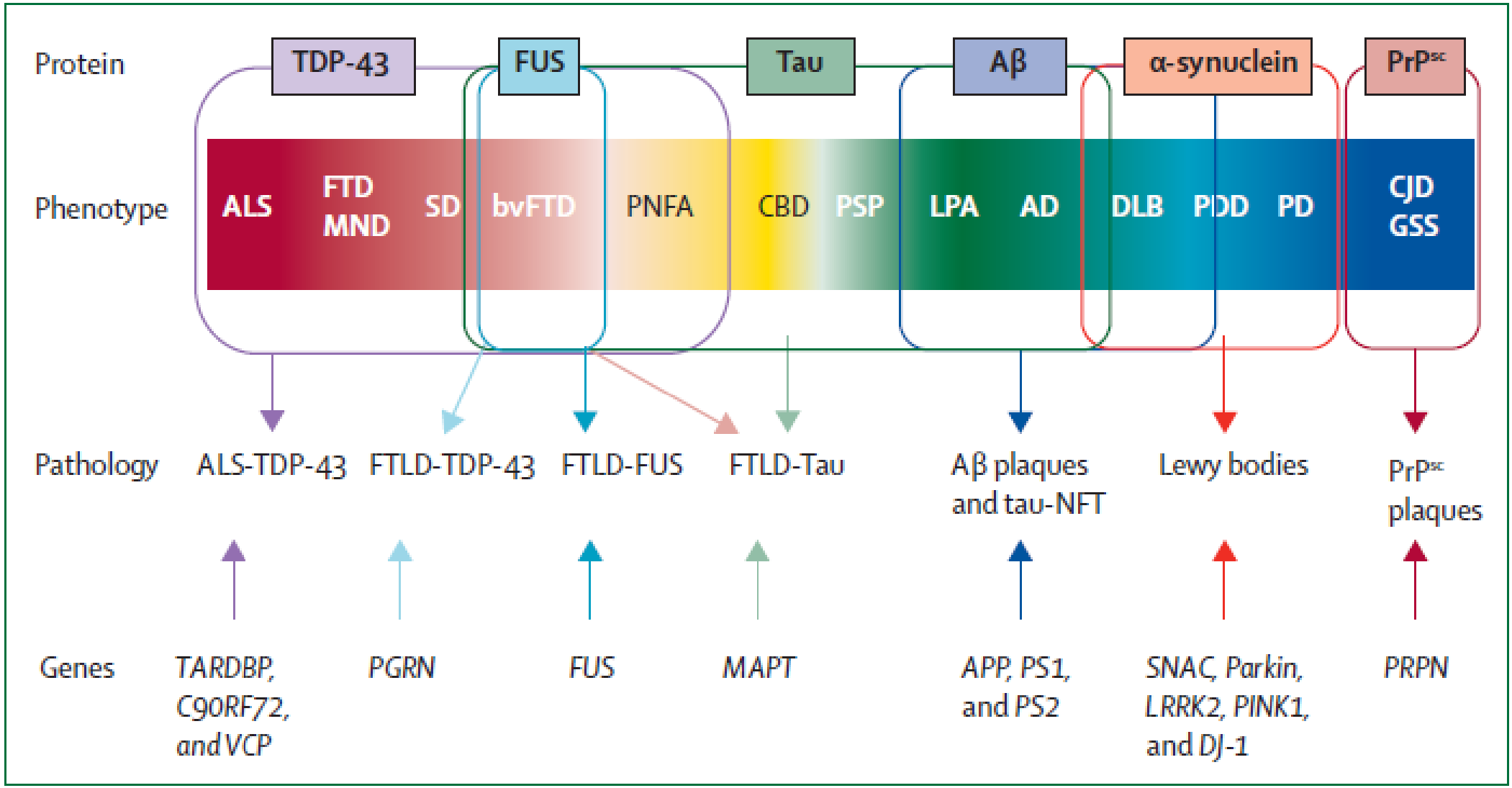




- Evidence on autopsy of:
  - Amyloid beta (Aβ) plaques and neurofibrillary tangles (NFTs)
  - In a certain density and distribution

- NFTs - Bundles of twisted threads that are the product of collapsed neural structures (contain abnormal forms of *tau* protein
- Aβ plaques - dense deposits of deteriorated *amyloid* protein, surrounded by clumps of dead nerve and glial cells

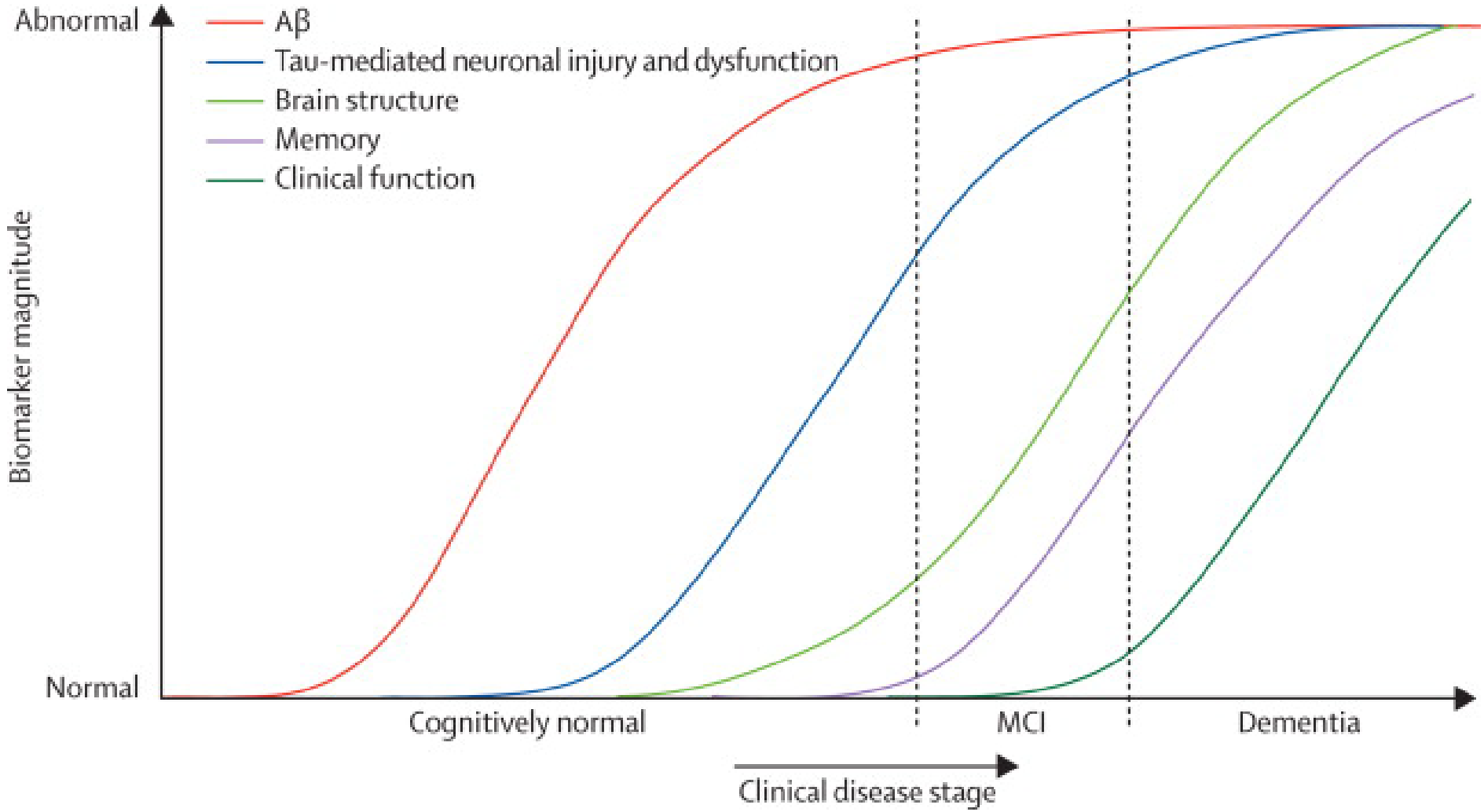


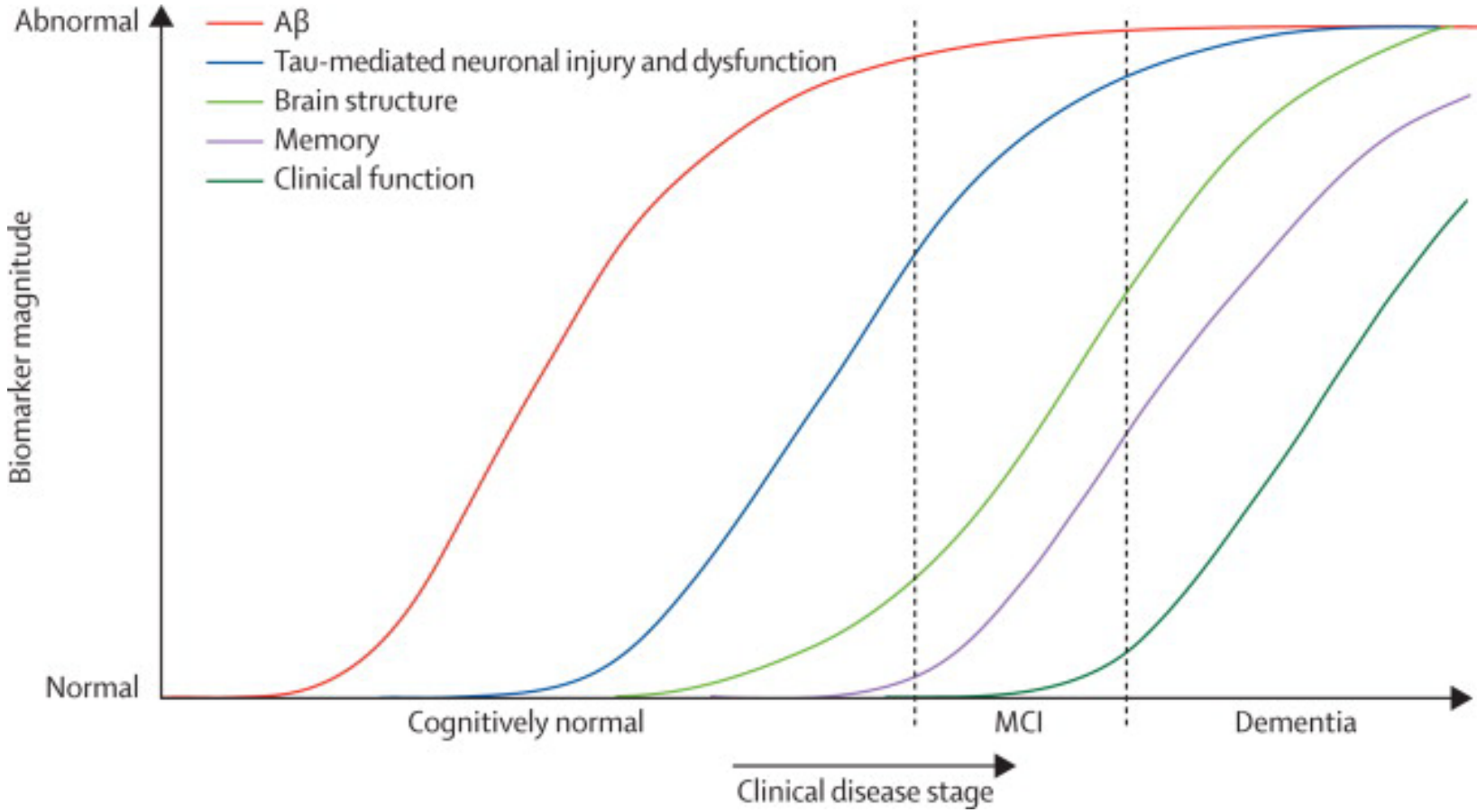


Villemagne, et al, Lancet Neurology, 2015

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade.

Jack, et al. 2010. Lancet



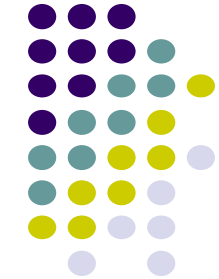


DIAGNOSTIC CHALLENGES/ADVANCES

MRI – research/clinical scans

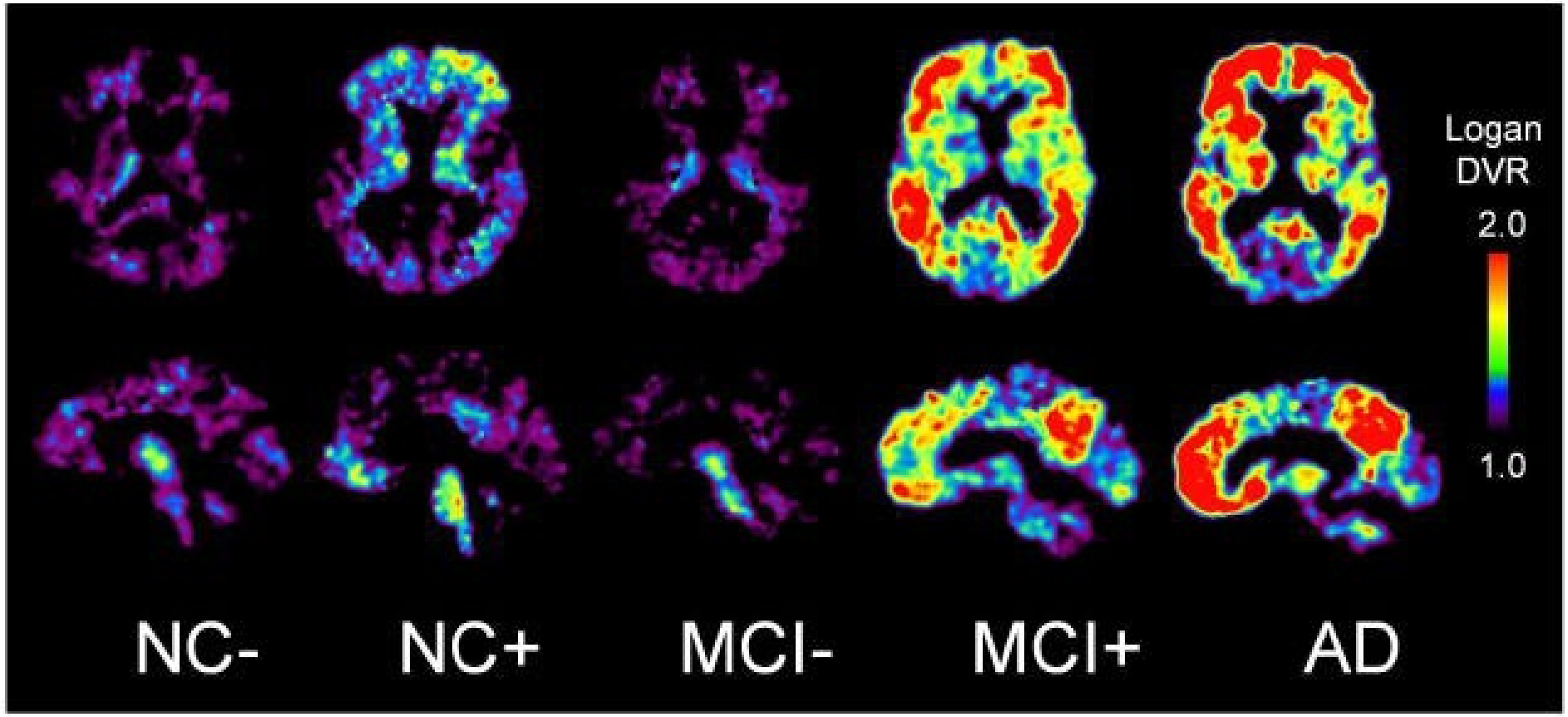
- Manual and semi-automated and automated methods
  - Voxel-based morphometry
  - Cortical thickness mapping
- Imaging markers can detect early AD with good accuracy (e.g., Frisoni, et al, 2010; Cuingnet, et al, 2011) and can predict AD (Cuingnet, et al, 2011; Wolz, et al, 2011)
  - Still prediction accuracy 18 months before conversion was ~65% (Wolz, et al, 2011)
- Clinical tools are available which can bolster diagnosis (e.g., MTA score, Scheltens, et al, 1992)

PET imaging



- Uses radiolabeled ligands to measure metabolic and neurochemical processes
- Initial dementia PET research:
  - FDG = fluorodeoxyglucose; marker for brain metabolism (glucose) for ~30 years
  - Amyloid tracers bind to fibrillar amyloid plaques: Pittsburgh compound B (PiB; research since 2004) and Florbetapir (^{18}F), FDA-approved in 2012

Amyloid Imaging:
Normal Cognition to Alzheimer's Dementia



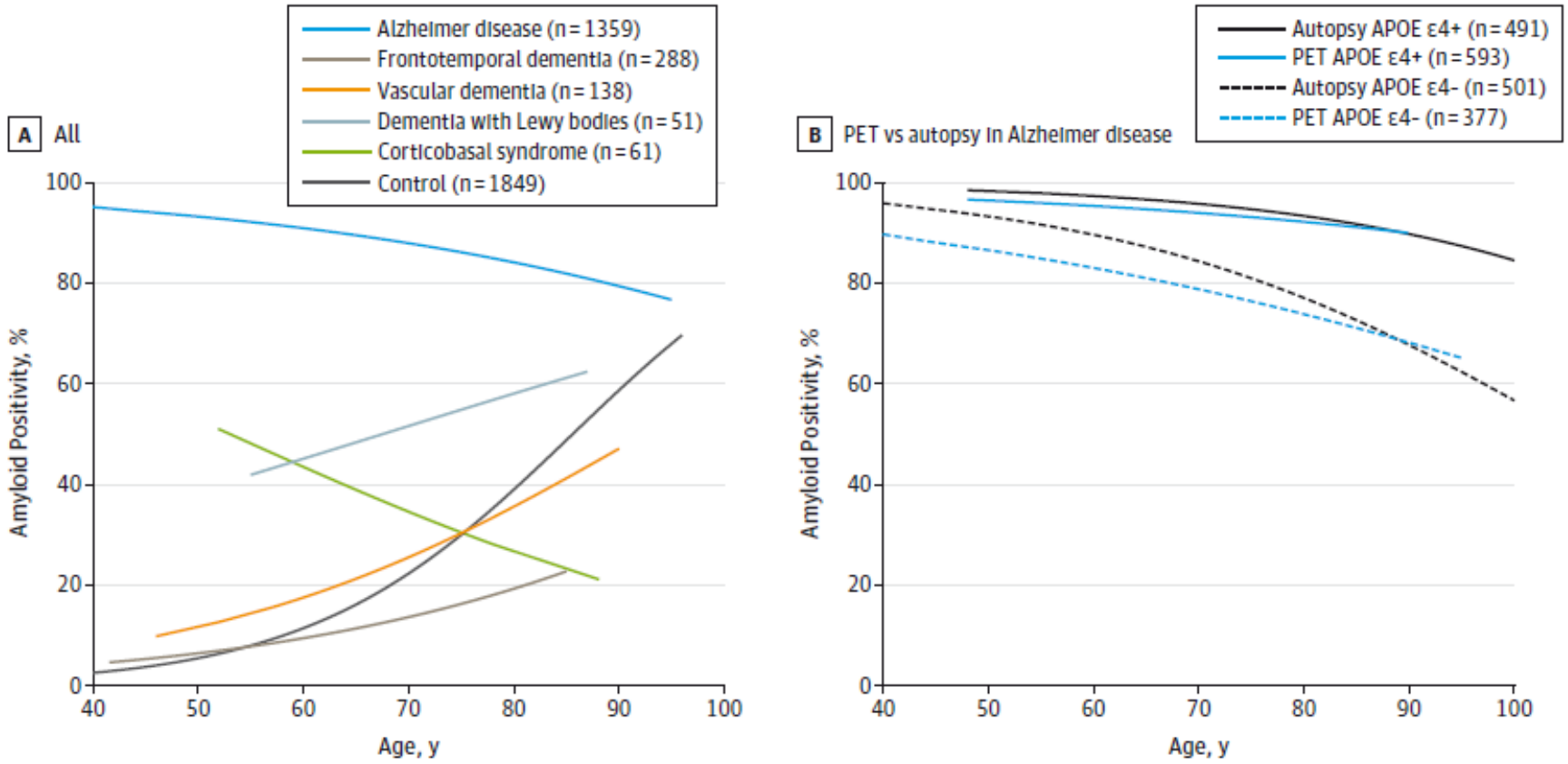
Wolk & Klunk, Curr Neurol Neurosci Rep, 2009

Original Investigation

Prevalence of Amyloid PET Positivity in Dementia Syndromes
A Meta-analysis

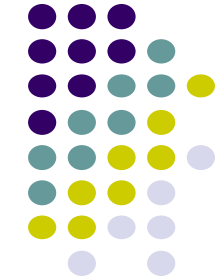
Rik Ossenkoppele, PhD; Willemijn J. Jansen, MSc; Gil D. Rabinovici, MD; Dirk L. Knol, PhD; Wiesje M. van der Flier, PhD; Bart N. M. van Berckel, MD, PhD; Philip Scheltens, MD, PhD; Pieter Jelle Visser, MD, PhD; and the Amyloid PET Study Group

Figure 2. Prevalence of Amyloid Positivity on PET According to Age for the Different Dementia Diagnostic Groups

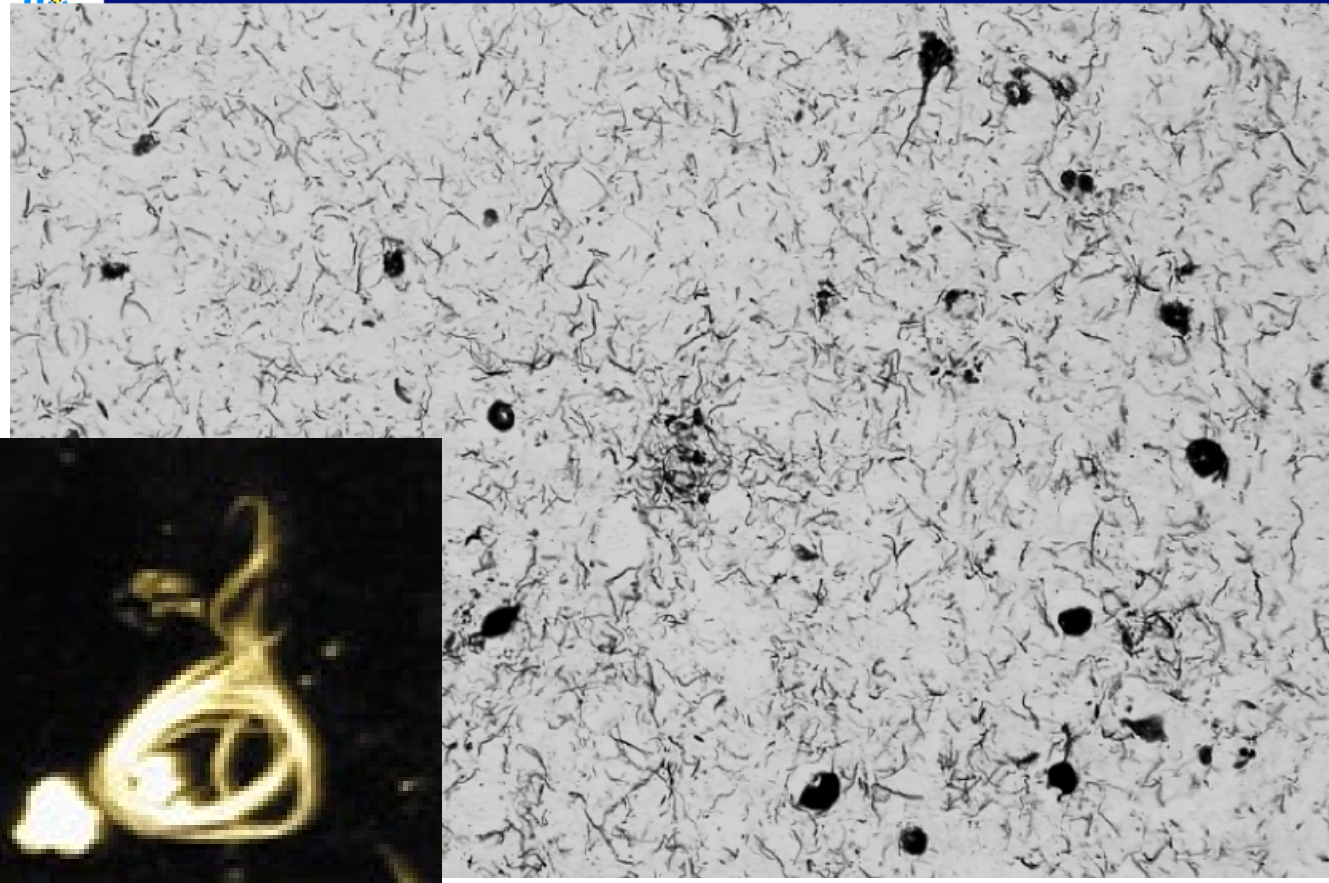


Ossenkoppele, et al, JAMA, 2015

PET imaging in Normal Controls



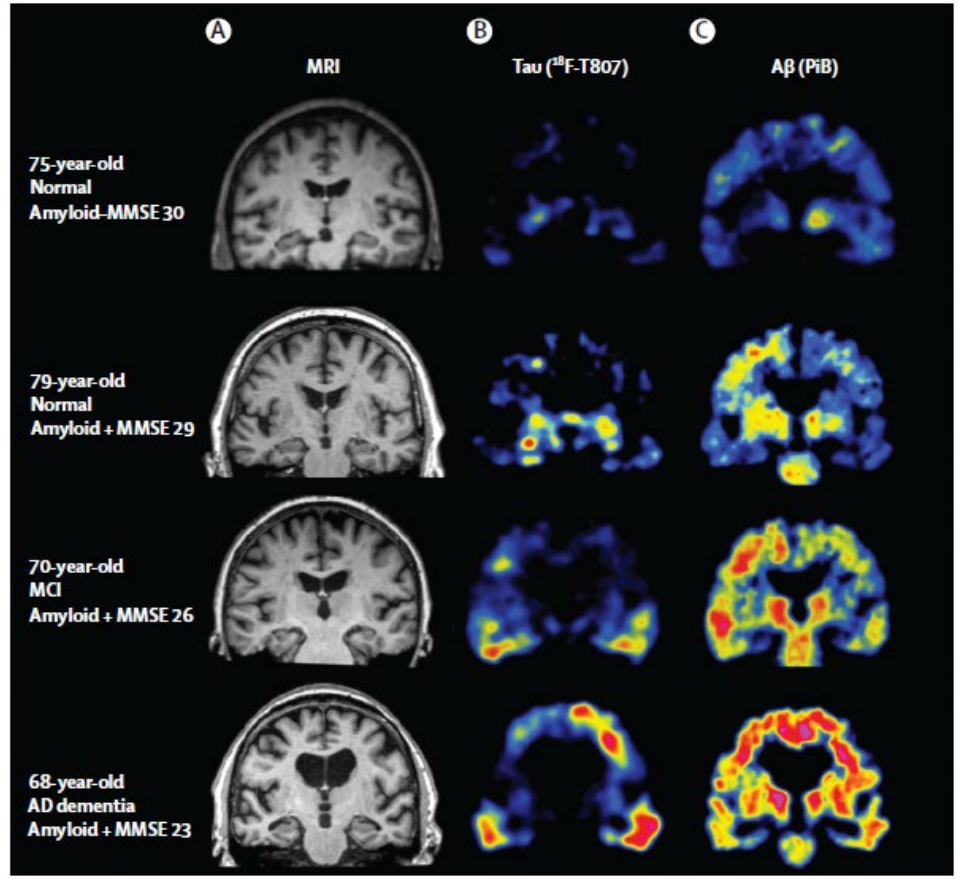
- Approximately 25-30% of older adults with normal cognition are amyloid positive (Johnson et al. 2012, Mintun et al. 2006, Villemagne et al. 2008)
- Follow-up suggests they are more likely to progress to MCI or AD (Mintun et al. 2006, Villemagne et al. 2008)
- Cognitive reserve independently modulates the relationship between amyloid and cognition in healthy older adults (Rentz et al. 2010) as well as in patients with MCI and AD (Kemppainen et al. 2008, Vemuri et al. 2011)



WHAT ABOUT TAU?

Tau Imaging

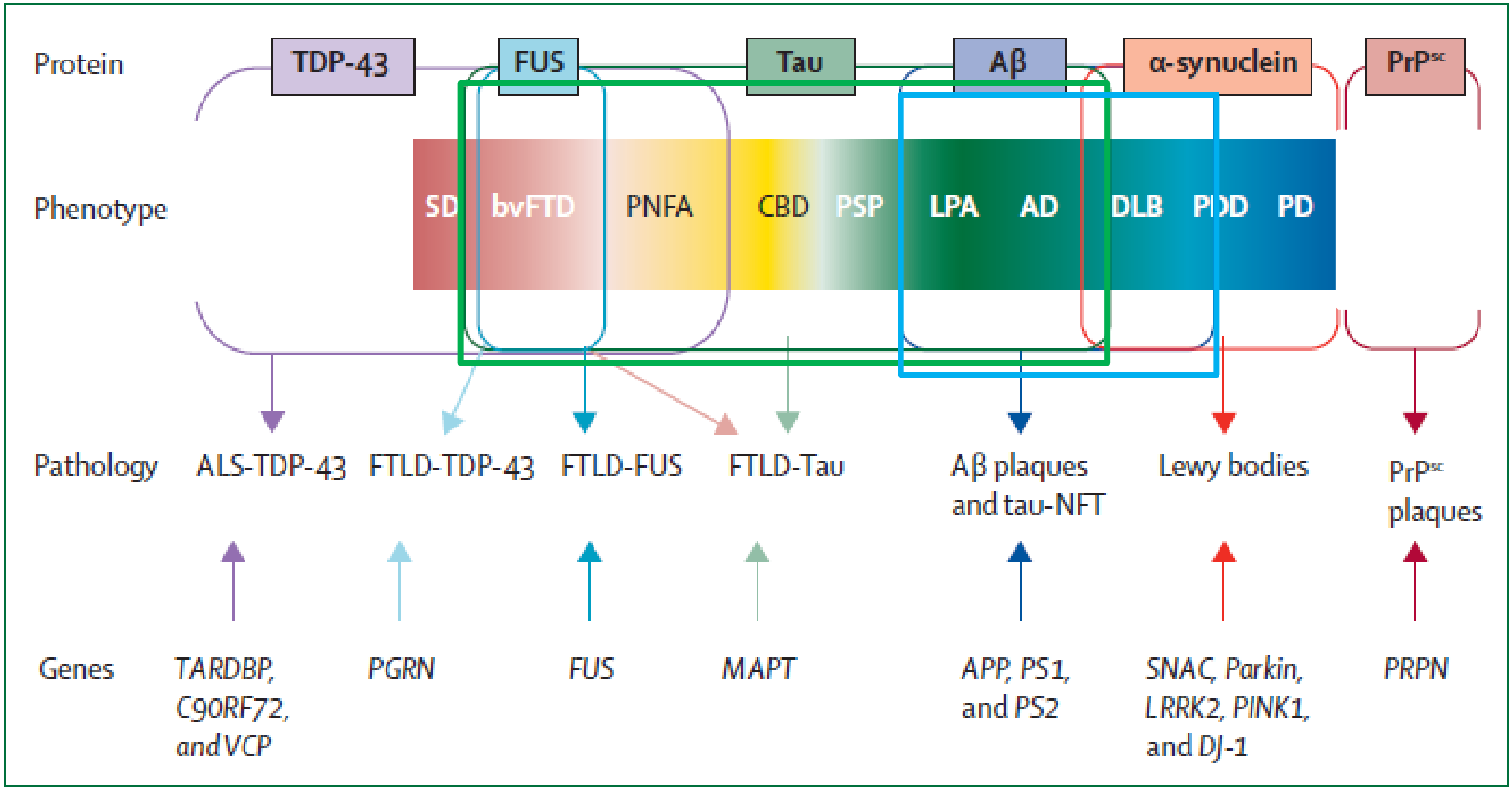
- Tau imaging challenges:
  - Intracellular
  - Six tau isoforms with different structures
  - In AD, tau aggregates are coexistent with beta amyloid
  - In AD, tau is in lower concentrations than beta amyloid
- Must have high selectivity for tau over Aβ
  - High binding affinity
  - Low non-specific binding
- Ability to cross the BBB, long half-life, not metabolized
- May 2020 FDA approval 1st gen tau PET radiopharmaceutical: flortaucipir
- 3 tracers are currently FDA approved



Villemagne, et al, Lancet Neurology, 2015

Other biomarker methodologies

- Presence of an APOE e4 allele increases risk of AD and can be done clinically to add to diagnostic workup
- CSF – e.g., phosphorylated tau (ptau) ratio to Abeta 40/42
- Plasma biomarkers of amyloid and tau are rapidly improving; should achieve clinical utility
  - These could become incredibly important as screening measures – can be more accessible



WHY SO EXCITING?

Short 0N3R isoform	Myotonic dystrophy	Neurofibrillary tangles	NA

Adapted from Villemagne et al,[19] by permission of Future Medicine. 3R–three repeat. 4R–four repeat. NA–data not available. Short 0N3R–the shortest isoform of fetal tau (where N denotes the number of N-terminal inserts and R the number of microtubule-binding domains). *Tau conformation at much lower prevalence.

Table: **Morphological and ultrastructural conformations of tau isoforms in tauopathies**

Research Framework

ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

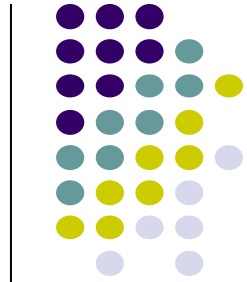
Table 5
Risk of short-term cognitive decline based on the biomarker profile and cognitive stage

Biomarker Profile	Syndromal Cognitive Stage: Cognitively unimpaired	MCI	dementia
$A^- T^- (N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
$A^+ T^- (N)^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
$A^+ T^- (N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
$A^+ T^+ (N)^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI (Prodromal AD)	Alzheimer's disease with dementia
$A^+ T^+ (N)^+$			

Non-Alzheimer's continuum profiles are not included in table because the risk associated with different combinations of T+(N)-, T+(N)+, T-(N)+ among A- individuals has not been established

□ rate of short term clinical progression expected to be low

■ rate of short term clinical progression expected to be high



- 1993 Cognex is first FDA approved drug to treat AD
- 1994 Possible effect of estrogen on AD is postulated
- 1996 Aricept FDA approved
- 1997 Effect of antioxidants on AD studied
- 1999 Genetic mutations linked to programmed cell death of neurons
  - Development of techniques toward direct genetic manipulation for treatment of AD
  - First anti-AD vaccine tested
- 2000 Exelon FDA approved to treat AD
  - Brain imaging used to study AD
- 2001 Razadyne (previously Reminyl) FDA approved
- 2002 Clinical trial of anti-Alzheimer's disease vaccine conducted
- 2003 Namenda FDA approved
- 2004 President Reagan dies of AD; Diabetes linked with increased risk of Alzheimer's; PiB compound (amyloid PET imaging) published
- 2020 1st tau tracer for PET (tau PET imaging)
- **2021** aducanumab, FDA grants controversial, accelerated approval
- 2023 lecanemab, FDA accelerated approval Jan, July full approval
- 2023 donanemab results released July, still not yet FDA approved

What can you expect from medications for dementia?

if chronic fatigue and mild depression make simple tasks seem this big...

Ritalin® (methylphenidate CIBA) relieves chronic fatigue that depresses and mild depression that fatigues

Ritalin gently overcomes mild depression and the fatigue so often associated with it. The drug brightens mood and improves performance, helps restore alertness, enthusiasm, and drive. Patients often report that fatigue and worry seem to vanish; they are able to go all day without getting tired.

Widely cited for its outstanding record of safety, Ritalin is virtually free of the toxic effects of the more potent antidepressants. Its action is usually uncomplicated by excessive stimulation or sudden letdown.

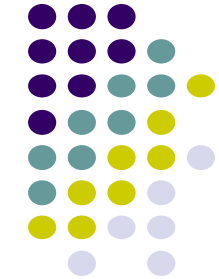
Ritalin is exceptionally well tolerated, even by the elderly.

CONTRAINDICATIONS: Marked anxiety, tension, agitation. Contraindicated in patients with glaucoma and with epilepsy, except to combat lethargy induced by anticonvulsant drugs. WARNINGS: Should not be used for severe depression (exogenous or endogenous) except in the hospital under careful supervision Should not be used to increase mental or physical capacities beyond physiological limits.
PRECAUTIONS: Patients with an element of agitation may react adversely; discontinue therapy if necessary. Use cautiously with vasopressors (*e.g.*, epinephrine, levarterenol, angiotensin amide) and in patients with hypertension.
SIDE EFFECTS: Nervousness, insomnia, anorexia, nausea, dizziness, palpitation, headache, drowsiness, skin rash. Rarely, blood pressure and pulse changes, both up and down, occur. Overt psychotic behavior and psychic dependence in emotionally unstable persons have occurred rarely.

DOSAGE: Administer orally in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Dosage will depend upon indication and individual response, the average range being 20 to 60 mg daily.
SUPPLIED: Ritalin® hydrochloride (methylphenidate hydrochloride CIBA) *Tablets*, 20 mg (peach), 10 mg (pale green) and 5 mg (pale yellow).
Consult complete product literature before prescribing.
CIBA Pharmaceutical Company, Summit, N. J.

CIBA

Categories of Medication for Dementia



Acetylcholinesterase Inhibitors

Memantine

Antibodies (“Nemabs”)

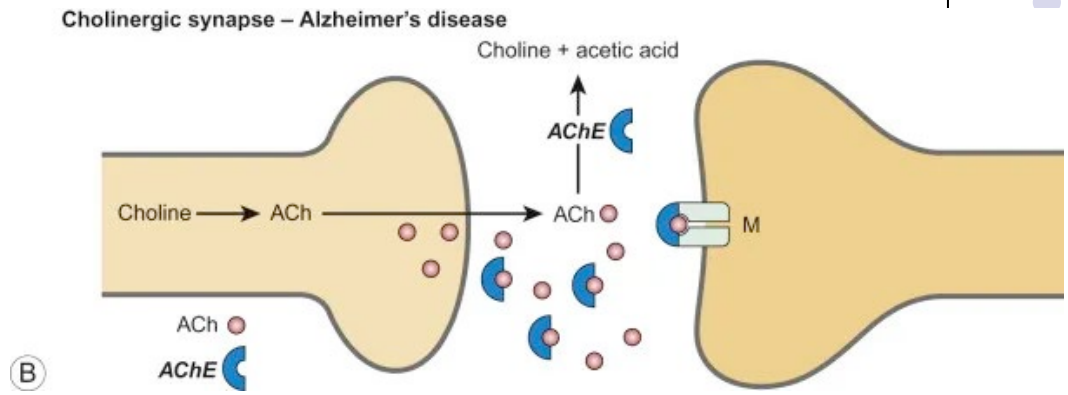
Antipsychotic

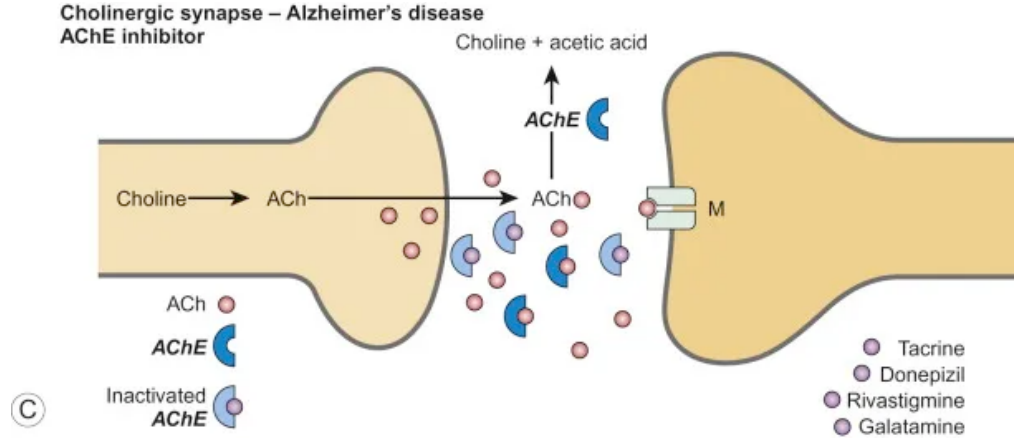
Cholinesterase Inhibitors

Donepezil

Rivastigmine

Galantamine





The ad


atHOME
thanks to ARICEPT®'s overall effectiveness
ARICEPT helps patients
be more like themselves longer™
Helped keep patients in the community for more than 5 years[1*†]
Is proven effective in cognition, function, and behavior[3-5]
Caregivers spend less time assisting patients with everyday activities[6]
Established safety and tolerability
NOW AVAILABLE!
ARICEPT ODT
donepezil HCl

The package insert

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

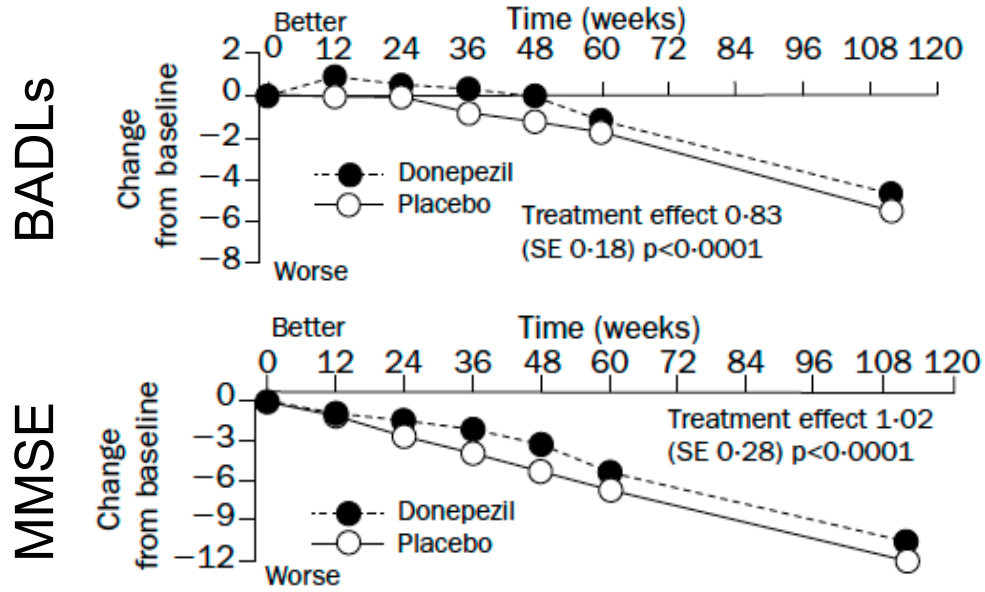
Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's disease attribute some of them to a deficiency of cholinergic neurotransmission.

Donepezil hydrochloride is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. There is no evidence that donepezil alters the course of the underlying dementing process.

Best-case effects of cholinesterase inhibitors compared to placebo:

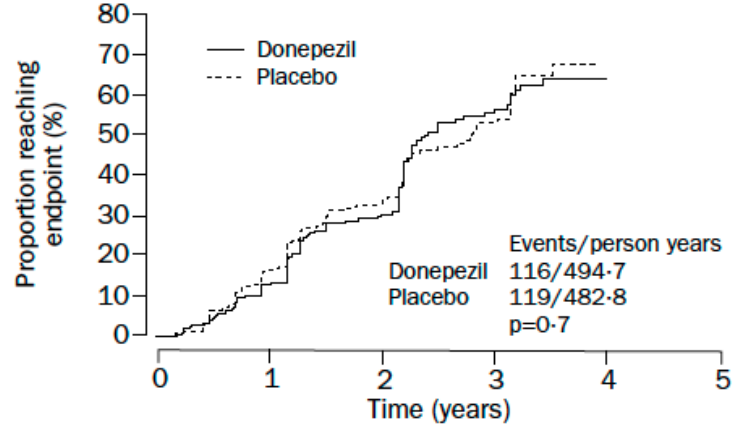
About 1 ADL on a 17-point scale

0.8 point on a 30-point cognition scale



Courtney, 2004

"no significant differences were seen between donepezil and placebo in behavioural and psychological symptoms, carer psychopathology, formal care costs, unpaid caregiver time, adverse events or deaths"



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**

Courtney, 2004

bmj.com

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

Hanna Kaduszkiewicz, Thomas Zimmermann, Hans-Peter Beck-Bornholdt and Hendrik van den Bussche

BMJ 2005;331;321-327

What is already known on this topic

It is generally assumed that several randomised controlled trials have proved the beneficial effect of cholinesterase inhibitors in patients with Alzheimer's disease on cognitive and global outcome measures

---

Numerous "evidence based reviews" support this assumption

What this study adds

Recommendations for the use of cholinesterase inhibitors do not seem to be evidence based

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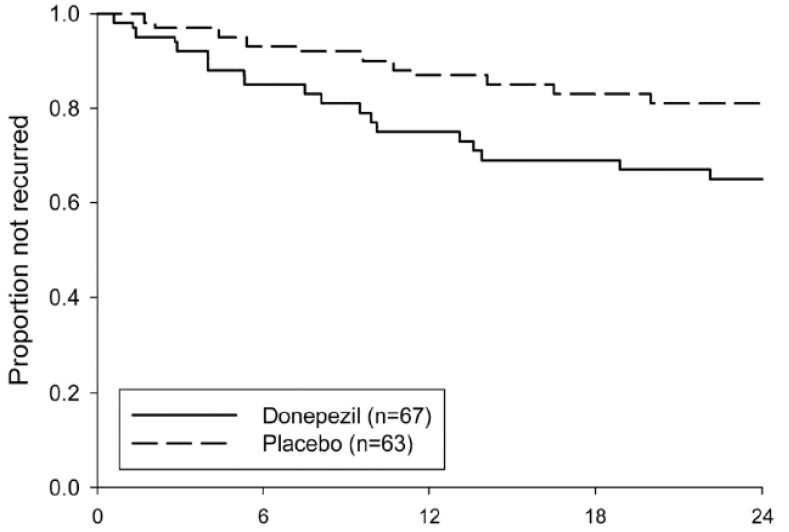
Benefits measured on rating scales were minimal

The methodological quality of the available trials was poor

Risks of Cholinesterase Inhibitors: Depression & Weight Loss



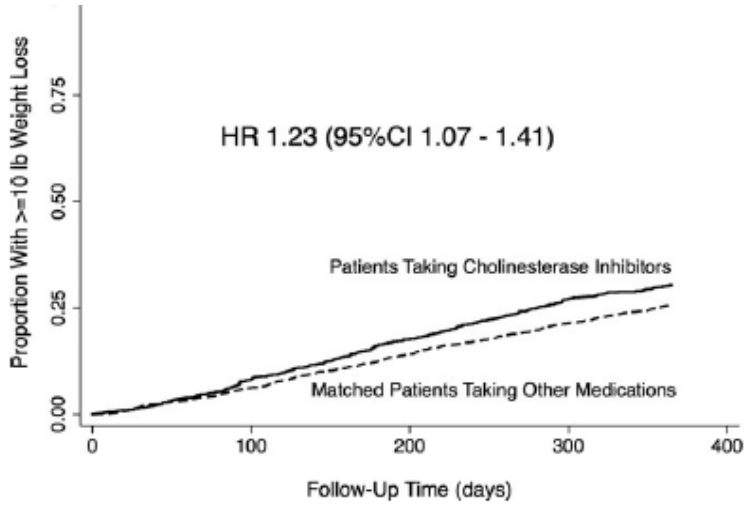
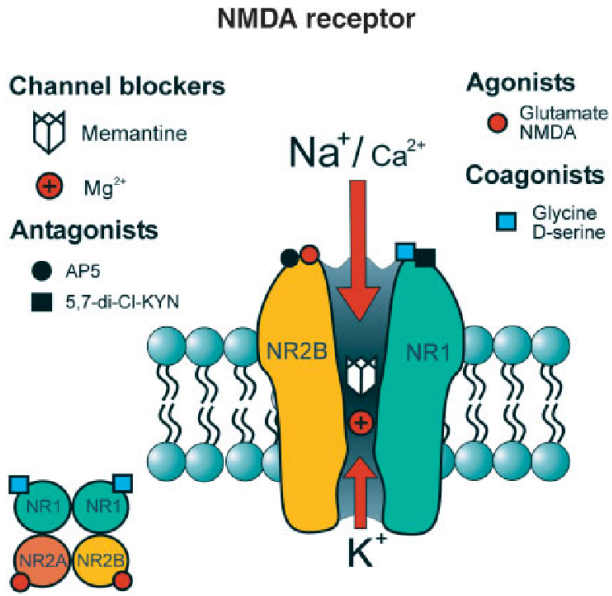


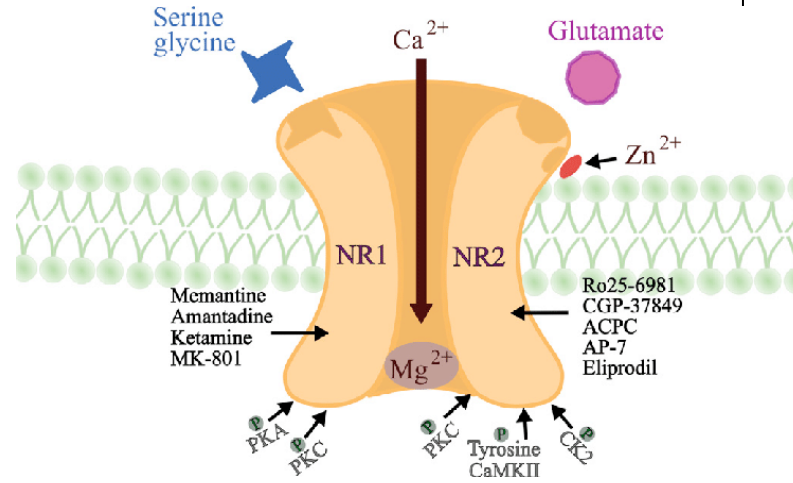
Figure 1. Time to 10-pound or more weight loss in new users of cholinesterase inhibitors vs matched controls.

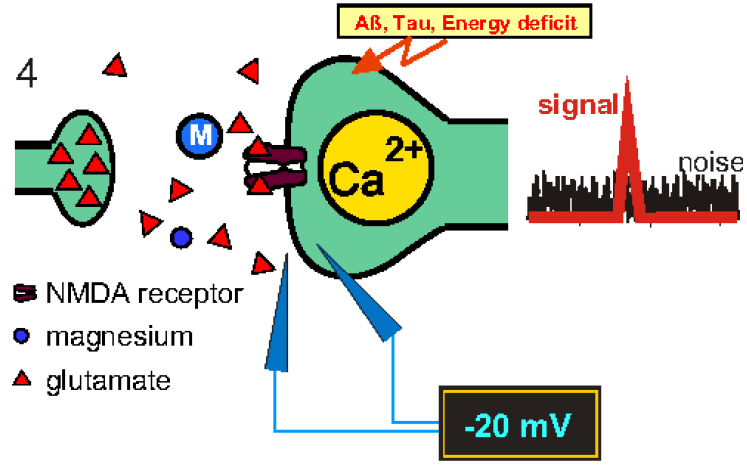
Reynolds, C. F. et al. Recurrence of depressive symptoms for patients with early to moderate dementia, starting donepezil *Arch Gen Psychiatry* 2011;68:51-60)

Weight Loss Associated with Cholinesterase Inhibitors in Individuals with Dementia in a National Healthcare System. Sheffrin, et al, *JAGS* 2015

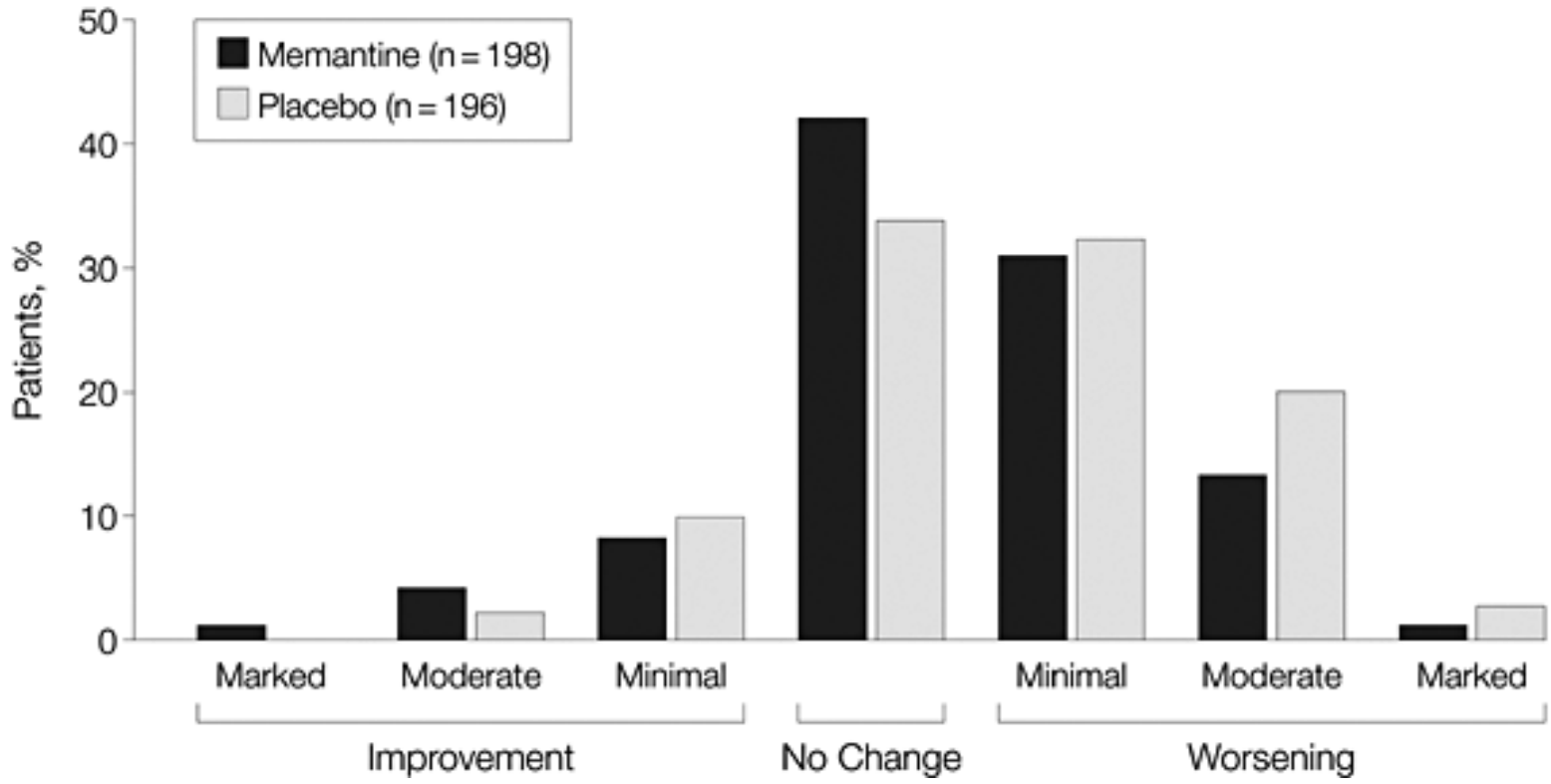
Memantine – works at NMDA receptor





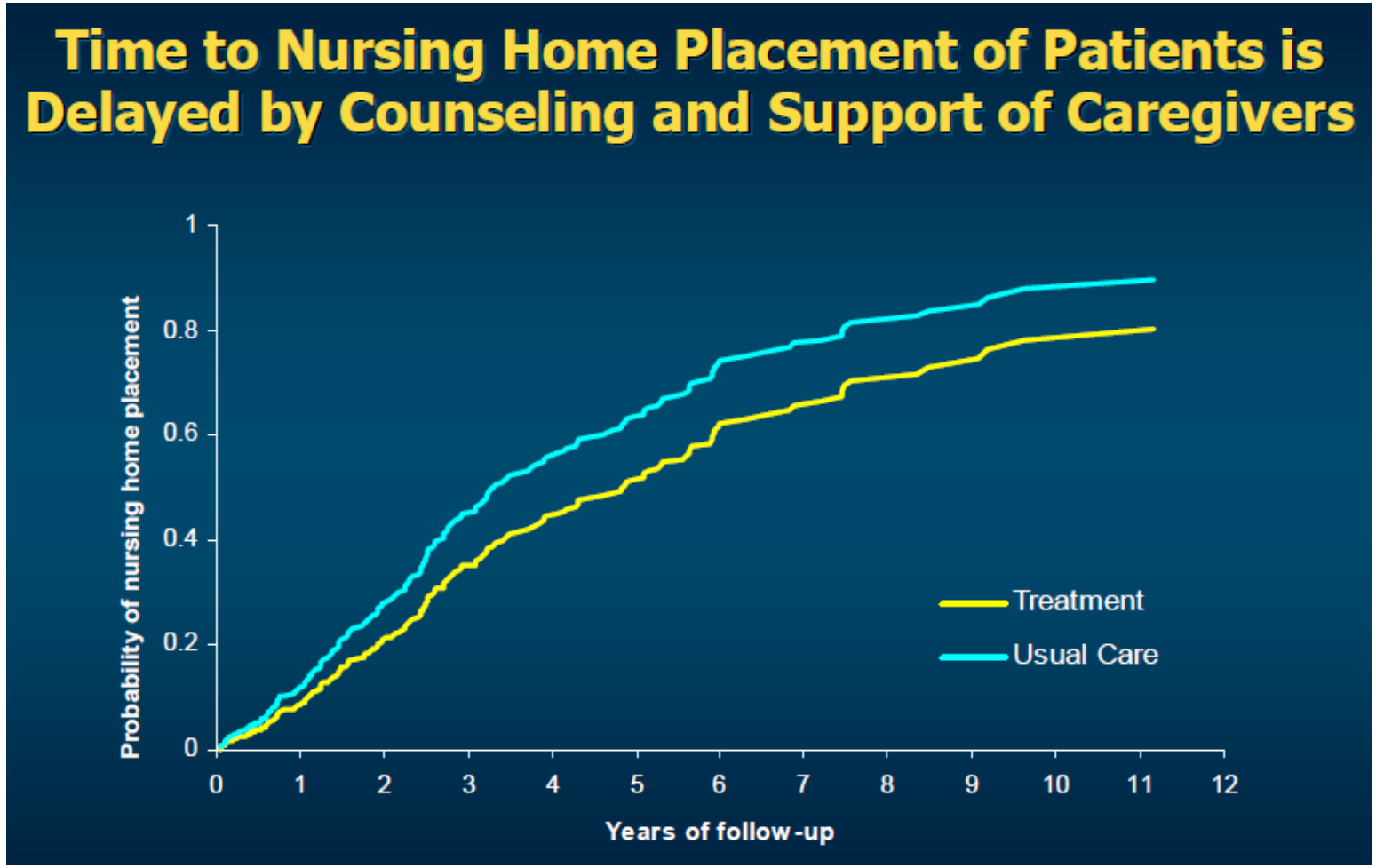


Memantine


Memantine (n = 198)
Placebo (n = 196)
Patients, %
50
40
30
20
10
0
Marked
Moderate
Minimal
Minimal
Moderate
Marked
Improvement
No Change
Worsening

"Although statistical improvements were noted in the analyses, they do not necessarily translate into clinically relevant benefits for the patients receiving these drugs or for their caregivers."

Perras C, Shukla VK, Lessard C, et al. 2005.



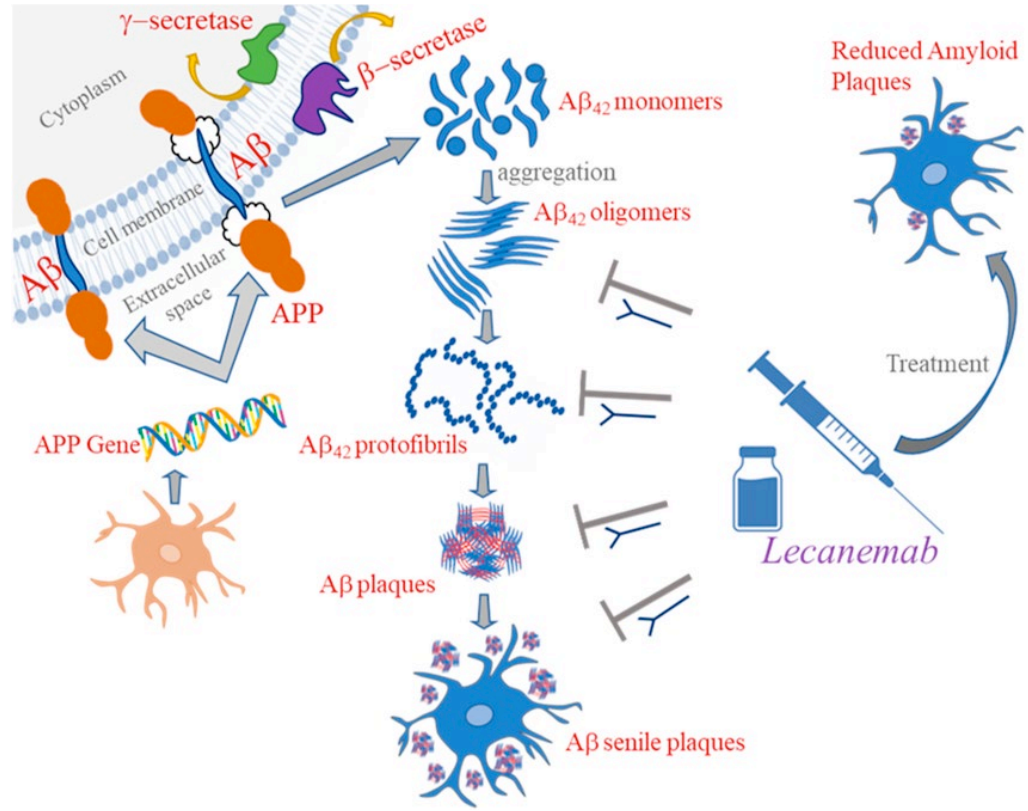
Mittelman MS, Haley WE, Clay OJ, Roth DL. Improving caregiver well-being delays nursing home placement of patients with Alzheimer disease. *Neurology.* Nov 14 2006;67(9):1592-1599.

Antibodies

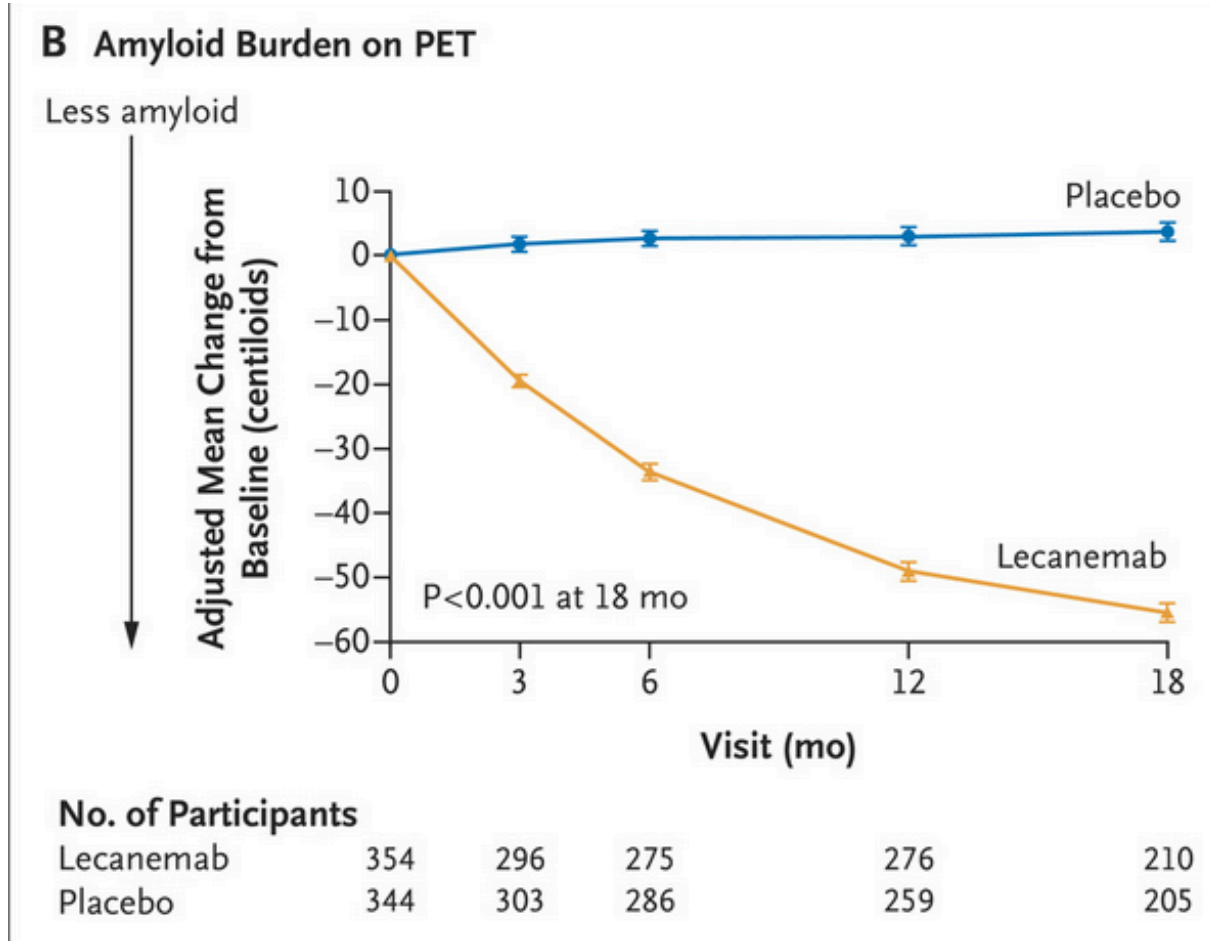
Aducanumab

Lecanemab

Donanemab

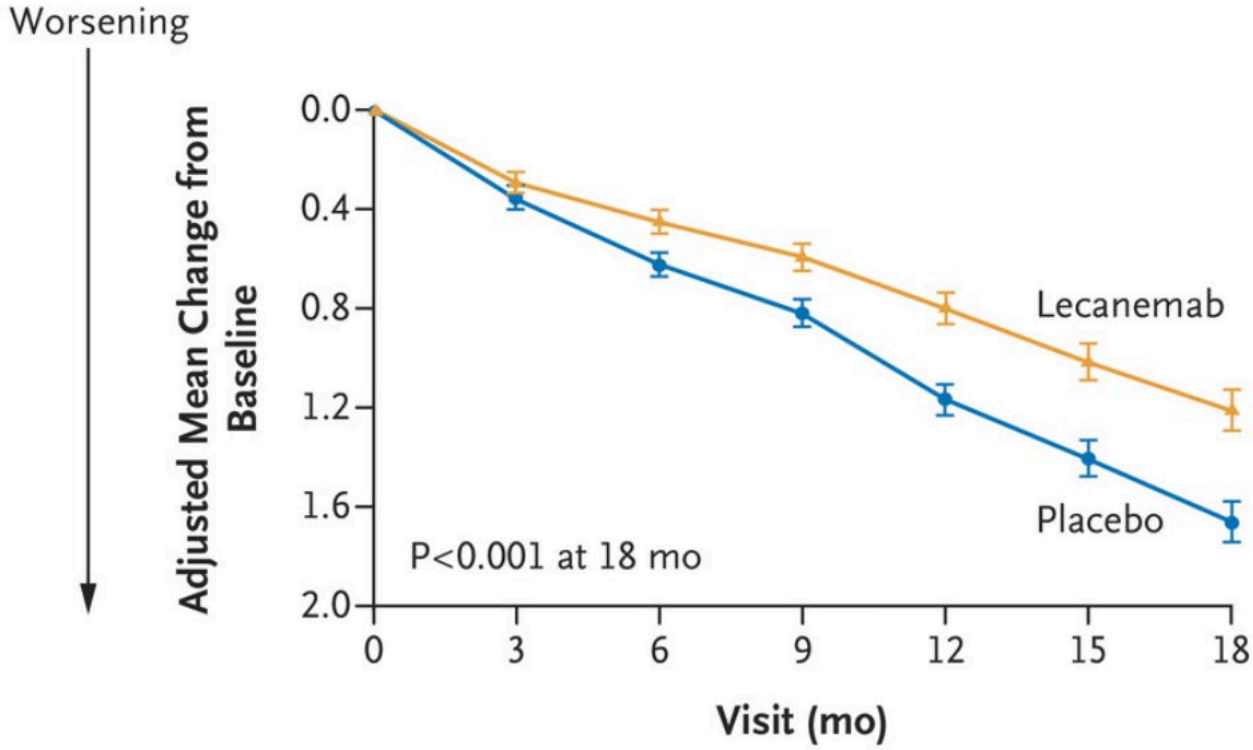


Change in Amyloid



Van Dyck et al, Lecanemab in Early Alzheimer's Disease. *N Engl J Med* 2023; 388:9-21

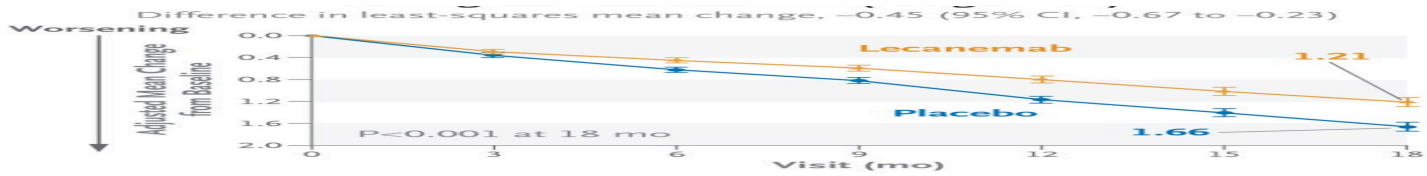
Change in “CDR-SB”



No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

Van Dyck et al, Lecanemab in Early Alzheimer’s Disease. *N Engl J Med* 2023; 388:9-21

Clinical Dementia Rating Scale – Sum of Boxes



18 point scale

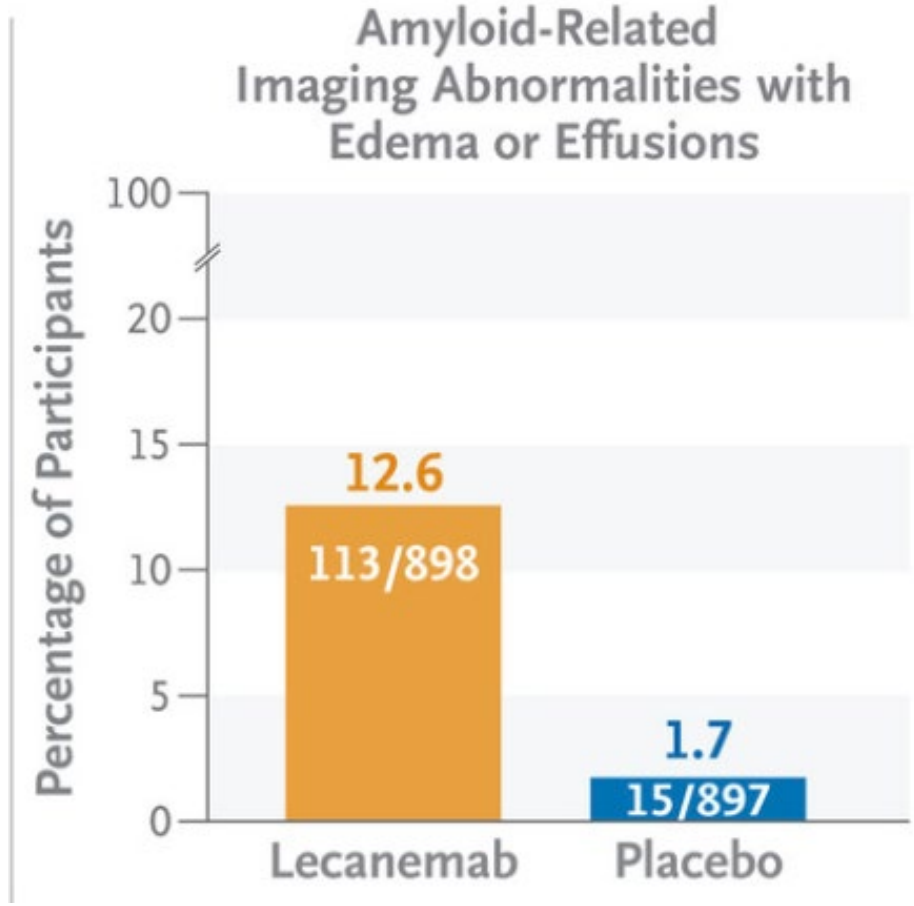
0.5 points is considered the smallest clinically meaningful change

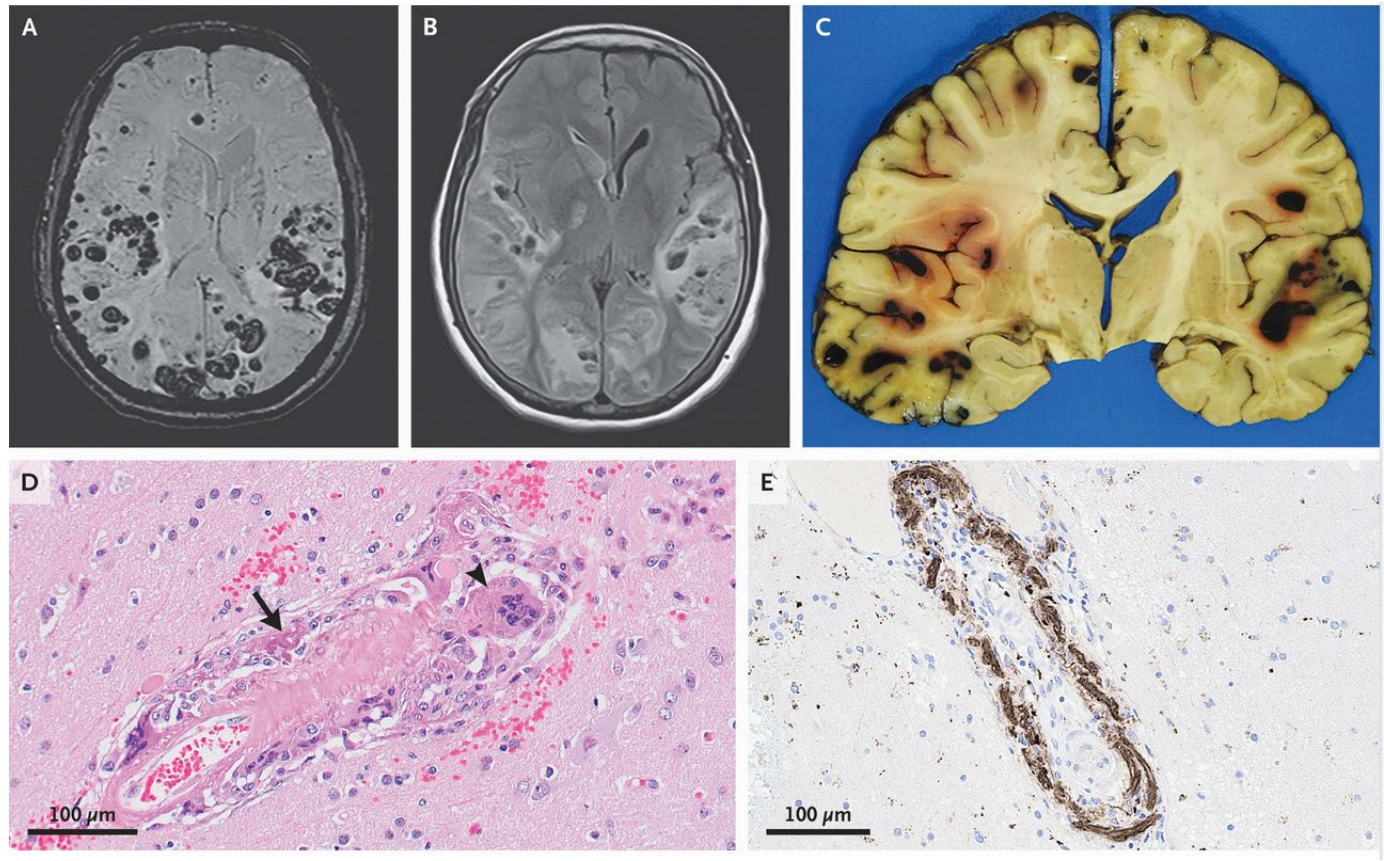
0.45-point difference

CDR Boxes

CDR Score	0 Healthy	0.5 Very Mild Impairment	1 Mild	2 Moderate	3 Severe
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss, only fragments remain
Orientation	Fully orientated	Fully orientated except for slight difficulty with time relationships	Moderate difficulty with time relationships; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disorientated in time, often to place	Orientated to person only
Judgment Problem Solving	Solves everyday problems and business affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, differences	Moderate difficulty in handling problems, similarities, differences	Severely impaired in handling problems, similarities, differences	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities though may still be engaged in some	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	No pretense of independent function outside home Appears too ill to be taken to functions outside a family home
Home & Hobbies	Life at home, hobbies, intellectual interests well maintained	Life at home, hobbies, intellectual interests slightly impaired	Mild but definite impairment of function at home; more complicated hobbies abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self care	Fully capable of self care	Needs prompting	Requires assistance in hygiene, keeping of personal effects	Requires much help with personal care

Brain Edema or Bleeding

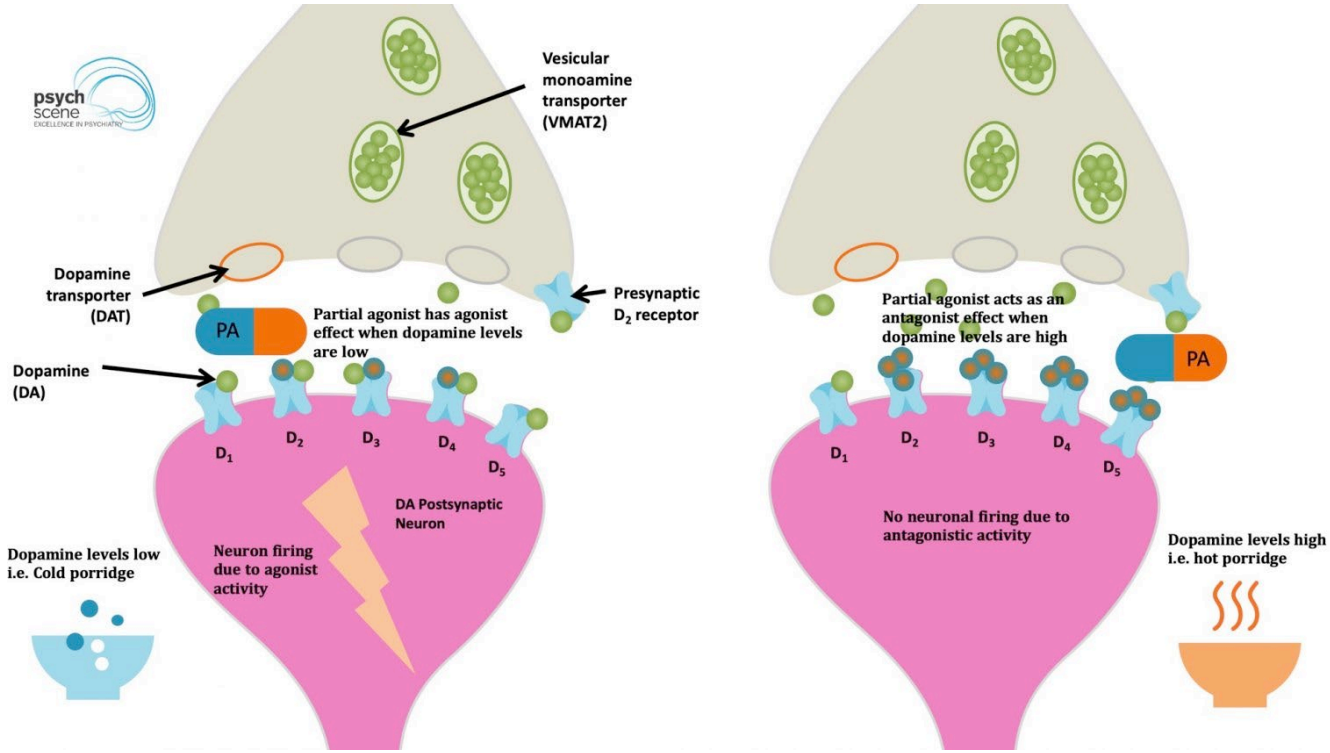




Reish et al. Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke. N Engl J Med 2023; 388:478-479

Antipsychotic:

Brexiprazole

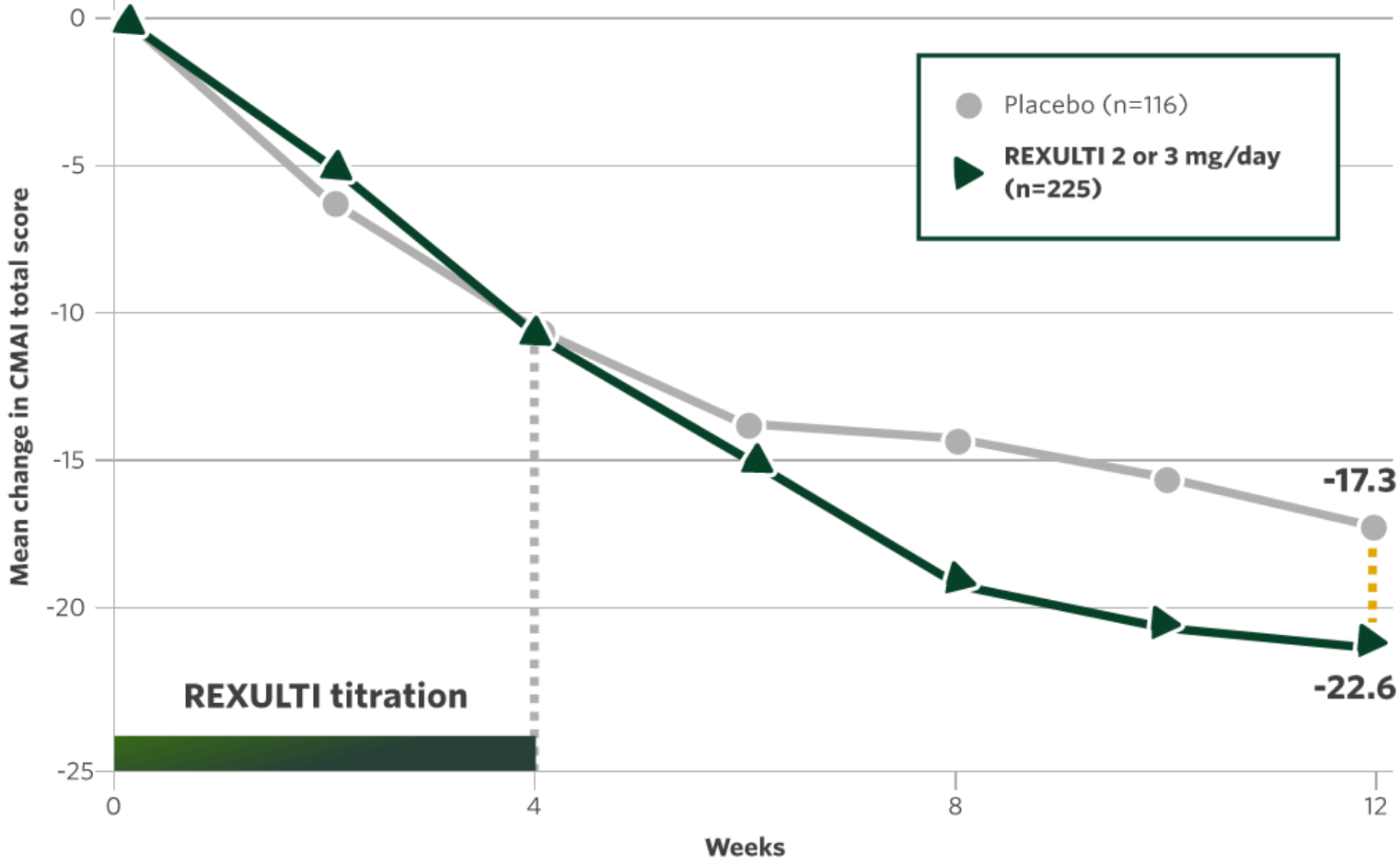


The ad

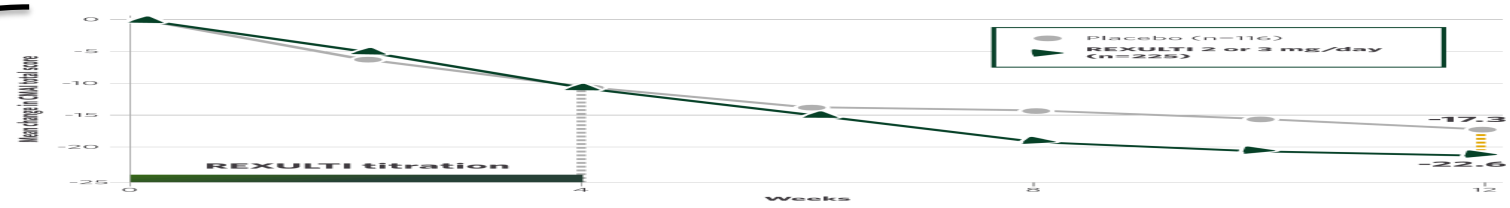
REXULTI is the only FDA-approved treatment for agitation that may happen with dementia due to Alzheimer's disease.

Until recently, there hasn't been an FDA-approved medicine for doctors to treat agitation that may happen with dementia due to Alzheimer's disease. But now there's REXULTI. For those struggling with this condition, REXULTI may offer hope for less symptoms of agitation. In clinical studies, REXULTI helped patients see:

www.rexulti.com



www.rexulti.com



174 point scale

17 points is considered clinically meaningful difference

5.3-point differenc e

- **Increased risk of death in elderly people with dementia-related psychosis. Medicines like REXULTI can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). REXULTI is not approved for the treatment of people with dementia-related psychosis without agitation that may happen with dementia due to Alzheimer's disease.**

REXULTI should not be used as an "as needed" treatment for agitation that may happen with dementia due to Alzheimer's disease.

www.rexulti.com

FDA's Shocking Approval: Rexulti Fast-Tracked Despite Deadly Risks

British Medical Journal, October 6, 2023

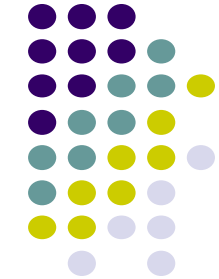
News Flash!

Miraculous Medical Breakthrough Reduces Risk of Death by 38% in Group of Dementia Patients

BLACK BOX WARNING: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. These drugs are not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients…in trials of ANTIPSYCOTIC in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with ANTIPSYCHOTIC compared to patients treated with placebo. ANTIPSYCHOTIC is not approved for the treatment of patients with dementia-related psychosis.

Drugs Trials Attempted for Dementia-Related Behaviors



Buspirone
Alpha blockers
Beta blockers
Antihistamines
Cannabinoids
Opioids
Methylphenidate
Lamotrigine
Antiepileptic drugs
Lithium
Estrogen
Vitamin E

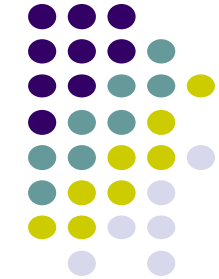
Homocysteine
B Vitamins
Resveratrol
Ginseng
Cyproterone
NSAIDs
COX2 Inhibitors
H2 blockers
Thiazide diuretics
Calcium channel blockers
ACE inhibitors
Statins

What is the therapeutic value of antidepressants in dementia? A narrative review

Nicolas Farina[1], Lucy Morrell[1] and Sube Banerjee[1]

Results: Thirty-six randomized controlled trials were identified (participant $n = 3386$). A consistent finding in well-designed blinded placebo controlled trials in dementia is the lack of positive effect of antidepressants on outcomes of interest, including depression. One large well-designed study has reported a significant reduction in agitation in people with dementia, but at the expense of clinically significant adverse events. Otherwise, change observed in open trials is also seen in the placebo group, suggesting that any effect is not attributable to the prescription of antidepressants.

What can you expect from medications for dementia?



Anticipated changes in the next five years

WHAT IS NEXT?
WHAT SHOULD HAPPEN NEXT?

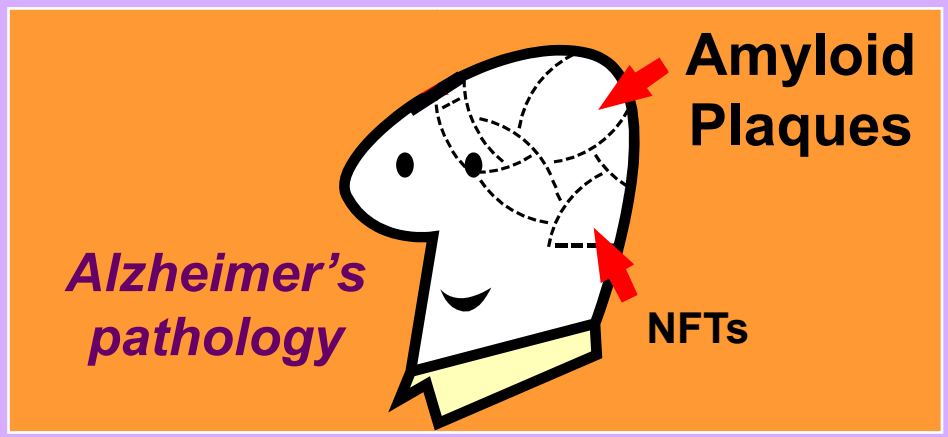
Risk Factors

Environment

AGE

Head Injury
Presence of APOE e4 allele
Chronic Illness

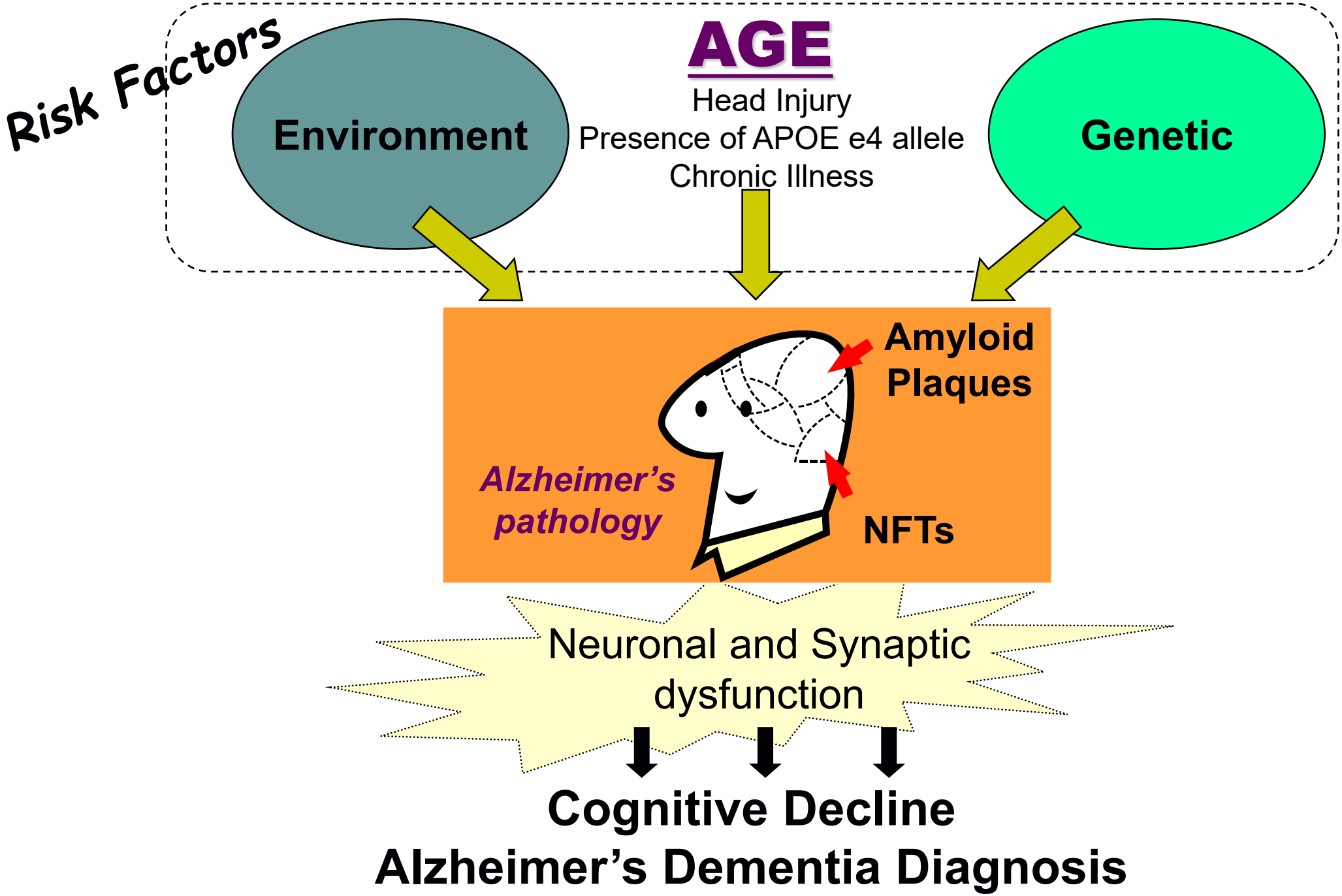
Genetic



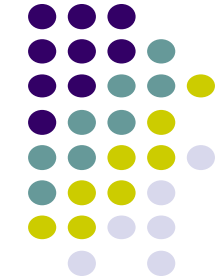
Amyloid + Biomarker: CSF, PET, plasma = **Alzheimer's Disease Dx** → Infusion treatment?

Neuronal and Synaptic dysfunction

Cognitive Decline


Risk Factors
Environment
AGE
Head Injury
Presence of APOE e4 allele
Chronic Illness
Genetic
Amyloid Plaques
Alzheimer's pathology
NFTs
Neuronal and Synaptic dysfunction
Cognitive Decline
Alzheimer's Dementia Diagnosis

Thank you.



Time for questions?