Dementia
A younger perspective

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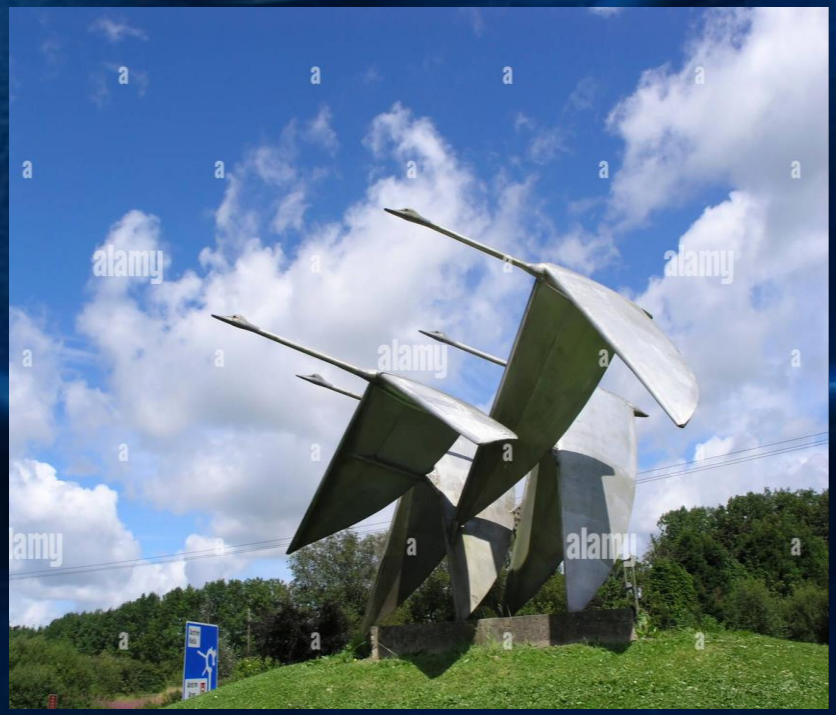


Objective

- Overview of Dementias/Subtypes with emphasis on younger onset (<65yo)
- Aetiology and pathogenesis of Alzheimer's Disease
- Update on what's new in Alzheimer's disease

Declaration

- Nothing to declare wrt this talk

- Previously;
  - Bohringer Ingelheim
  - Eisai
  - Shire
  - Pfizer
  - Bayer
  - Astra Zeneca
  - Daiichi Sankyo

DSM-IV and DSM-5 criteria for dementia

DSM-IV criteria for dementia	DSM-5 criteria for major neurocognitive disorder (previously dementia)
A1. Memory impairment	**A.** Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains*: - Learning and memory - Language - Executive function - Complex attention - Perceptual-motor - Social cognition
A2. At least one of the following: - Aphasia - Apraxia - Agnosia - Disturbance in executive functioning	
B. The cognitive deficits in A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.	**B.** The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
C. The cognitive deficits do not occur exclusively during the course of delirium.	**C.** The cognitive deficits do not occur exclusively in the context of a delirium.
	D. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia).

The Higher Functions of the Cerebral Cortex

- Consciousness
- Mood (Emotion)
- Personality
- Cognition Function

- Coma
- Behavioural Problems
- Cognitive Impairment

Cognitive Functions

Orientation

Memory

Concentration

Learning Capacity

Comprehension

Judgement

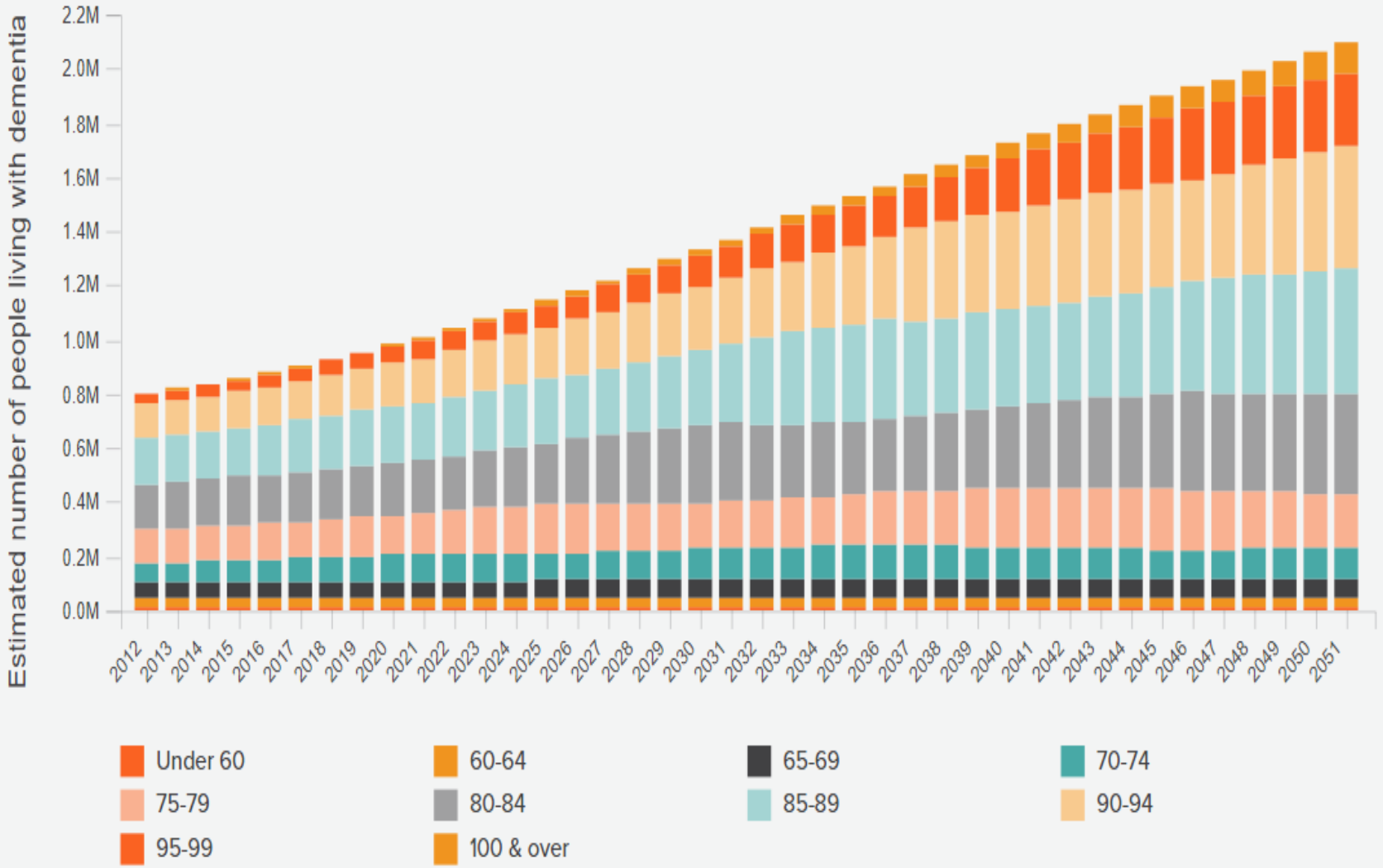
Cognitive Function v Intelligence

Cognitive Function
Are the tools to process information.

Intelligence
Is a measure of excellence of cognitive function.

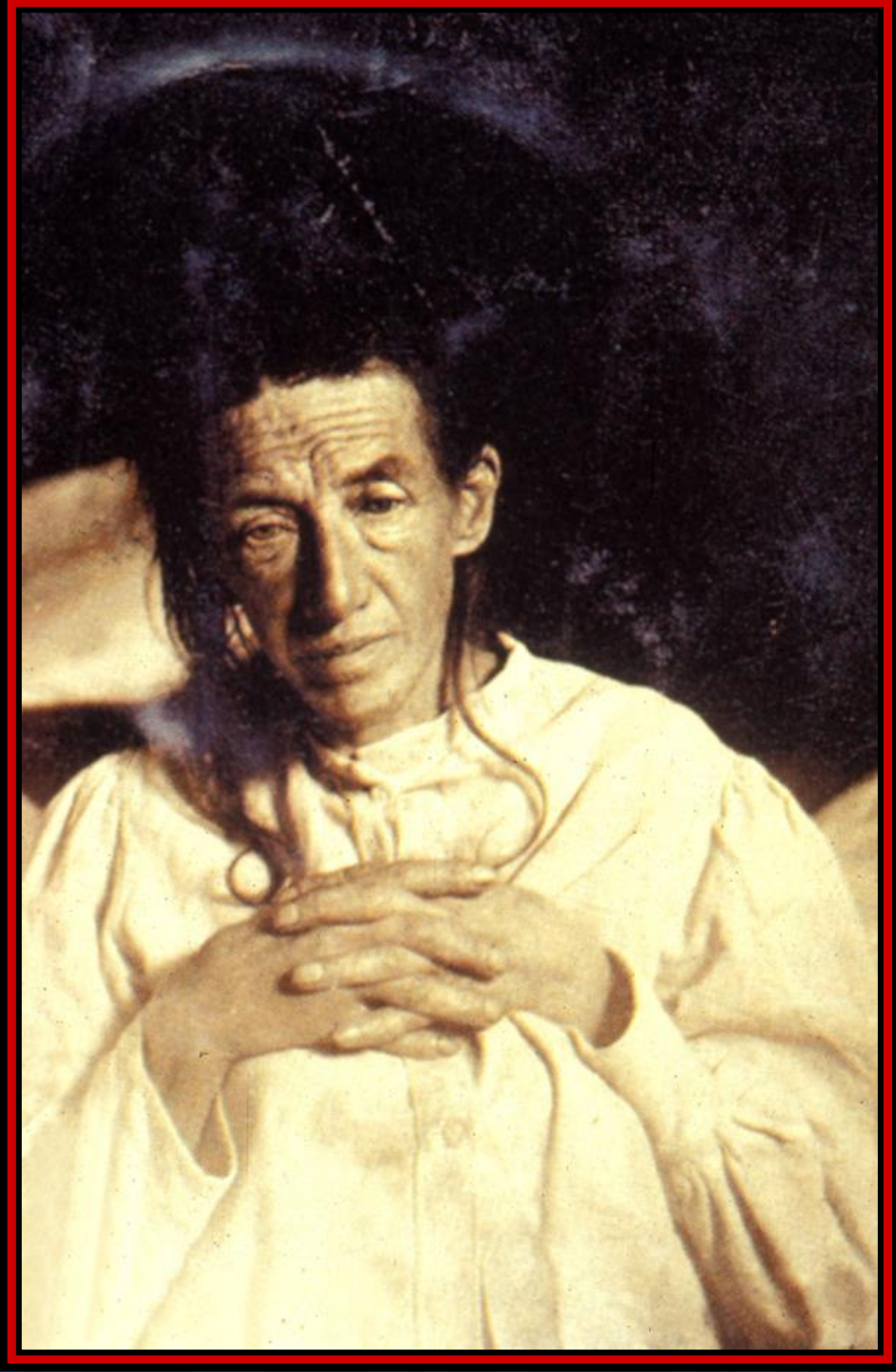
Dementia (Prevalence)

- 24m world-wide (x2 every 20 years)
- 1000,000 in UK
- 50,000 below retirement age-Early-onset (5%)
- 20-30,000 in NI
- 1991-92 cost £1.039 billion (17 billion 2007)

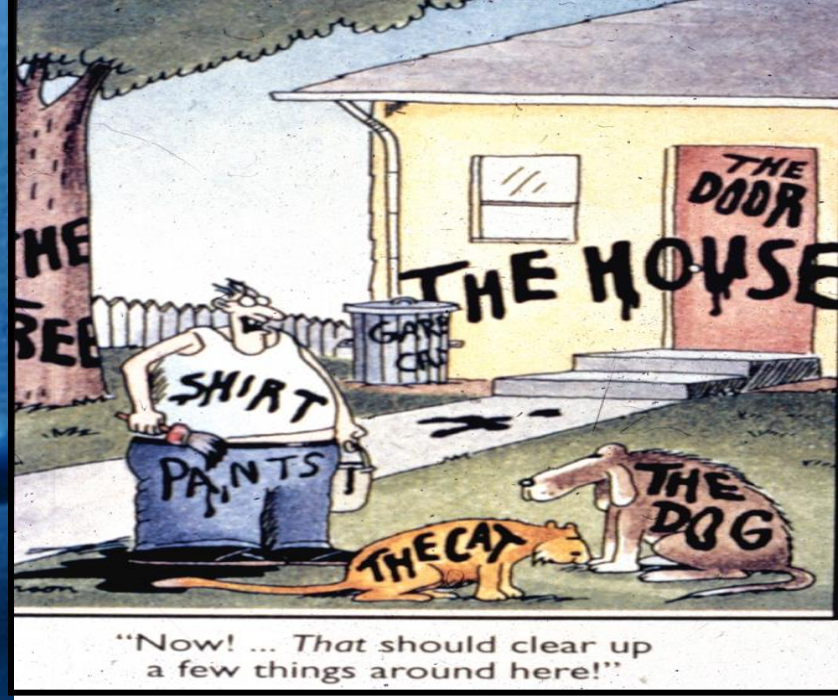


ALZHEIMER'S RESEARCH UK FOR A CURE

Superman in his later years



- **Early AD**
  - Insidious, forgetfulness, reminders, insight, anxiety and depression, POA
- **Moderate AD**
  - Significant memory loss, reduced range of thinking, personality change, self neglect, loss of executive function
- **Advanced AD**
  - Full care, behavioural changes, poor nutritional status, recurrent infections, advanced care planning/directives, palliation



<u>As You Like It 2/7</u> (Shakespear)

Last scene of all, That ends this strange eventful history,
Is second childishness and mere oblivion,

Sans teeth, sans eyes, sans taste, sans everything.

Dementia Assessment/Diagnosis

- History
- Examination **(including Cognitive State)**
- Investigations

FBP	ECG
CRP	CXR
U&E,LFT,BP	CT Brain/FDG
TFT	MRIB
B12&Folate	EEG/LP

VDRL/TPHA/HIV/Genetic

- Diagnosis
  - Probable/Possible v Definite
  - Diagnosis of Exclusion
-

Nicotinic Treatment inAD

	Donepezil	Galantamine	Rivastigmine	Memantine
Indication	Mild to moderate AD	Mild to moderate AD	Mild to moderate AD	Moderate to severe AD
Mode of action	Selective AChE inhibition	Selective AChE inhibition and allosteric nicotine receptor modulation	Slowly reversible AChE and BuChE inhibition	Non-competitive NMDA-receptor antagonist
CYP450 metabolism	Yes (CYP2D6 and CYP3A4)	Yes (CYP2D6 and CYP3A4)	No, hydrolysed by esterases	No
Half-life	Long (70 h)	Short (7–8 h)	Very short (1 h)	Long (60–100 h)
Doses per day	One	Two (tablets) One (prolonged release capsule)	Two	Two (first week once a day)
Given with food	Irrelevant	Recommended	Yes (increased bio-availability)	Irrelevant
Initial dose	5 mg/day	8 mg/day	3 mg/day (1·5 mg×2)	5 mg/day
Dose escalation	4–6 weeks	Every 4 weeks, up to recommended or tolerated dose	Every 2 weeks, up to recommended or tolerated dose	Every week, up to recommended or tolerated dose
Recommended clinically efficient dose	10 mg/day	16–24 mg/day	6–12 mg/day	20 mg/day

AD=Alzheimer's disease. AChE=acetylcholinesterase. BuChE=buturylcholinesterase. CYP450=cytochrome P450. NMDA=N-methyl-D-aspartate.

Table 1: **Characteristics of drugs for symptomatic treatment of Alzheimer's disease**

Science

Current Issue First release papers Archive About

SCIENCE · 10 Apr 1992 · Vol 256, Issue 5054 · pp. 184-185 · DOI: 10.1126/science.1566067

3,248 19

PERSPECTIVE

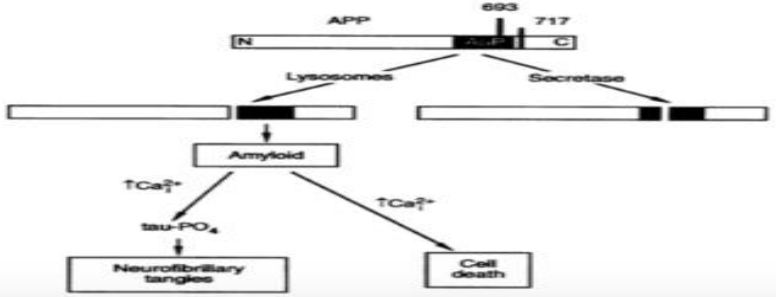
Alzheimer's Disease: The Amyloid Cascade Hypothesis

John A. Hardy and Gerald A. Higgins

Alzheimer's disease causes dementia in many elderly people and in some individuals with Down syndrome who survive to age 50. Alzheimer's is characterized by various pathological markers in the brain—large numbers of amyloid plaques surrounded by neurons containing neurofibrillary tangles (*1*), vascular damage from extensive plaque deposition (*2*), and neuronal cell loss (*1*). Because it is not known if the amyloid plaques or the neurofibrillary tangles are the earliest lesion in the disease process, the role of these markers in the etiology of the disease is controversial.

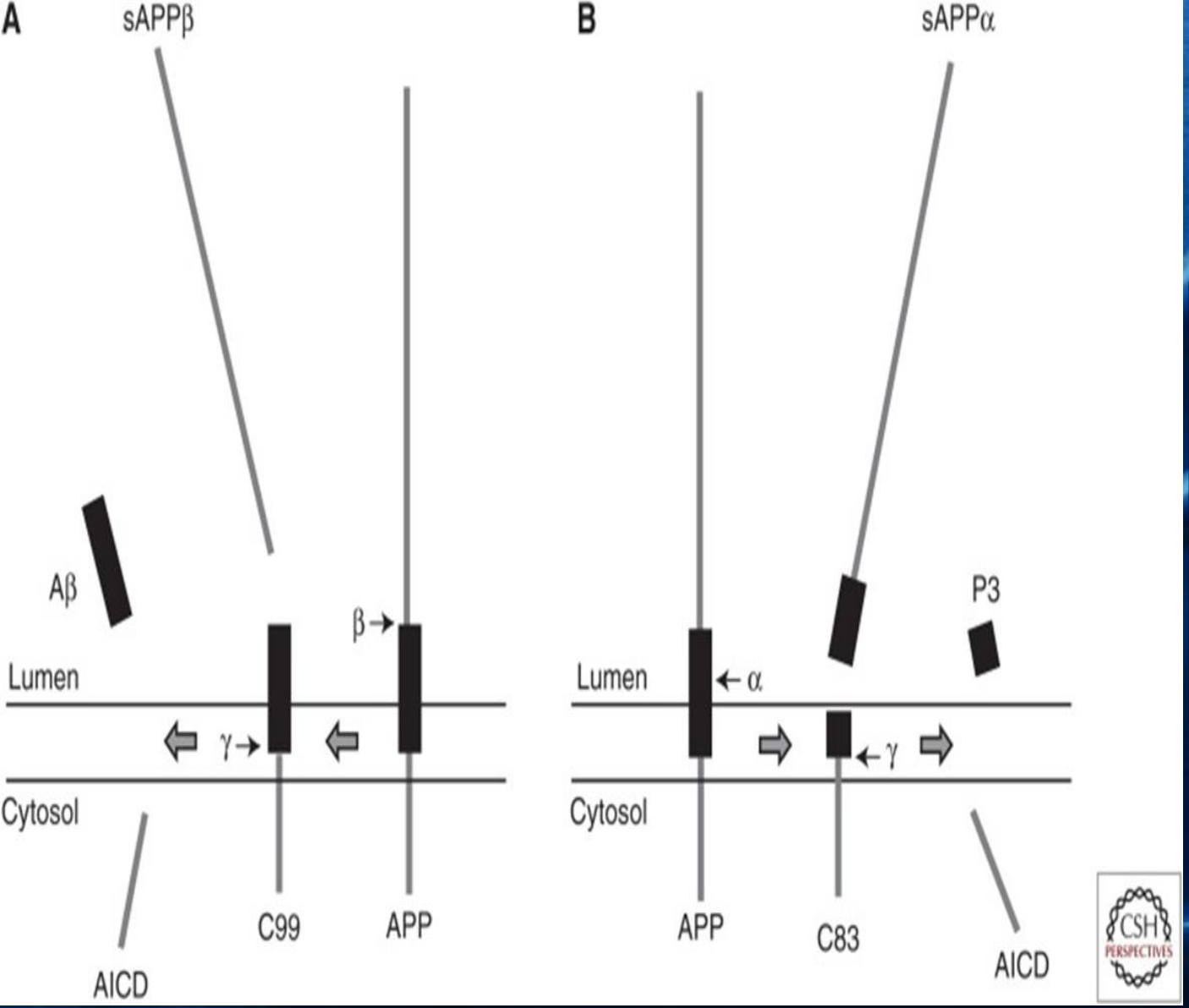
Our hypothesis is that deposition of amyloid β protein (AβP), the main component of the (*3*) plaques, is the causative agent of Alzheimer's pathology and that the neurofibrillary tangles, cell loss, vascular damage, and dementia follow as a direct result of this deposition. AβP is a peptide product of the larger amyloid precursor protein (APP) (*4*). Because Down syndrome is caused by trisomy of the region of chromosome 21 that contains the APP gene, deposition of AβP is likely to be an early event in the disease (*5*). The AβP molecule is a 39– to 42–amino acid peptide (*4, 6*), part of which forms the hydrophobic transmembrane domain in the COOH-terminal portion of APP (Fig. 1). AβP is one of a diverse group of "amyloid" (starch-like) proteins that forms insoluble extracellular deposits. The APP gene undergoes alternative RNA splicing to produce several protein isoforms; the predominant variant in brain lacks a serine protease inhibitor domain that is present in APP molecules in cerebrospinal fluid (*9*). The APP secretase that cuts within the AβP region has an extraordinarily broad sequence specificity and recognizes the secondary structure of APP, cleaving at a defined distance from the membrane (*10*). Several recent studies suggest that APP can also be processed by the endosomal-lysosomal pathway, after recycling of membrane-bound APP and possibly via an intracellular metabolic route (*11–13*). Carboxyl-terminal fragments containing the entire AβP sequence can be derived from this alternate normal processing of APP (*12, 14*) and may eventually lead to amyloid deposition (*12, 14*) (Fig. 1).

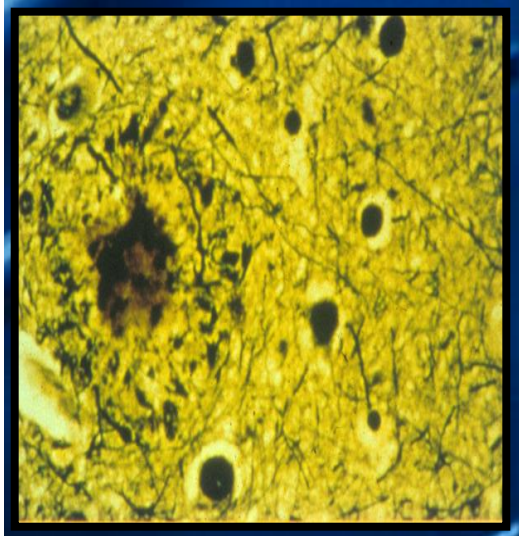
Fig. 1. The amyloid cascade hypothesis. Processing of APP can occur via two pathways: (i) Cleavage within AβP by the secretase, which generates peptide products that do not precipitate to form amyloid and (ii) cleavage in the endosomal-lysosomal compartment, resulting in intact AβP that precipitates to form amyloid and, in turn, causes neurofibrillary tangles and cell death, the hallmarks of Alzheimer's disease.



Alzheimer's disease. These mutations all occur at codon 717 of the protein (*15, 16*) and change the native valine, located three residues from the COOH-terminal end of AβP, to isoleucine, phenylalanine, or glycine (Fig. 1). It is unclear how these mutations cause amyloid deposition, but they may inhibit the breakdown of a COOH-terminal fragment of APP that contains AβP (*15*), alter the anchoring of APP in the cell membrane, or stabilize AβP-containing amyloidogenic fragments within lysosomes (*12, 15*).

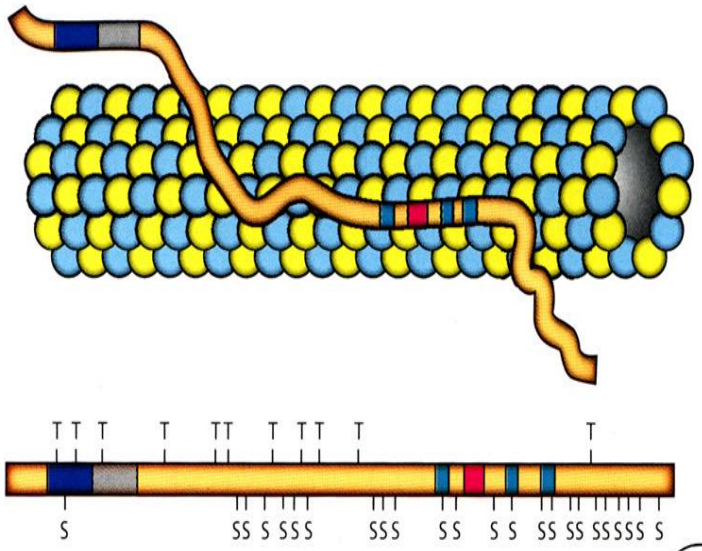
Our cascade hypothesis states that AβP itself, or APP cleavage products containing AβP, are neurotoxic and lead to neurofibrillary tangle formation and cell death. Thus, two successive events are needed to produce Alzheimer's pathology. First, AβP must be generated as an intact entity, either by accumulation of AβP or as an AβP-containing fragment of APP. Second, this molecule must facilitate or cause neuronal death and neurofibrillary tangle formation. Neve and her colleagues have reported that



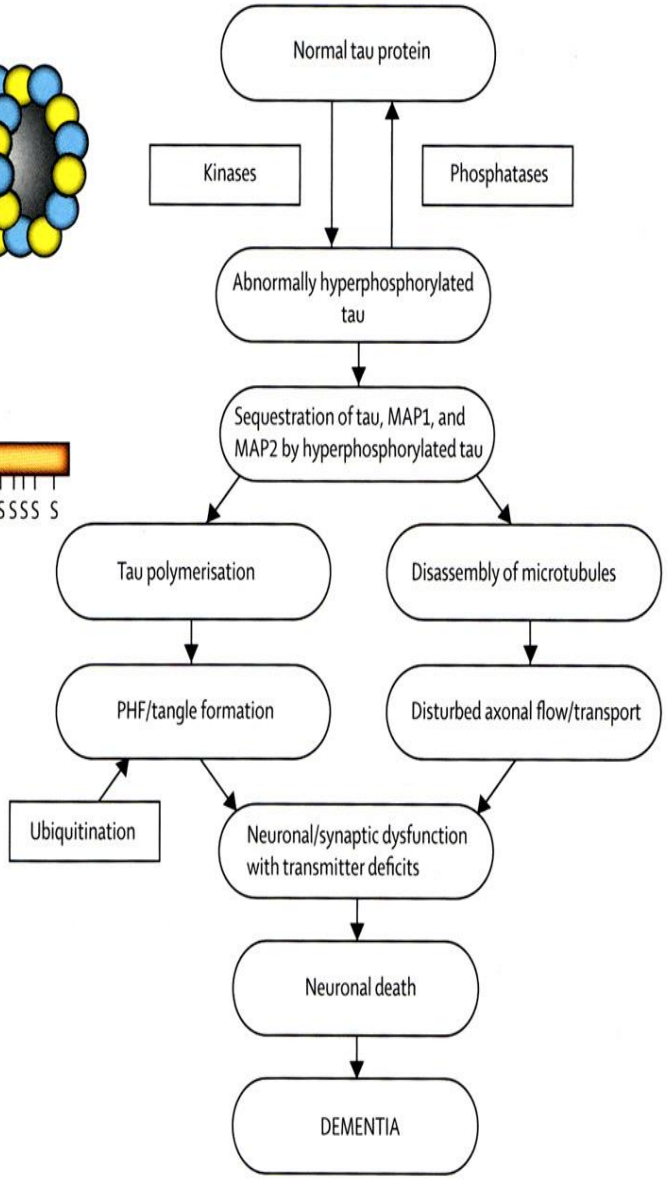


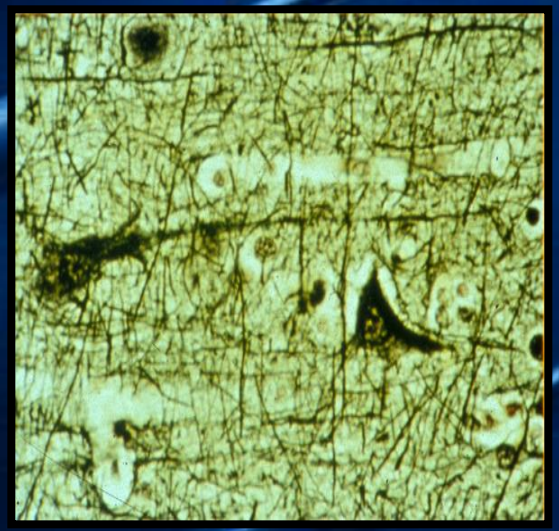
Processing of β-amyloid precursor protein (APP) by the secretases: (A) amyloidogenic processing and (B) nonamyloidogenic processing.

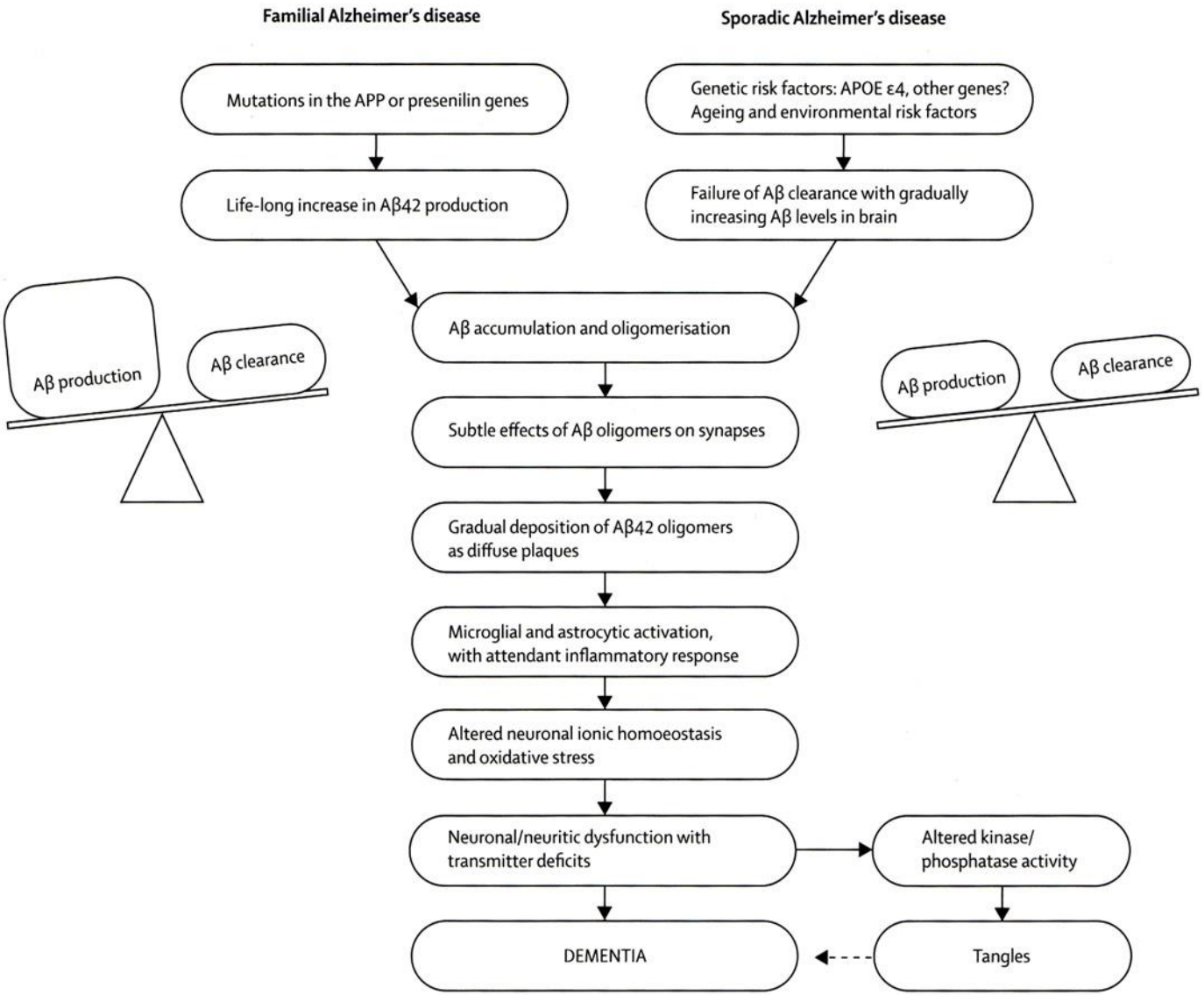
A


T T T T T T T T T T
S S S S S S S S S S S S S S S S S S

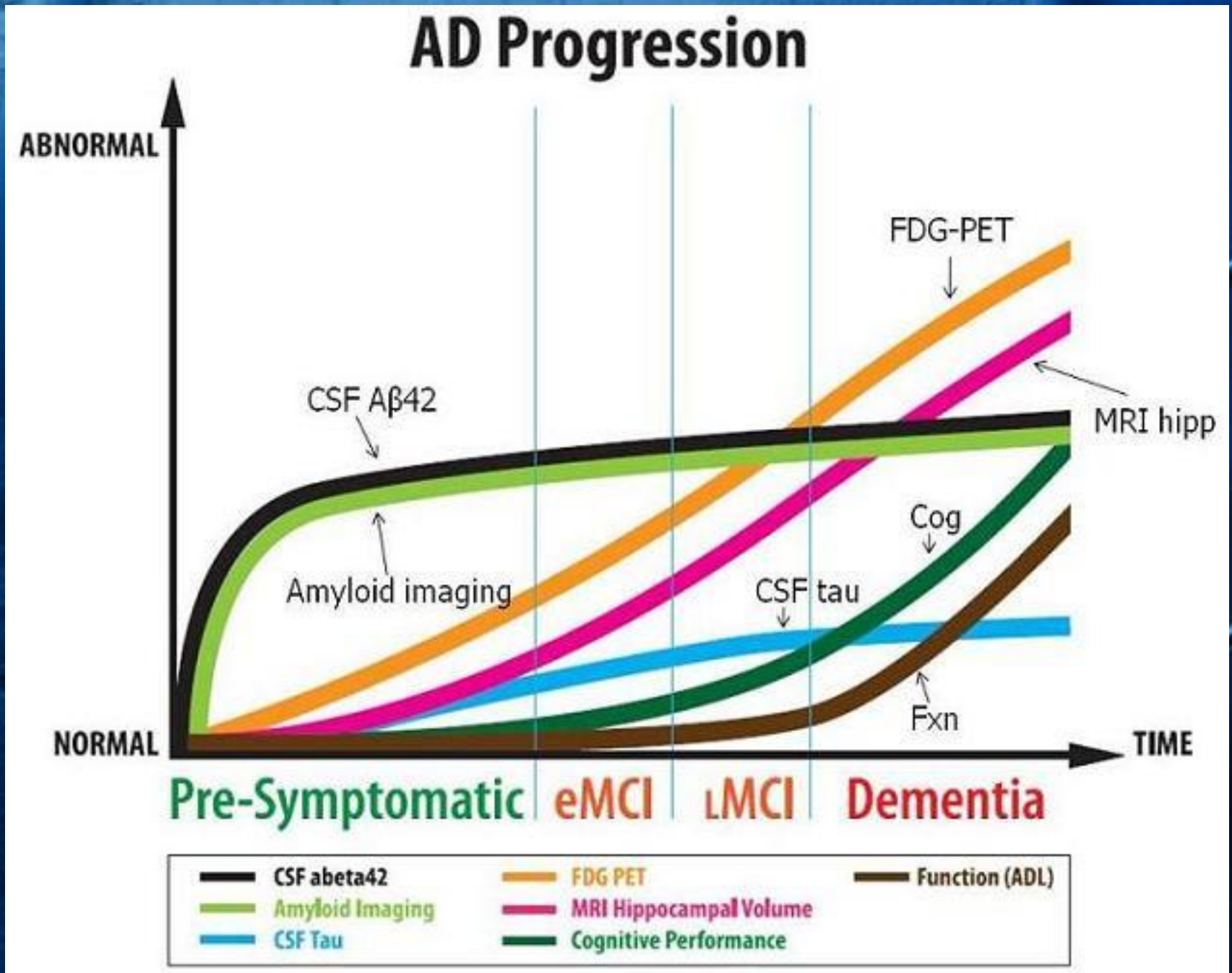
B


Normal tau protein
Kinases
Phosphatases
Abnormally hyperphosphorylated tau
Sequestration of tau, MAP1, and MAP2 by hyperphosphorylated tau
Tau polymerisation
Disassembly of microtubules
PHF/tangle formation
Disturbed axonal flow/transport
Ubiquitination
Neuronal/synaptic dysfunction with transmitter deficits
Neuronal death
DEMENTIA



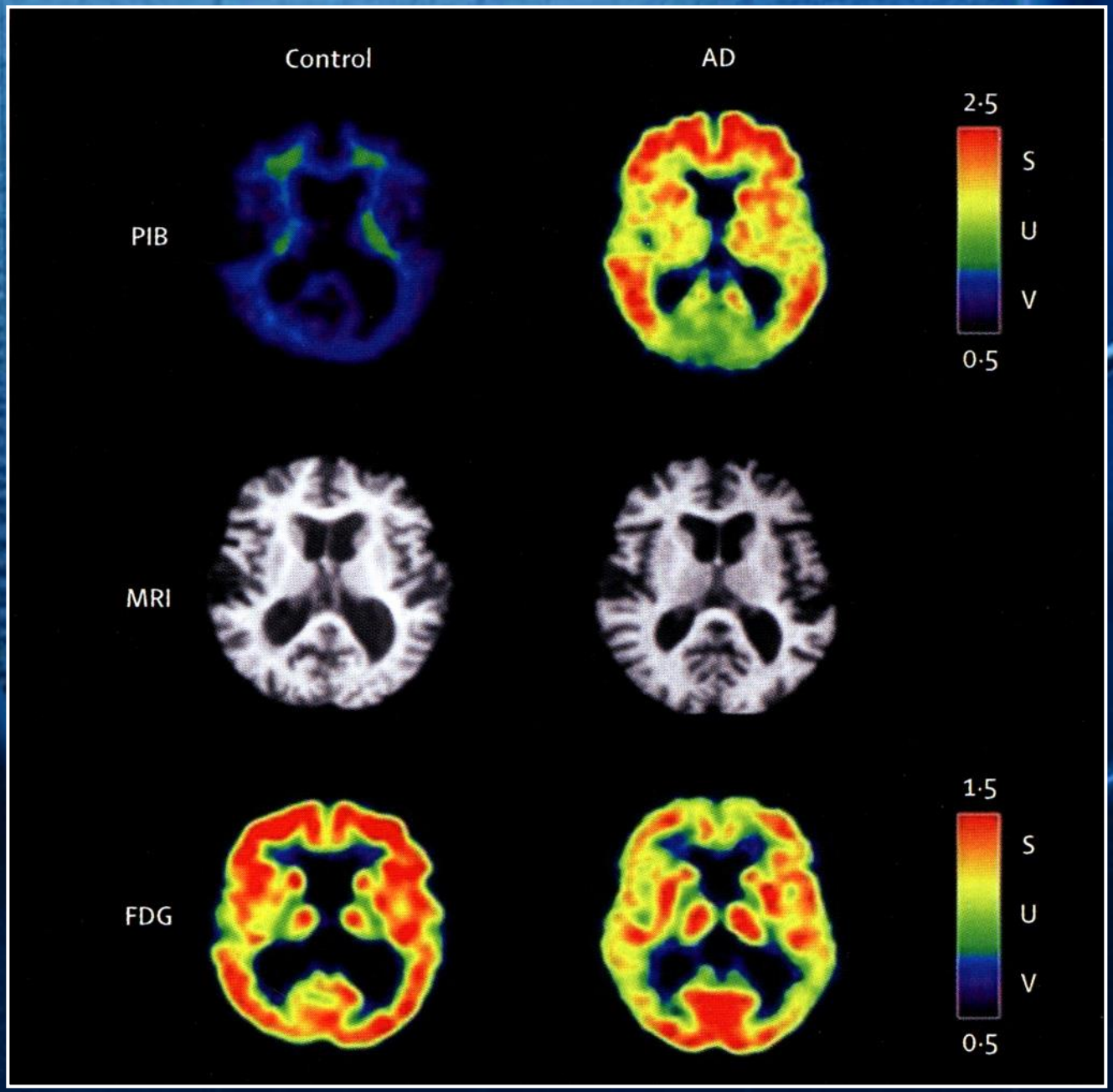

Familial Alzheimer's disease
Sporadic Alzheimer's disease
Mutations in the APP or presenilin genes
Genetic risk factors: APOE ε4, other genes?
Ageing and environmental risk factors
Life-long increase in Aβ42 production
Failure of Aβ clearance with gradually increasing Aβ levels in brain
Aβ production
Aβ clearance
Aβ accumulation and oligomerisation
Aβ production
Aβ clearance
Subtle effects of Aβ oligomers on synapses
Gradual deposition of Aβ42 oligomers as diffuse plaques
Microglial and astrocytic activation, with attendant inflammatory response
Altered neuronal ionic homoeostasis and oxidative stress
Neuronal/neuritic dysfunction with transmitter deficits
Altered kinase/ phosphatase activity
DEMENTIA
Tangles

So What's new


AD Progression
ABNORMAL
NORMAL
TIME
FDG-PET
CSF Aβ42
MRI hipp
Cog
Amyloid imaging
CSF tau
Fxn
Pre-Symptomatic
eMCI
LMCI
Dementia
CSF abeta42
Amyloid Imaging
CSF Tau
FDG PET
MRI Hippocampal Volume
Cognitive Performance
Function (ADL)

Biochemical markers of AD

- Low cerebrospinal fluid (CSF) Aβ42 (or Aβ42:Aβ40 ratio)
- Positive amyloid PET imaging using one of the amyloid PET tracers
- Biomarkers of tau deposition (a key component of neurofibrillary tangles) include:
  - Increased CSF total tau and phospho-tau
  - Tau PET imaging using flortaucipir F-18
  - Serum levels show reasonable correlation but not commertially available


Control
AD
PIB
MRI
FDG
2·5
S
U
V
0·5
1·5
S
U
V
0·5

Non-nicotinic treatment strategies in AD

1. Secretase modulators
2. Aβ immunotherapy (active and passive)
3. Aβ fibrillisation inhibitors
4. Anti-tau drugs
5. Anti-inflammatories
6. Cholesterol lowering drugs
7. Oestrogens
8. Antioxidants

Aβ immunotherapy

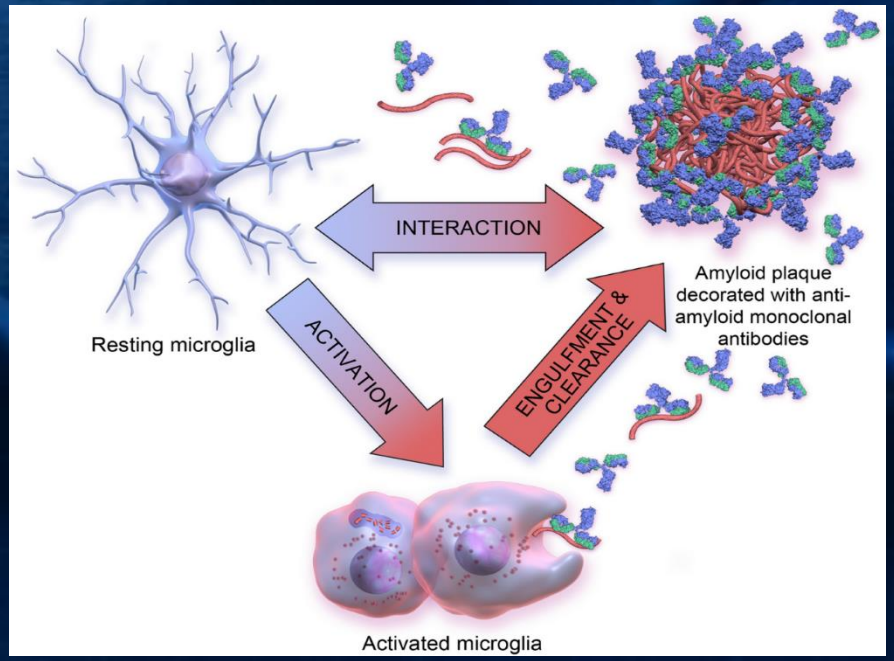
1. **Active immunisation**

   Vaccine AN1792 (pre-aggregated Aβ42)

   6% incidence of encephalitis in phase 2 trial (Orgogozo JM et. al, 2003)

2. **Passive immunisation**

   humanised anti-Aβ monoclonal antibodies



Disease Modifying Drugs in AD

- Bapineuzumab
- Solaneuzumab (EXPEDITION 1& 2, Extend)
- **Aducanamab (ENGAGE/EMERGE trials)**
- **Lecanamab (CLARITY AD)**
- **Donanemab (Trailblazer trial)**
- Gantenerumab (GRADUATE I&II)

Aducanumab (EMERGE/ENGAGE)

- Mild cognitive impairment (MCI) due to AD or mild AD (MMSE ≥21, MoCA≥17,CDR 0.5

- **Documented amyloid pathology** CSF analysis, amyloid PET CT, MRI for strokes/amyloid angiopathy and APOE genotype

- **Contraindications** –
  - No LBD, VaD or Down syndrome until more information is available
  - High risk of hemorrhagic side effects, including hemorrhagic findings on brain MRI including >4 microhemorrhages, cortical superficial siderosis, prior macrohemorrhage, and underlying brain lesion or vascular malformation, anticoagulant or antiplatelet use (other than aspirin 81 mg daily), bleeding disorders, or any other condition leading to increased risk of central nervous system (CNS) hemorrhage.

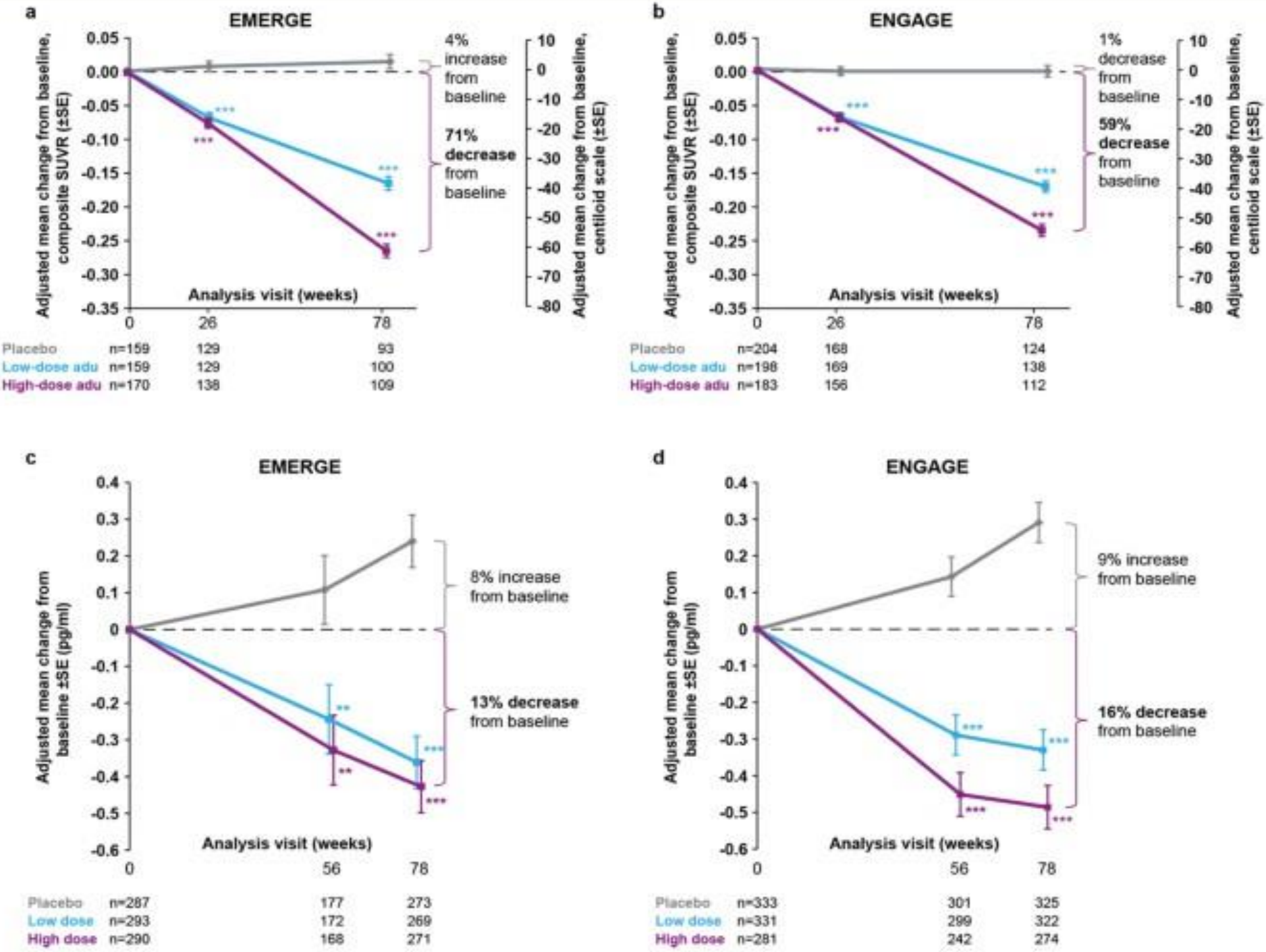

a
EMERGE
Adjusted mean change from baseline, composite SUVR (±SE)
Adjusted mean change from baseline, centiloid scale (±SE)
Analysis visit (weeks)
4% increase from baseline
71% decrease from baseline
***
Placebo n=159 129 93
Low-dose adu n=159 129 100
High-dose adu n=170 138 109
b
ENGAGE
Adjusted mean change from baseline, composite SUVR (±SE)
Adjusted mean change from baseline, centiloid scale (±SE)
Analysis visit (weeks)
1% decrease from baseline
59% decrease from baseline
***
Placebo n=204 168 124
Low-dose adu n=198 169 138
High-dose adu n=183 156 112
c
EMERGE
Adjusted mean change from baseline ±SE (pg/ml)
Analysis visit (weeks)
8% increase from baseline
13% decrease from baseline
**
***
Placebo n=287 177 273
Low dose n=293 172 269
High dose n=290 168 271
d
ENGAGE
Adjusted mean change from baseline ±SE (pg/ml)
Analysis visit (weeks)
9% increase from baseline
16% decrease from baseline
***
Placebo n=333 301 325
Low dose n=331 299 322
High dose n=281 242 274

Table 2 Primary and secondary endpoints at week 78

From: Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease

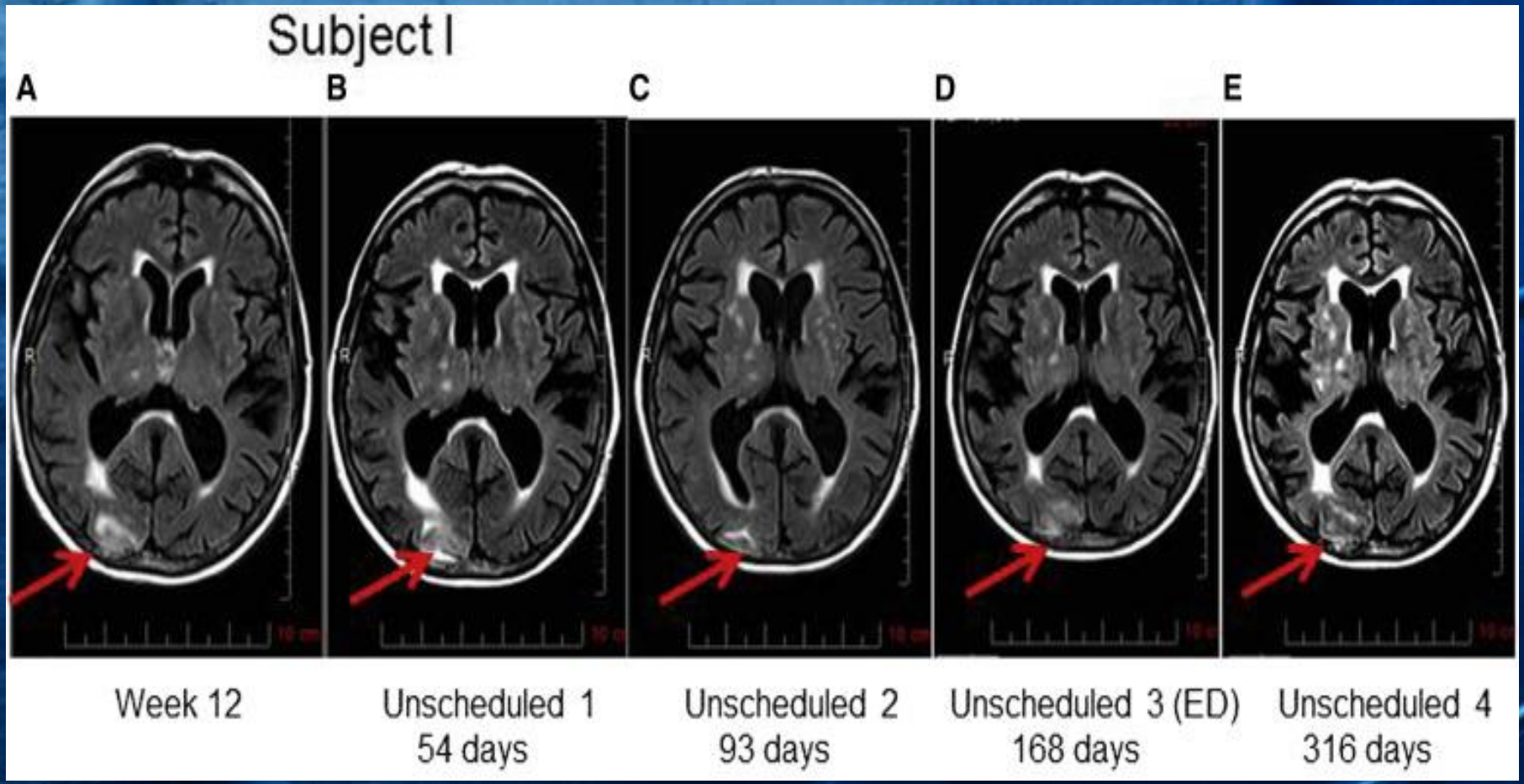
Endpoint	EMERGE			ENGAGE		
	Difference vs placebo (%)‖ 95% CI P			Difference vs placebo (%)‖ 95% CI P		
	Placebo decline ±; SE (n=548)	Low dose (n=543)	High dose (n=547)	Placebo decline ±; SE (n=545)	Low dose (n=547)	High dose (n=555)
Primary						
CDR-SB*	1.74±;0.11	-0.26 (-15%)	-0.39 (-22%)	1.56±;0.11	-0.18 (-12%)	0.03 (2%)
		-0.57, 0.04	-0.69, -0.09		-0.47, 0.11	-0.26, 0.33
		.090	.012		.225	.833
Secondary						
MMSE†	-3.3±;0.2	-0.1 (3%)	0.6 (-18%)	-3.5±;0.2	0.2 (-6%)	-0.1 (3%)
		-0.7, 0.5	0.0, 1.1		-0.3, 0.7	-0.6, 0.5
		.758	.049		.479	.811
ADAS-Cog 13‡	5.16±;0.40	-0.70 (-14%)	-1.40 (-27%)	5.14±;0.38	-0.58 (-11%)	-0.59 (-11%)
		-1.76, 0.36	-2.46, -0.34		-1.58, 0.42	-1.61, 0.43
		.196	.010		.254	.258
ADCS-ADL-MCI§	-4.3±;0.4	0.7 (-16%)	1.7 (-40%)	-3.8±;0.3	0.7 (-18%)	0.7 (-18%)
		-0.3, 1.7	0.7, 2.7		-0.2, 1.6	-0.2, 1.6
		.151	<.001		.123	.151

Table 3 Summary of adverse events

From: Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease

	Event, n (%)					
	EMERGE			ENGAGE		
	Placebo	Low dose	High dose	Placebo	Low dose	High dose
Safety MRI population	n=544	n=537	n=541	n=532	n=545	n=554
ARIA-E	13 (2)	140 (26)	188 (35)	16 (3)	141 (26)	199 (36)
ApoE ε4 carriers	7/371 (2)	109/366 (30)	156/362 (43)	9/371 (2)	114/390 (29)	159/378 (42)
ApoE ε4 noncarriers	6/173 (4)	31/171 (18)	32/179 (18)	7/161 (4)	27/155 (17)	40/176 (23)
Brain microhemorrhage	37 (7)	87 (16)	108 (20)	34 (6)	89 (16)	104 (19)
Brain microhemorrhage in participants without ARIA-E	35 (7)	30 (8)	32 (9)	32 (6)	24 (6)	21 (6)
Localized superficial siderosis	14 (3)	52 (10)	73 (13)	10 (2)	51 (9)	89 (16)
Localized superficial siderosis in participants without ARIA-E	9 (2)	9 (2)	7 (2)	6 (1)	7 (2)	5 (1)
Safety population	n=547	n=544	n=547	n=540	n=549	n=558
Headache	84 (15)	110 (20)	107 (20)	81 (15)	99 (18)	115 (21)
Fall	71 (13)	68 (13)	76 (14)	57 (11)	80 (15)	86 (15)
Nasopharyngitis	91 (17)	71 (13)	89 (16)	64 (12)	65 (12)	68 (12)
Dizziness	44 (8)	42 (8)	55 (10)	54 (10)	49 (9)	54 (10)
SAE	81 (15)	72 (13)	73 (13)	70 (13)	76 (14)	79 (14)

The safety MRI population denotes all randomized participants who received at least one dose of study treatment and had at least one postbaseline MRI assessment. The safety population denotes all randomized participants who received at least one dose of study treatment;



Amyloid-related imaging abnormalities (ARIA)-mild/mod or severe

-**ARIAE**-oedema, like PRESS

-**ARIAH**- haemorrhages with new AA lesions, SCS or other new haemorrhages

Presentation with headache, confusion and seizure

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Lecanemab in Early Alzheimer's Disease

van Dyck CH et al. DOI: 10.1056/NEJMoa2212948

CLINICAL PROBLEM

Some evidence suggests that amyloid removal slows the progression of Alzheimer's disease. Lecanemab, an anti-amyloid monoclonal antibody with high affinity for soluble amyloid protofibrils, is being tested in early Alzheimer's disease.

CLINICAL TRIAL

Design: A phase 3, multicenter, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of lecanemab in patients 50 to 90 years of age with early Alzheimer's disease.

Intervention: 1795 participants in North America, Europe, and Asia were assigned to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary efficacy end point was the change in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB) from baseline, with higher scores indicating greater impairment.

RESULTS

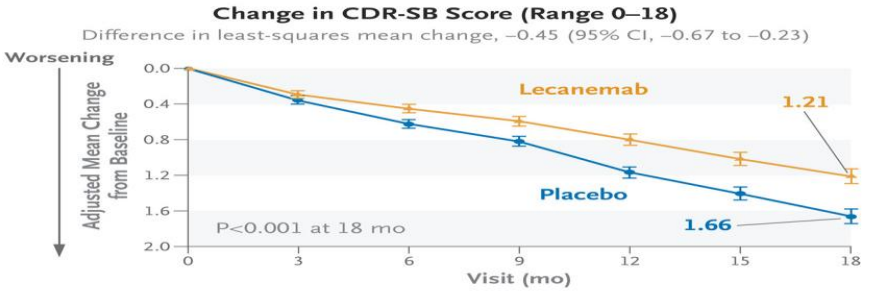
Efficacy: At 18 months, mean CDR-SB scores had worsened in both groups. The mean change in CDR-SB score was smaller (indicating less cognitive and functional decline) in the lecanemab group.

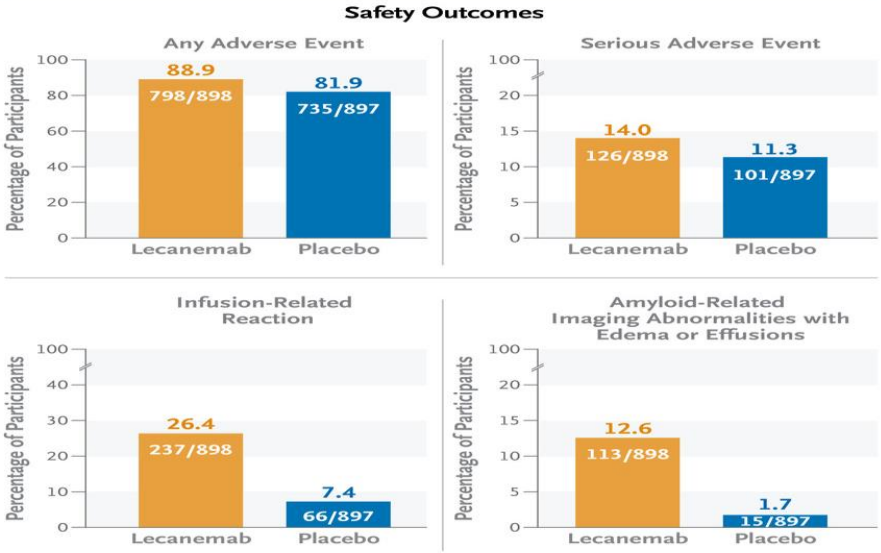
Safety: Overall incidences of adverse events were similar in the two groups. The most common adverse events in the lecanemab group included infusion-related reactions and amyloid-related imaging abnormalities with edema or effusions.

LIMITATIONS AND REMAINING QUESTIONS

- Longer-term follow-up is needed; an open-label extension study is ongoing.
- The trial was conducted during the Covid-19 pandemic and, as a result, faced challenges including missing data, missed doses, delayed assessments, and intercurrent illnesses.
- Occurrences of amyloid-related imaging abnormalities may have led to unblinding of participants and investigators.

Links: Full Article | NEJM Quick Take | Editorial

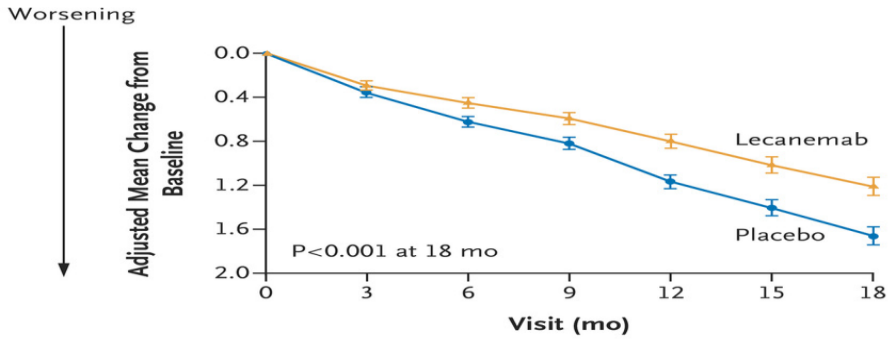




CONCLUSIONS

In patients with early Alzheimer's disease, lecanemab was associated with moderately less decline on measures of cognition and function than placebo over a period of 18 months.

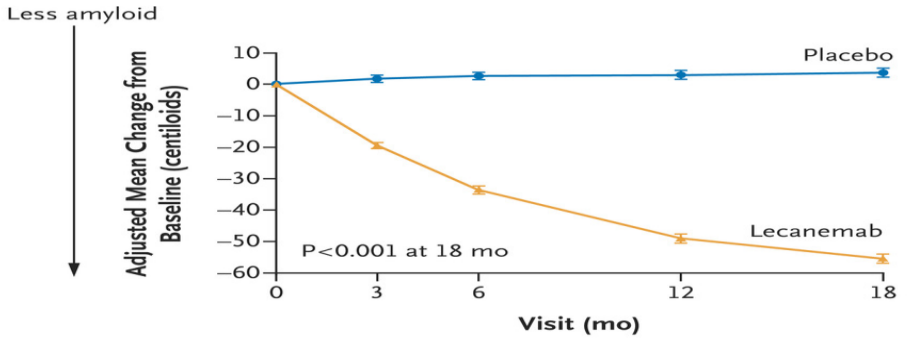
A CDR-SB Score



No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

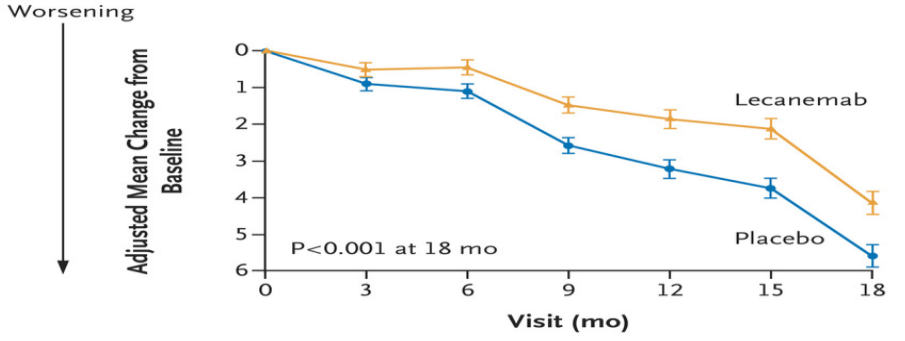
B Amyloid Burden on PET



No. of Participants

Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

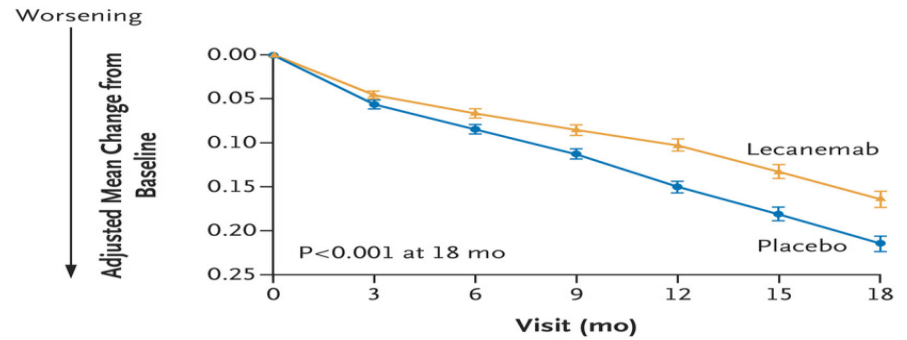
C ADAS-Cog14 Score



No. of Participants

Lecanemab	854	819	793	771	753	730	703
Placebo	872	844	823	807	770	762	738

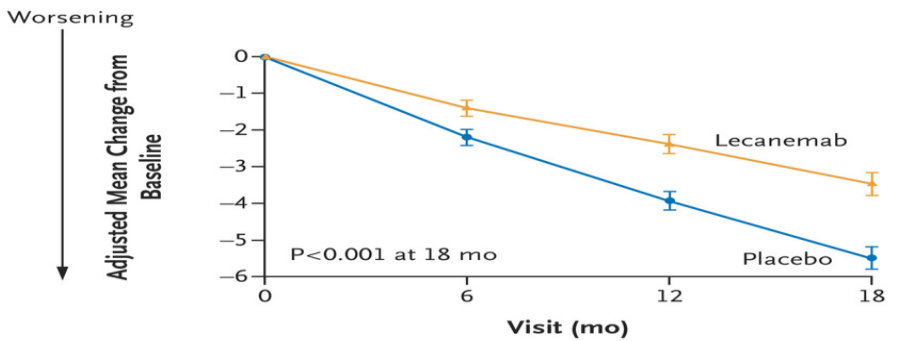
D ADCOMS



No. of Participants

Lecanemab	857	820	796	774	757	733	708
Placebo	875	847	822	808	775	764	749

E ADCS-MCI-ADL Score



No. of Participants

Lecanemab	783	756	716	676
Placebo	796	783	739	707

Trailblazer-Donanamab trial

JAMA

QUESTION Does donanemab, a monoclonal antibody designed to clear brain amyloid plaque, provide clinical benefit in early symptomatic Alzheimer disease?

CONCLUSION Among patients with early symptomatic Alzheimer disease and amyloid and tau pathology, donanemab significantly slowed clinical progression at 76 weeks in low/medium tau and combined low/medium and high tau pathology populations.

POPULATION

996 Women
740 Men

Adults aged 60-85 years with symptomatic Alzheimer disease and amyloid and tau pathology

Mean age: 73 years

LOCATIONS

277 Medical sites in 8 countries

INTERVENTION

1736 Patients randomized
1599 Patients analyzed

860
Donanemab
Administered intravenously every 4 weeks for up to 72 weeks

876
Placebo
Administered intravenously every 4 weeks for up to 72 weeks

PRIMARY OUTCOME

Least-squares mean change in integrated Alzheimer Disease Rating Scale (iADRS) score (range, 0-144; lower scores indicate greater impairment) from baseline to 76 weeks

FINDINGS

Least-squares mean change in iADRS

Donanemab

Low/medium tau population: −6.02

Combined population: −10.19

Placebo

Low/medium tau population: −9.27

Combined population: −13.11

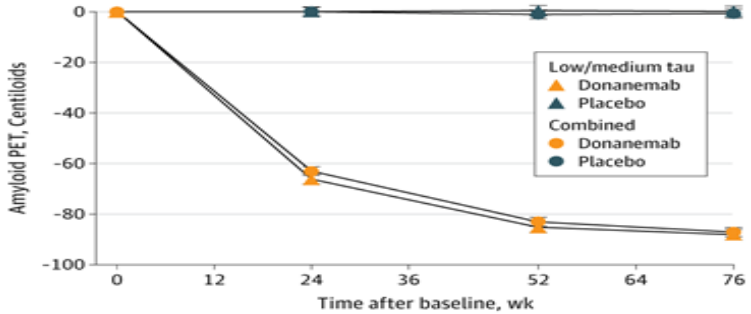
Differences were statistically significant:

Low/medium tau: 3.25 (95% CI, 1.88-4.62); $P < .001$

Combined: 2.92 (95% CI, 1.51-4.33); $P < .001$

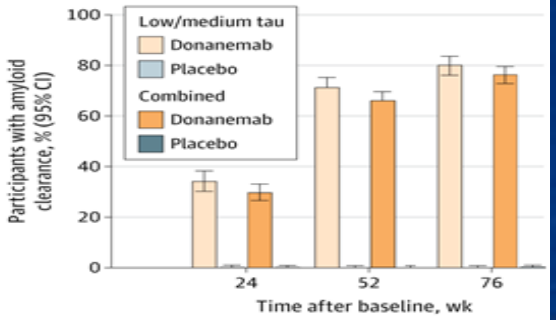
Sims JR, Zimmer JA, Evans CD, et al; TRAILBLAZER-ALZ 2 Investigators. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. Published online July 17, 2023. doi:10.1001/jama.2023.13239

A Adjusted mean change (95% CI) in amyloid PET



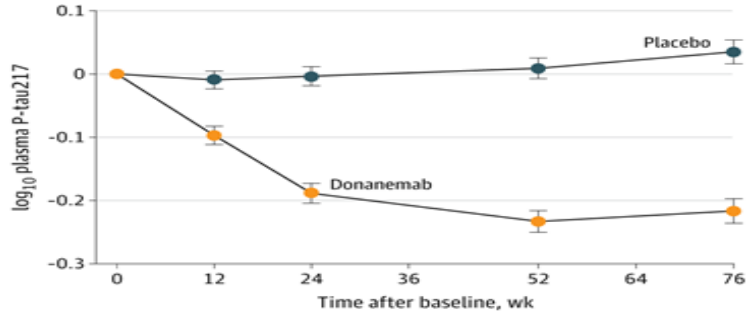
No. of participants					76-wk value, Centiloids	Difference from baseline %
Low/medium tau						
Donanemab	525	521	463	433	-88.0	-85.5
Placebo	556	552	498	470	0.2	0.2
Combined						
Donanemab	765	760	670	614	-87.0	-83.7
Placebo	812	805	729	690	-0.7	-0.7

B Participants with amyloid clearance (<24.1 Centiloids)



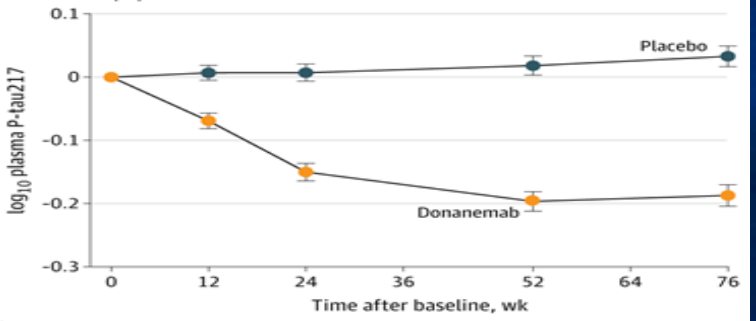
No. of participants			
Low/medium tau			
Donanemab	521	463	433
Placebo	553	498	470
Combined			
Donanemab	761	670	614
Placebo	805	730	690

C Adjusted mean change (95% CI) of $\log_{10}$ plasma P-tau217 in low/medium tau population



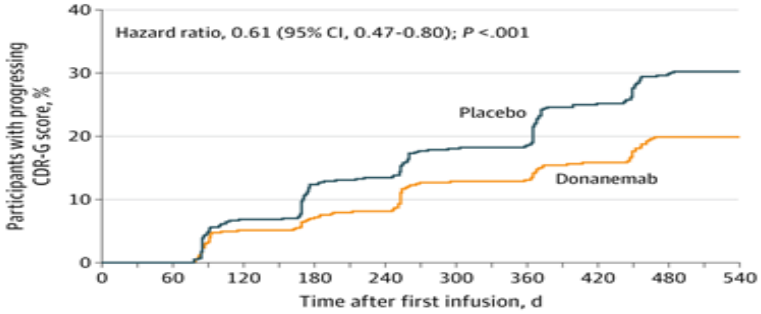
No. of participants					
Placebo	537	517	511	449	429
Donanemab	522	493	464	410	395

D Adjusted mean change (95% CI) of $\log_{10}$ plasma P-tau217 in combined population



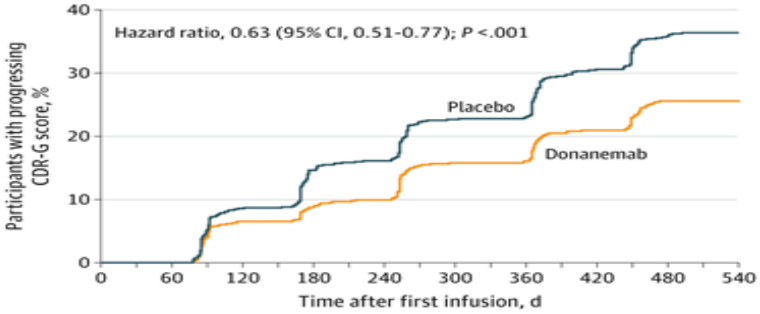
No. of participants					
Placebo	786	758	734	658	620
Donanemab	758	717	686	602	568

E CDR-G score in low/medium tau population



Treatment	No. of participants at risk 60 d	120 d	180 d	240 d	360 d	480 d
Placebo	570	529	489	474	425	345
Donanemab	552	514	492	470	412	335

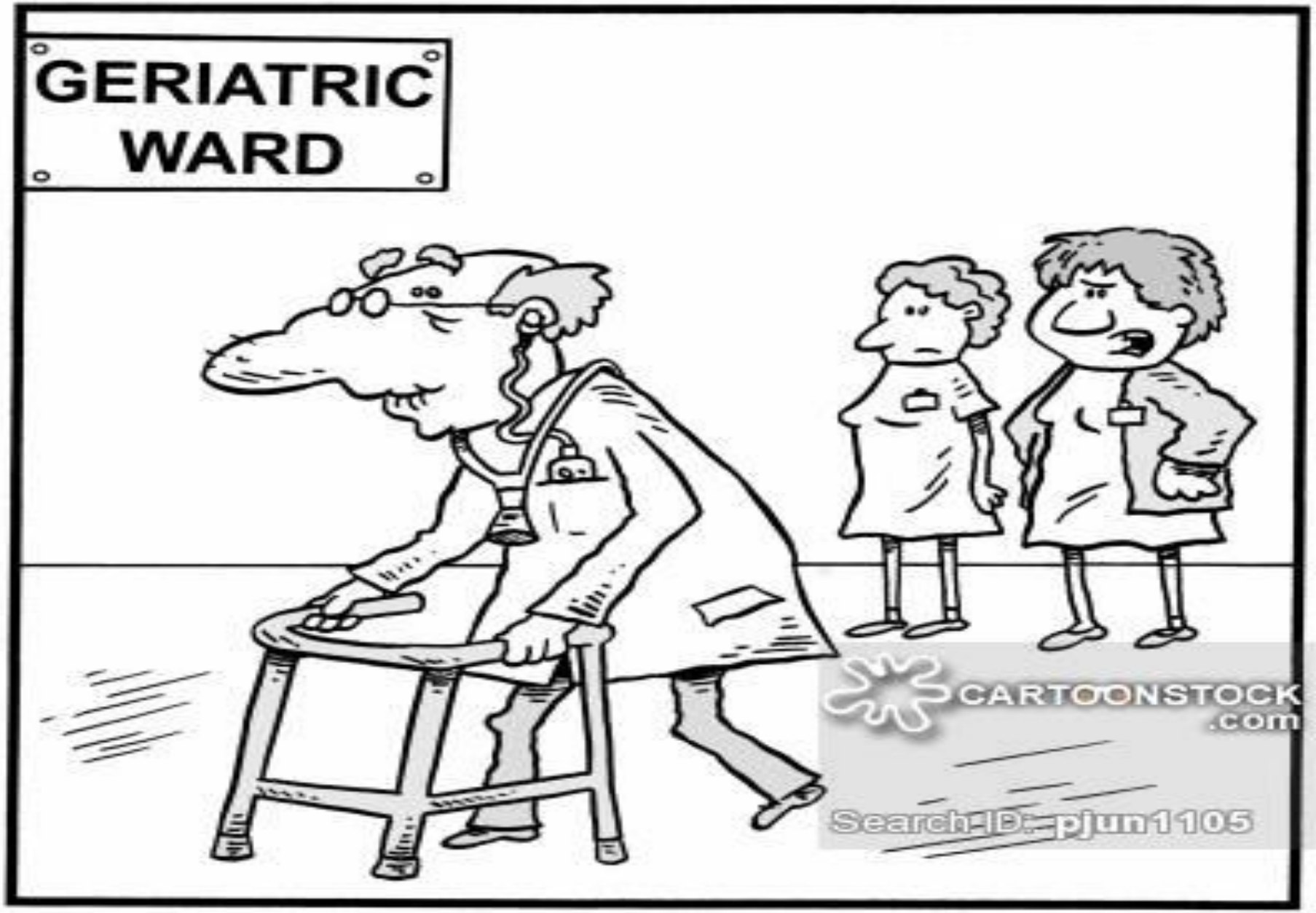
F CDR-G score in combined population



Treatment	No. of participants at risk 60 d	120 d	180 d	240 d	360 d	480 d
Placebo	840	764	700	671	587	462
Donanemab	801	737	696	696	575	474

DMDs in AD-’’Food for Thought’’

- Selected patient group-one size doesn’t fit all
- Good evidence for amyloid clearance
- Modest benefit in mild/early AD
- Progression of cerebral atrophy and cognitive decline
- Side-effect- unique to therapy
- Cost implication-NICE
- Service delivery challenges in NHS-imaging (MRIs, amyloid PET), LPS, follow up etc
- Role in familial ADs



"He's our new Geriatric specialist!"

Early Onset Dementias

1. Neurodegenerative

- Alzheimer's disease and variants
- FTLD
- Taupathies (PSP, CBD)
- LBD/PKD with dementia

2. Vascular

- MID
- CADASIL/CARASAL
- CAA
- Primary angiitis of CNS
- Secondary CNS Vasculitis
- RVCS (rare cause)

3. Infectious

- Prion
- HIV-associated ND (HAND)
- Others (HSV, Neurosyphilis, Whipples, PML)

4. Inflammatory/AI conditions

- MS
- Limbic Encephalitis (AI/Paraneoplastic)
- Encephalopathy with systemic AI disease (Sjogren's, Behcet, SLE)

5. Neurometabolic disorders

- Mitochondrial disease (MELAS, MERRF, CPEO, Kearn-Sayre Syndrome)
- Leucodystrophies
- Adult Neuronal Ceroid Lipofuscinosis

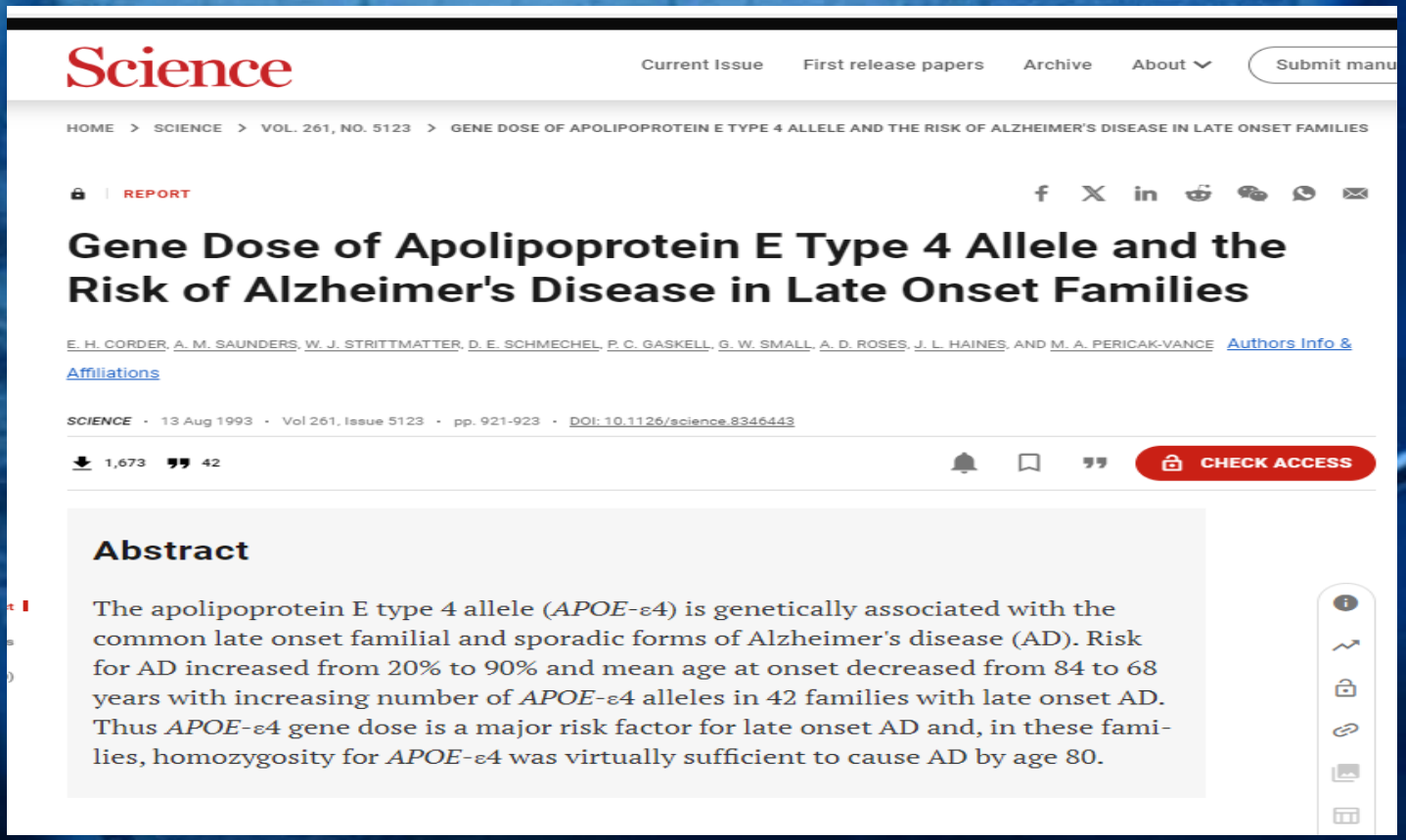
6. Others

- CTE
- Alcohol related
- NPH
- Frontotemporal Brain Sagging Syndrome (FBSS)
- Wilson's Disease
- Huntington's Chorea

Summary of Gene Associations

AD Type	Chromosome	Gene	Reference
Familial AD			
1.Early Onset *(30-65)*	21q	APP (10-15%)	St George Hyslop *et al. 1987* Goate *et al.* (1991)
2.Early Onset (30-60)	14q	PS-1 (70%)	Schellenberg *et al.* (1992) Levy-Lahad *et al.* (1995)
3.Early Onset (VG) (40-75)	1q	PS-2 (5%)	Schellenberg *et al.* (1992) Sherrington *et al.* (1995)
4.Late Onset	19	Not Known APOE*4	Pericak-Vance *et* al. (1991) Strittmatter *et al.* (1993)

VG - Volga German



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REPORT

Gene Dose of Apolipoprotein E Type 4 Allele and the Risk of Alzheimer's Disease in Late Onset Families

E. H. CORDER, A. M. SAUNDERS, W. J. STRITTMATTER, D. E. SCHMECHEL, P. C. GASKELL, G. W. SMALL, A. D. ROSES, J. L. HAINES, AND M. A. PERICAK-VANCE Authors Info & Affiliations

SCIENCE · 13 Aug 1993 · Vol 261, Issue 5123 · pp. 921-923 · DOI: 10.1126/science.8346443

1,673 42 CHECK ACCESS

Abstract

The apolipoprotein E type 4 allele (*APOE*-ε4) is genetically associated with the common late onset familial and sporadic forms of Alzheimer's disease (AD). Risk for AD increased from 20% to 90% and mean age at onset decreased from 84 to 68 years with increasing number of *APOE*-ε4 alleles in 42 families with late onset AD. Thus *APOE*-ε4 gene dose is a major risk factor for late onset AD and, in these families, homozygosity for *APOE*-ε4 was virtually sufficient to cause AD by age 80.

Late onset AD risk in those with a positive FHx- 20% with E4 heterozygous v 90% with E4 homozygous

Carriage of apoE epsilon 4 lowers the age of onset of Alzheimer's Disease in Northern Ireland

Djamil Vahidassr, D.S. Savage, Christopher Patterson, J.T. Lawson, Peter Passmore

School of Medicine, Dentistry and Biomedical Sciences, Centre for Public Health

Research output: Contribution to journal › Article › peer-review

Vahidassr, D., Savage, D. S., Patterson, C., Lawson, J. T., & Passmore, P. (2000). Carriage of apoE epsilon 4 lowers the age of onset of Alzheimer's Disease in Northern Ireland. *Alzheimer Reports*, *3*, 7-10.

Posterior Cortical Atrophy (PCA)

Benson syndrome

PCA- Clinical features

- Younger non-familial patients generally
- Deficits of higher visual and spatial functions (form of Balint's syndrome)
- Topographical disorientation with visual object agnosia, prosopagnosia and simultagnosia
- Visual apraxia with dyslexia, agraphia, acalculia, diff with copying and drawing (Pentagon and Clock drawing)
- Left right disorientation, dressing apraxia

PCA-Features

- Memory and language functions preserved better and longer than in the normal variant DAT
- SPECT and PET show deficits of perfusion and metabolism in both parietal and occipital lobes as well as temporal lobes
- Histopathological changes similar to DAT, located predominantly in posterior brain regions
- The diagnosis of PCA is based on neuropsychological and imaging findings.

Frontotemporal Lobe Dementia (Pick's Disease/Semantic dementia)

- **Primary Progressive Aphasia**
  - **Non-fluent variant**
  - **Semantic variant**

- **Behavioural Variant FTLD (bvFTLD)**

FTLD
(Clinical Features)

- Presenile Onset
- Memory Preserved
- Behavioural Features Dominate
  - -Inertia and Neglect (Poor Hygiene)
  - -Over Active (Wandering)
  - -Stereotypical Behaviour (Singing, Puns, Rituals)
  - -Food Fads (Overeating, Sweet tooth)
- Frontal Lobe Features (Dysphasia, Personality Breakdown, loss of etiquette, incontinence)

	AD	FTD
Behaviour	Maintained, Late feature, 2º to memory	Early and common impulsive
Memory	Impaired early	-Mildly Impaired late
Orientation	spatial disorientation in mod AD	Orientated in mod FTD
Language	Impairment ↓ cognition	Progressive impairment
Motor function	Rarely (PKD features)	More common (ALS-FTD Chrom 9)
Genetics	Ps-1, Ps-2, APP, APOE	Chromosome 17 (FTDP-17)
Radiology	Med temp lobe atrophy	Fronto-temporal atrophy
Pathology	Amyloid/Tauopathy	Tauopathy

Wernicke/Korsakoff

Wernicke encephalopathy (WE)

Relatively common, acute neurologic disorder caused by thiamine (B1) deficiency with clinical triad of encephalopathy, oculomotor dysfunction, and gait ataxia.

KS

- Any age but generally presenile
- Is a late neuropsychiatric manifestation of Wernicke encephalopathy (WE)
- Selective anterograde and retrograde amnesia with circumscribed memory impairment with secondary confabulation, repeat grief and joyous reaction

Risk factors for WE/KS

- Chronic heavy alcohol use (The Lost Mariner-Oliver Sacks)
- Anorexia nervosa or other psychiatric illness leading to poor intake
- Hyperemesis of pregnancy
- Prolonged IV feeding without proper supplementation
- Prolonged fasting/starvation, unbalanced nutrition, especially with refeeding
- Gastrointestinal disease or surgery (especially bariatric surgery)
- Systemic malignancy
- Transplantation
- Hemodialysis or peritoneal dialysis
- Acquired immunodeficiency syndrome

Diagnosis of WE/KS

Caine criteria (2/4):

-Dietary deficiency

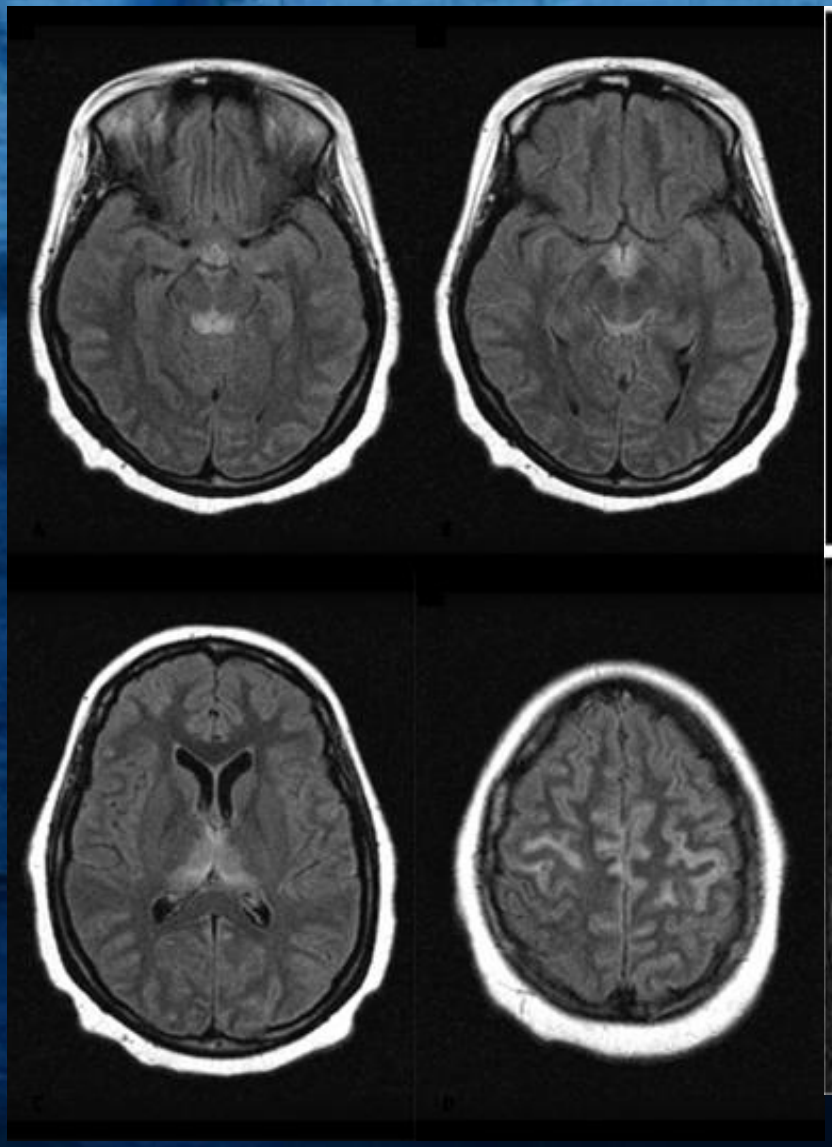
-Oculomotor abnormalities

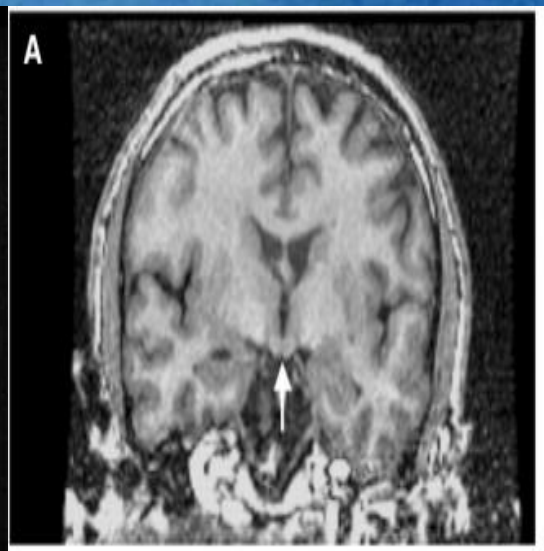
-Cerebellar dysfunction

-Either altered mental status or memory impairment

Ix

- ETKA, Thiamine or TPP level
- MRI-Hyperintesities in periaqueductal, 3rd ventricle, medial thalami and or cerebral cortecies
- Mamillary body atrophy
- SWI may show petechial hemorrhages not seen on standard T2-weighted images

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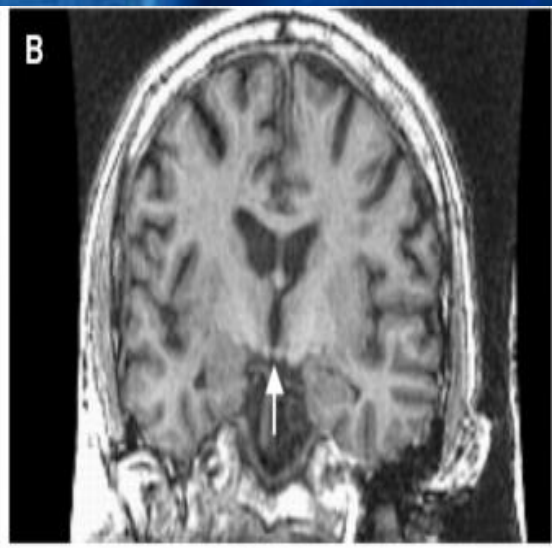
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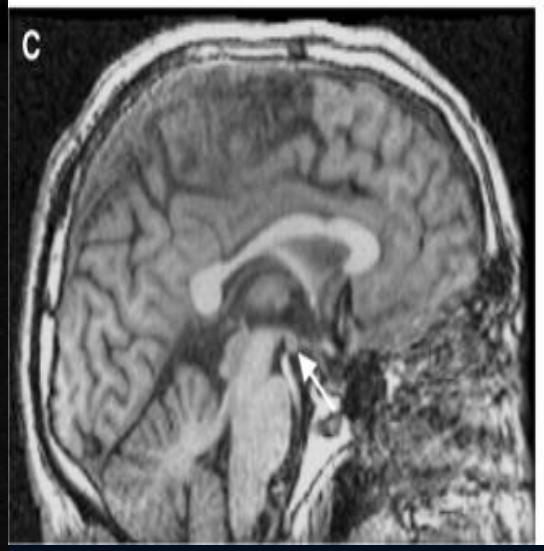
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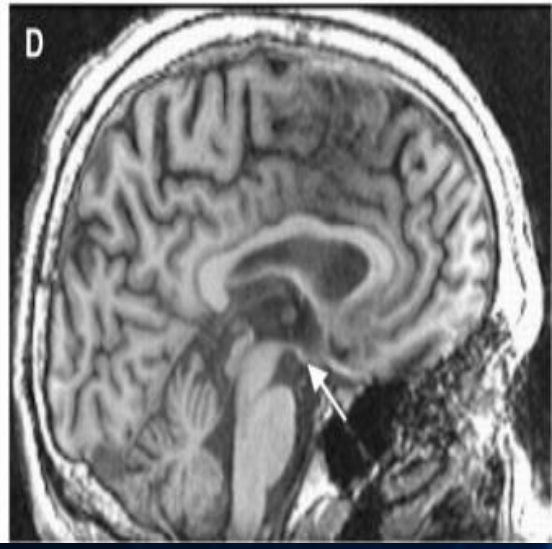

D

WE/KS Treatment

- High dose thiamine (parenteral)
- Glucose/Mg^{2+}
- Food thiamine supplementation reduces the risk of WE/KS
- Improvement in eye signs, vestivular function and gait abnormality with in days
- Improvement in cognition takes longer (weeks)
- High incidence of residual cognitive deficit

Prion Disease Classification
Tansmissible Songiform Encephalopathies-TSEs

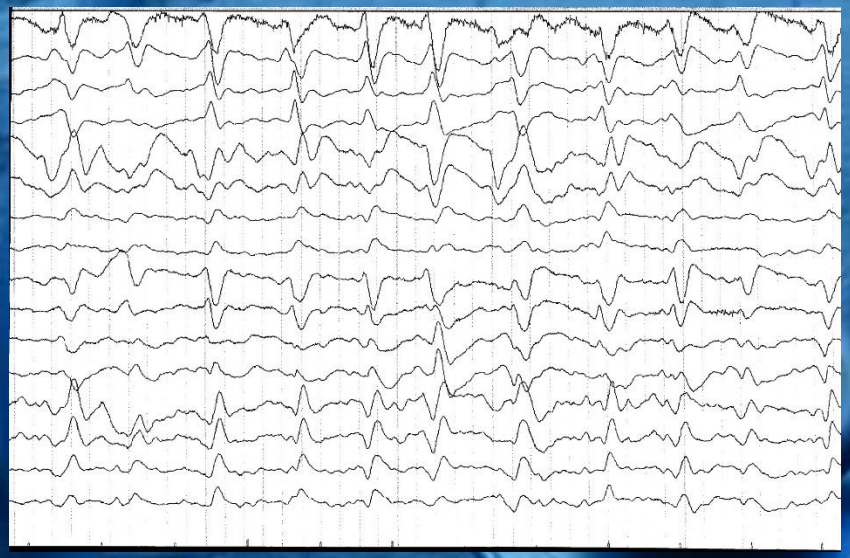
- Sporadic CJD-sCJD (85-90%)
- Iatrogenic CJD-iCJD (1%)
- Variant CJD-vCJD
- Kuru
- Familial (10-15%)
  - Gerstmann-Straussler-Scheinker disease (GSS)
  - Fatal familial insomnia (FFI)

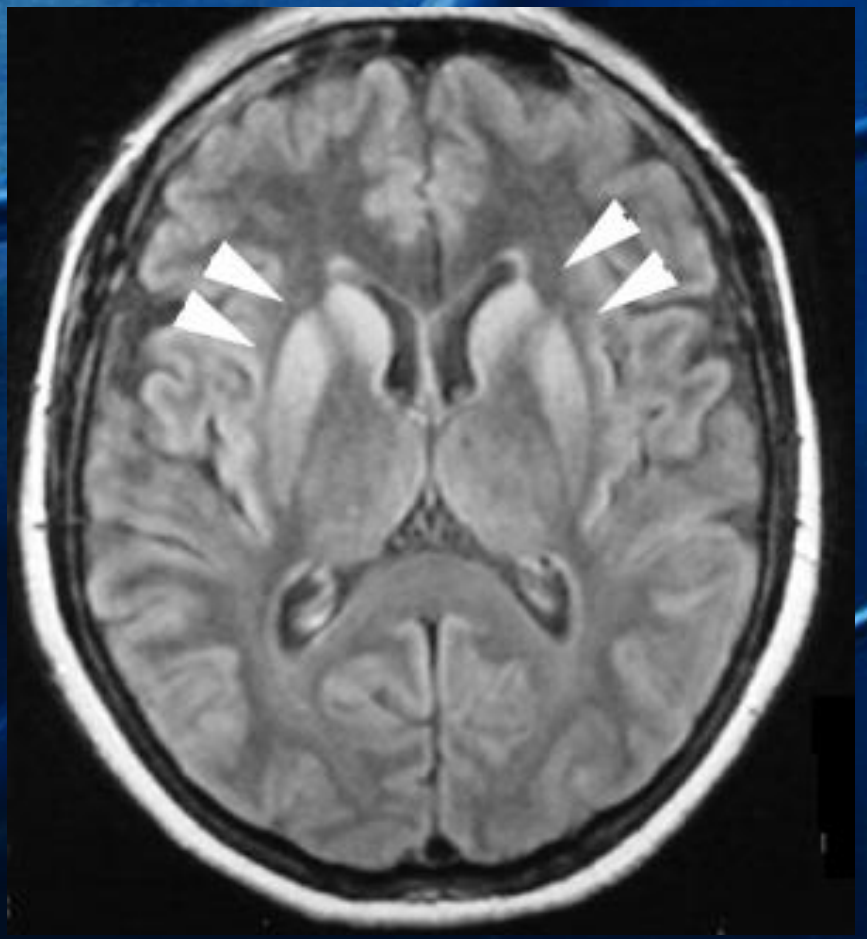
Sporadic CJD

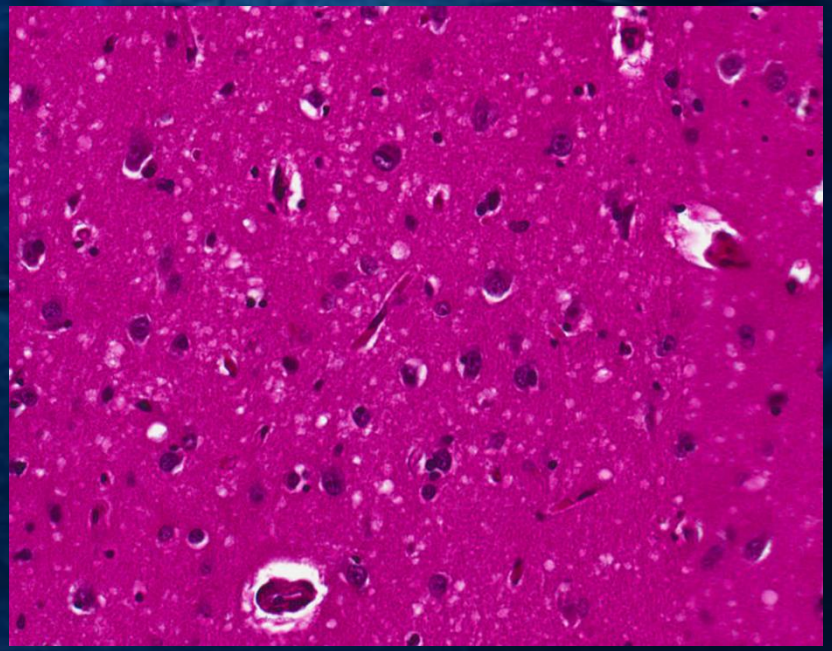
- Annual incidence of 1 per million
- Age of onset 45-75 years of age. Generally over 55 years of age
- Cases below 30 have been described but very rare
- Clinical heterogeneity and pathological findings depends on codon homozygosity for valine instead of methionine at codon129
- Neuropsychiatric, myoclonus, cerebellar, corticospinal tract and extrapyramidal signs/Akinetic Mutism
- Rapidly progressive with mean survival of 4-6/12.

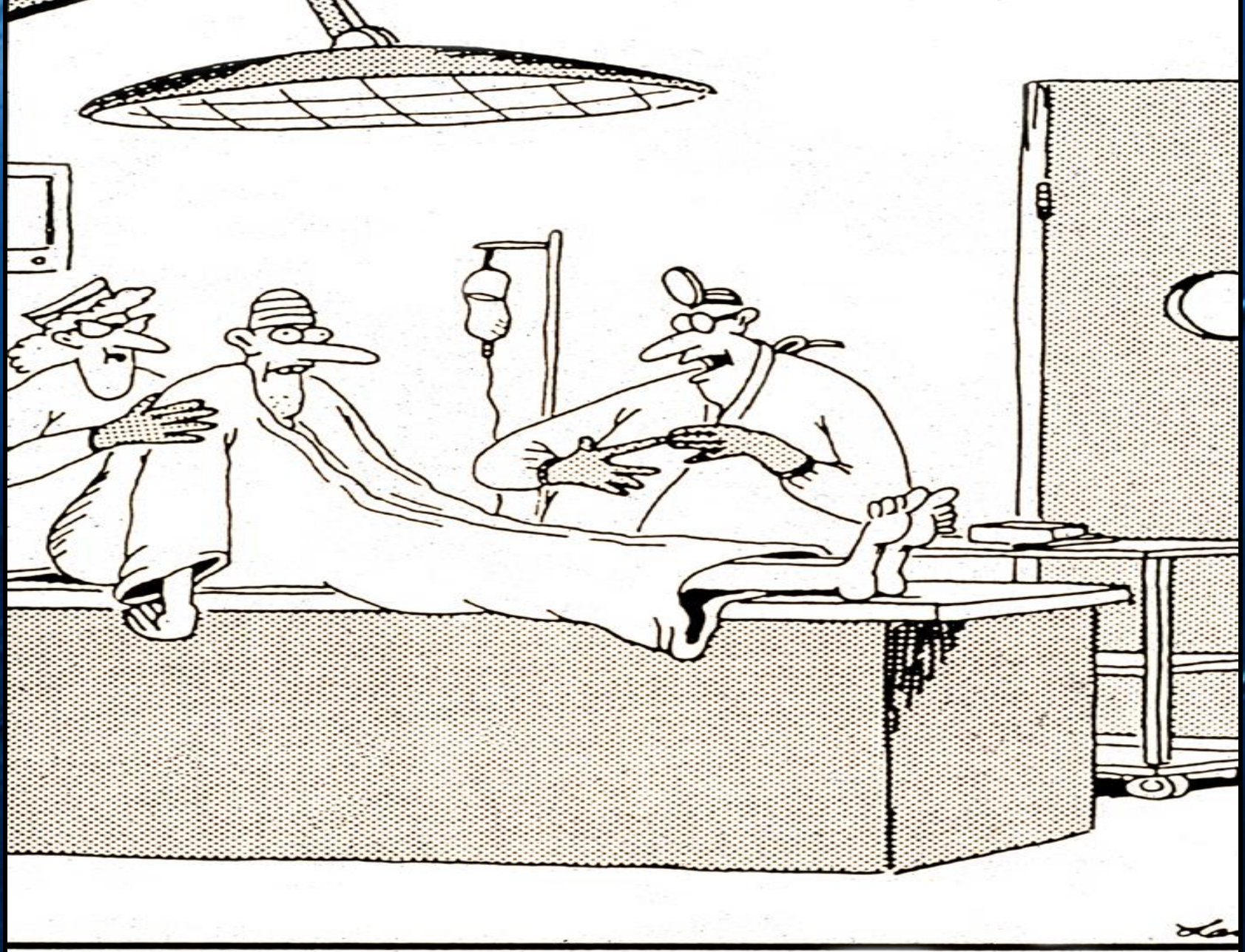
Sporadic CJD (Ix)

- **EEG** -Generalised periodic complexes at 1/sec (60% of cases)
- **CSF** - ↑protein (čout pleocytosis or olig bands)
  - ↑ CSF 14-3-3 protein (85-90%)
  - RT-QuIC
  - Tau and amyloid
- **MRI** -symmetrical high signals in the caudate and putamen/Gyral enhancement
- **Pathology** -Loss of neurons, gliosis, spongiform degeneration, or plaques positive for PrP^{Sc} on histopathology of brain tissue









"OK, Mr. Dittmars, remember, that brain is only temporary, so don't think too hard with it."


Questions???

Functional Cognitive Disorder

Main Manifestations are;

- Poor concentration and memory
- Impaired fluency
- Jumbling of words when speaking
- Word finding difficulty
- Variability in speed of response

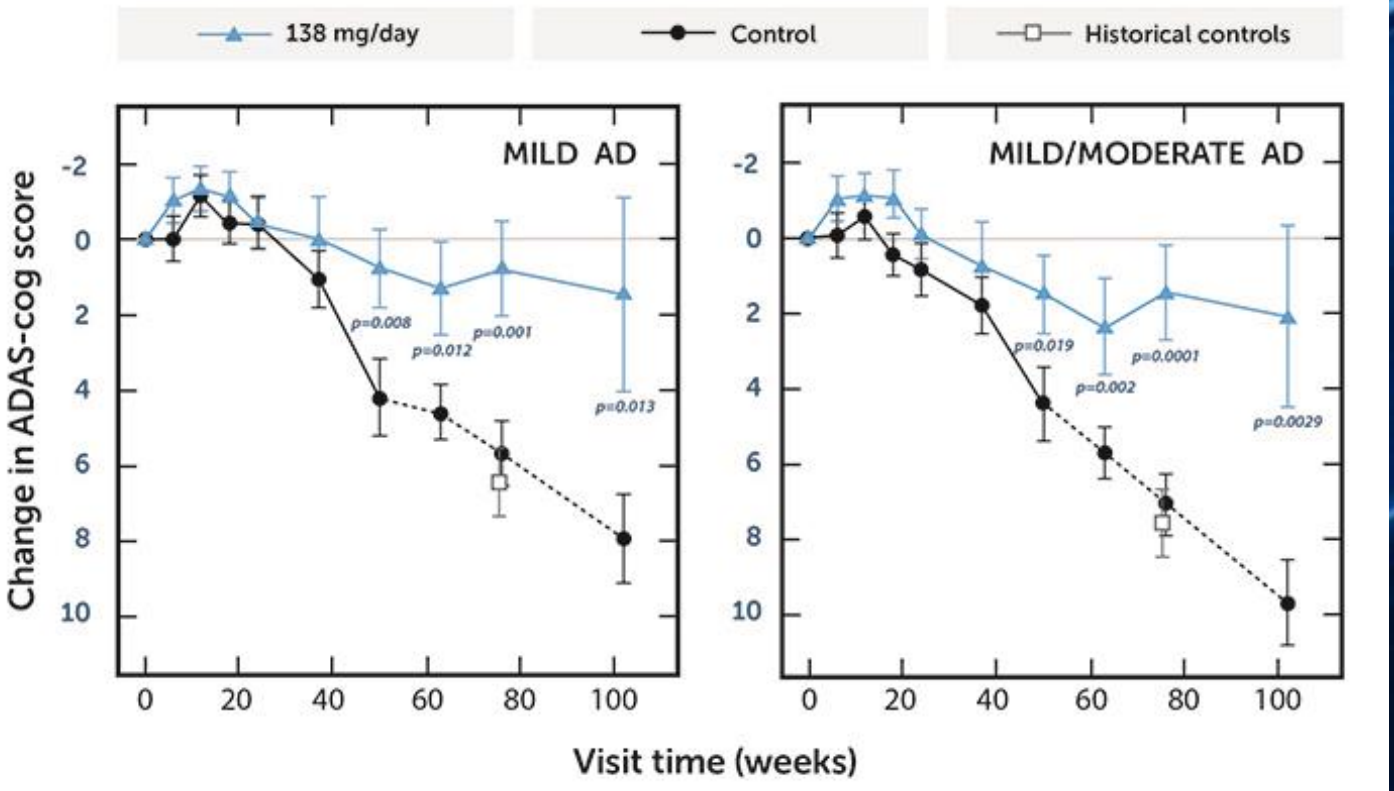
Functional cognitive disorder (FCD)

- Marked loss of remote autobiographical memory
- Inability to perform overlearned skills such as reading, spelling, or simple arithmetic
- Can perform complex implicit cognitive tasks but poor performance on simple explicit tasks
- Performance inconsistent with observed behavior
- Performance inconsistent at different points in the examination or across repeated evaluations
- Impaired performance on tests of effort specifically designed to assess validity of cognitive performance (although poor performance on these tests does not distinguish between intentional and unintentional poor performance)
- Some of these symptoms may also be attributable to anxiety or depressive disorders.

Anti-Tau

- Hydromethylthionine mesylate (HMTM), formerly LMTX®-second-generation tau aggregation inhibitor (TAI)
- The active component (MTC) binds preferentially to the abnormal Tau and removes the damaging tau tangles
- Evidence from laboratory and animal studies as well as Positive phase 2 studies of Rember (Wischick et al., 1996)
- Two phase 3 trails in AD showing no superiority compared with control (Wilcock et al., 2018, Gauthier et al., 2016)
- Another negative phase 3 trial in bvFTD (Shiells et al., 2020)

Phase 2


138 mg/day
Control
Historical controls
MILD AD
MILD/MODERATE AD
Change in ADAS-cog score
Visit time (weeks)
p=0.008
p=0.012
p=0.001
p=0.013
p=0.019
p=0.002
p=0.0001
p=0.0029

Anti-Tau (LUCIDITY Trail)

- Started recruitment Jan 2018 (375 recruited)
- 4mg bd and 8mg bd HMTM arms for 12/12 with 1 extra year of open label
- ADAS-Cog 11 and ADSC-ADL 23 composite measures
- Failed to reach primary endpoints (Wischik et al., 2022)
- Post hoc analysis-higher levels of plasma neurofilament in control v treated group
- Rate of conversion from CDR 0.5 to 1 was halved in MCI group taking 16mg/day dose for 24/12 (Mar 2024 conference news)