Mild Neurocognitive Disorder:
Evaluation and Decision-Making At The Gateway to Dementia

OPPA,
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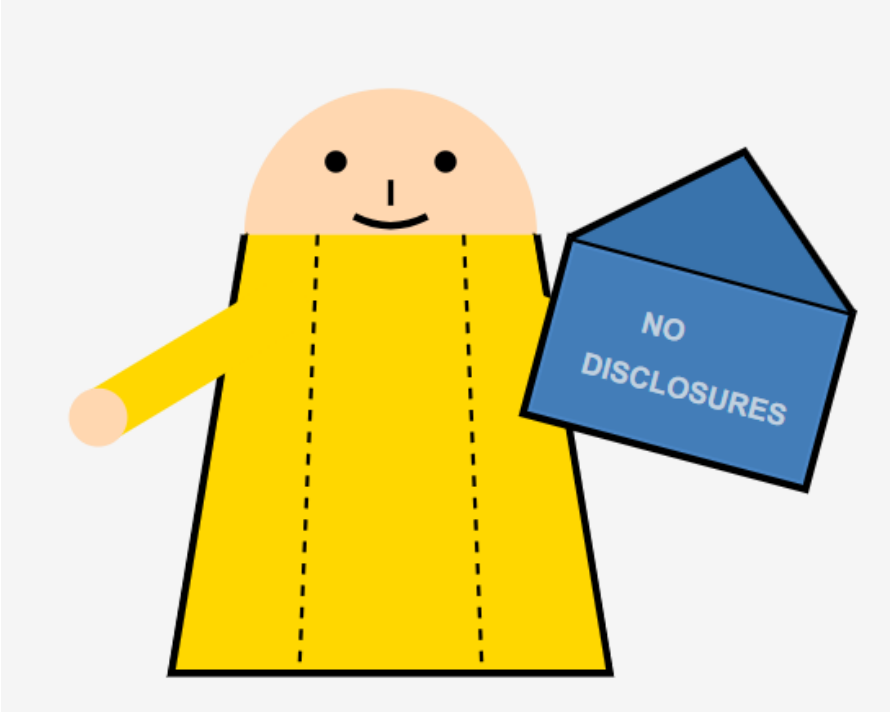
Disclosures

I have no relevant financial relationships to disclose.

Discussion of off-label uses of medications will be identified as such.



LEARNING OBJECTIVES

- Upon completion of this presentation,
- participants will be able to:

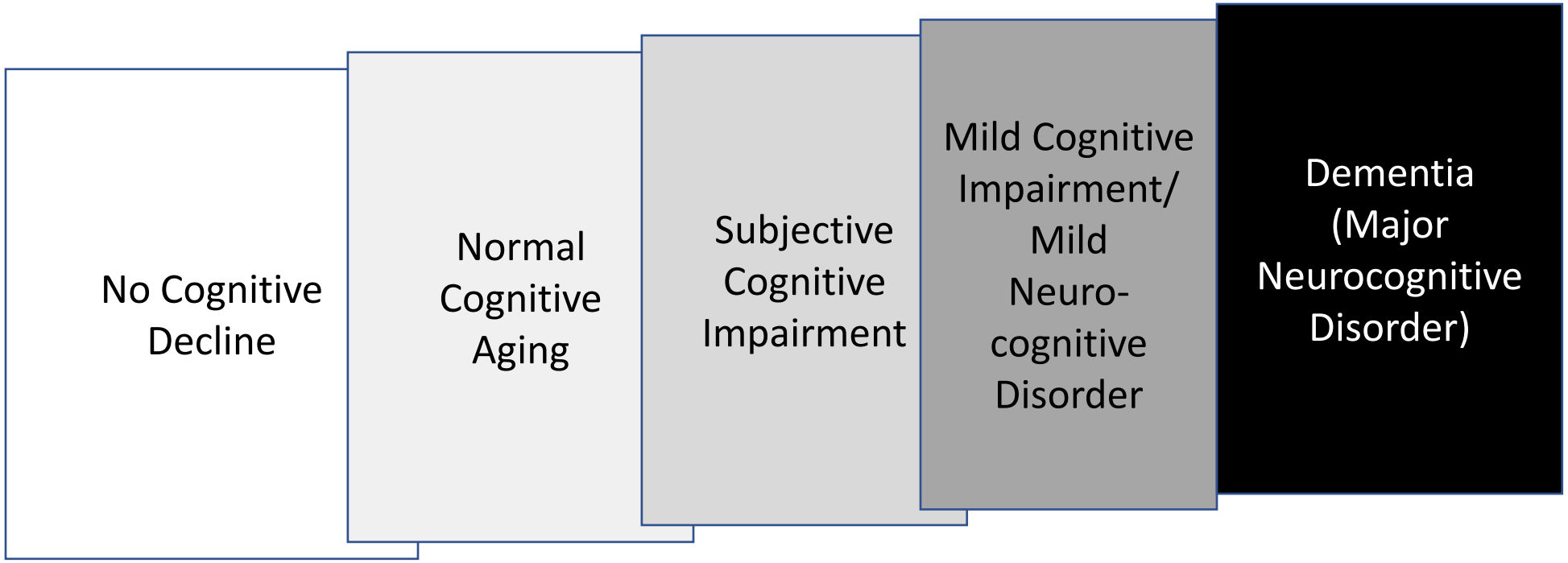
1. Recognize the distinctions between normal cognitive aging, subjective cognitive impairment, mild neurocognitive disorder, and dementia (major neurocognitive disorder).

2. Assess and diagnose mild neurocognitive disorder (MiND) according to its DSM5TR current definition.

3. Intervene with diagnosis disclosure, decision making, planning, and appropriate management including disease modifying immunotherapy.

4. Promote a “brain healthy” lifestyle for delay or prevention of cognitive decline.

Cognitive Aging Continuum: From Normal Aging To Dementia



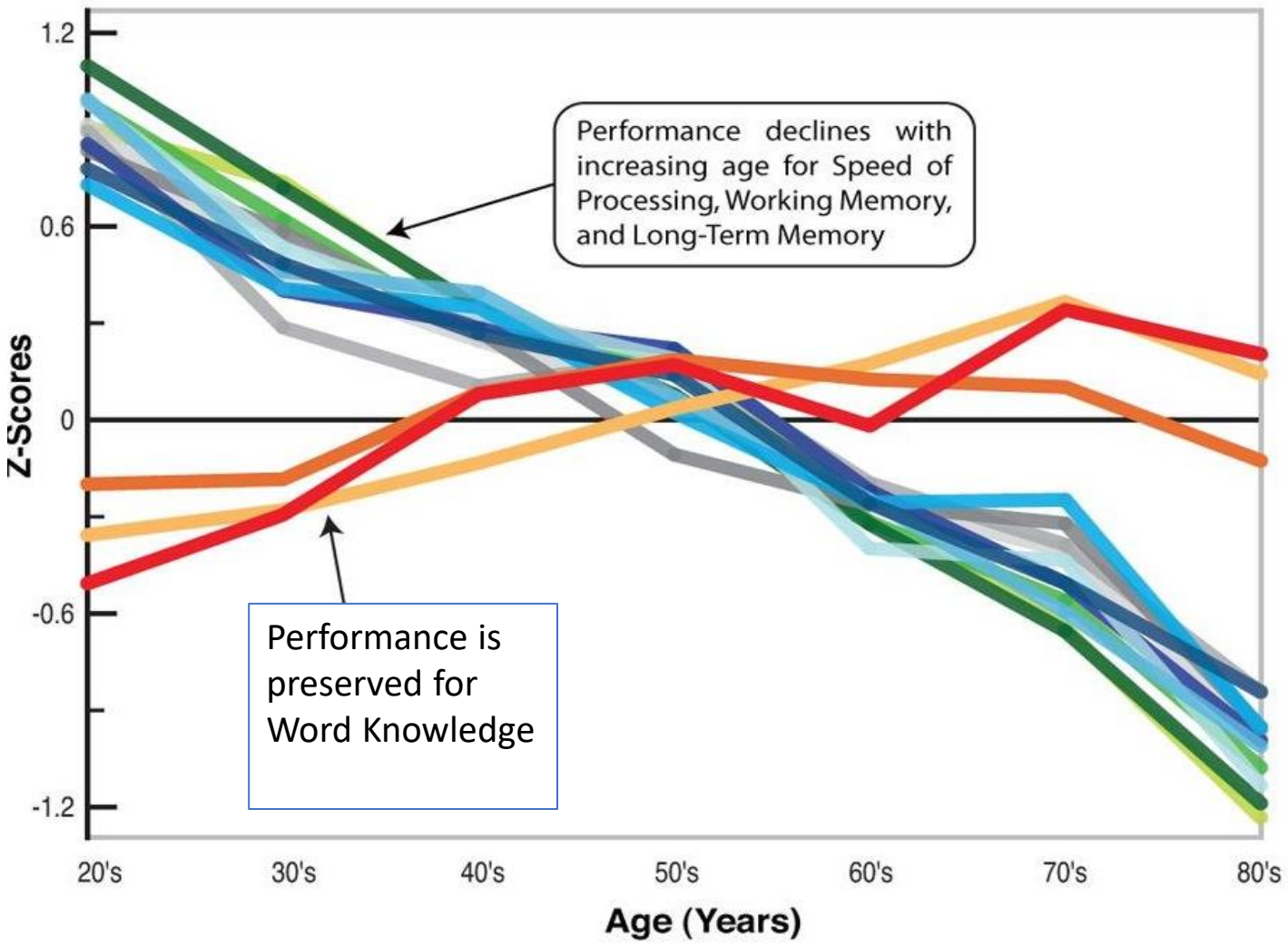
Positive Effects of Aging on Cognition: Crystallized Intelligence

Angela (age 67)
"Good health, retirement, family, travel, hobbies – It's a great time of life"!

- Aging is often associated with cognitive changes.[1]
- Cognitive aging is highly individualized.[2]
- Some mental functions can improve with aging[3,4]
  - Resilience
  - Stress tolerance
  - Compassion
  - Wisdom[5]

1. Durning SJ et al. J Contin Educ Health Prof 2010;30:153-60; 2. Eva KW. Acad Med 2002;77:S1-S6; 3. Moutier CY et al. J Med Regulation 2013;99:10-18; 4. Meeks TW and Jeste DV. Arch Gen Psychiatry 2009;66:355-65; 5. Jeste DV and Lee EE. Harv Rev Psychiatry 2019;27:127-40.

Aging Differentially Affects Cognitive Domains



Speed of Processing
- Digit Symbol
- Letter Comparison
- Pattern Comparison

Working Memory
- Letter Rotation
- Line Span
- Computation Span
- Reading Span

Long-Term Memory
- Benton
- Rey
- Cued Recall
- Free Recall

Word Knowledge
- Shipley Vocabulary
- Antonym Vocabulary
- Synonym Vocabulary

Park and Reuter-Lorenz. Ann Rev Psychol 2009;60:173-196.

Additional Changes with Normal Aging

Function	Definition
Processing Speed	Rapidity of encoding and use of input
Working Memory	Manipulation of information kept in awareness
Long Term Memory	Encoding and storage
Inhibitory Control	Suppression of attention to irrelevant information
Sensory Perception	Especially visual and auditory input

Reuter-Lorenz PA, Park DC. J Gerontol B Psychol Sci Soc Sci 2010;65:405-15; Luszcz and Bryan. Gerontology 1999 ;45:2-9

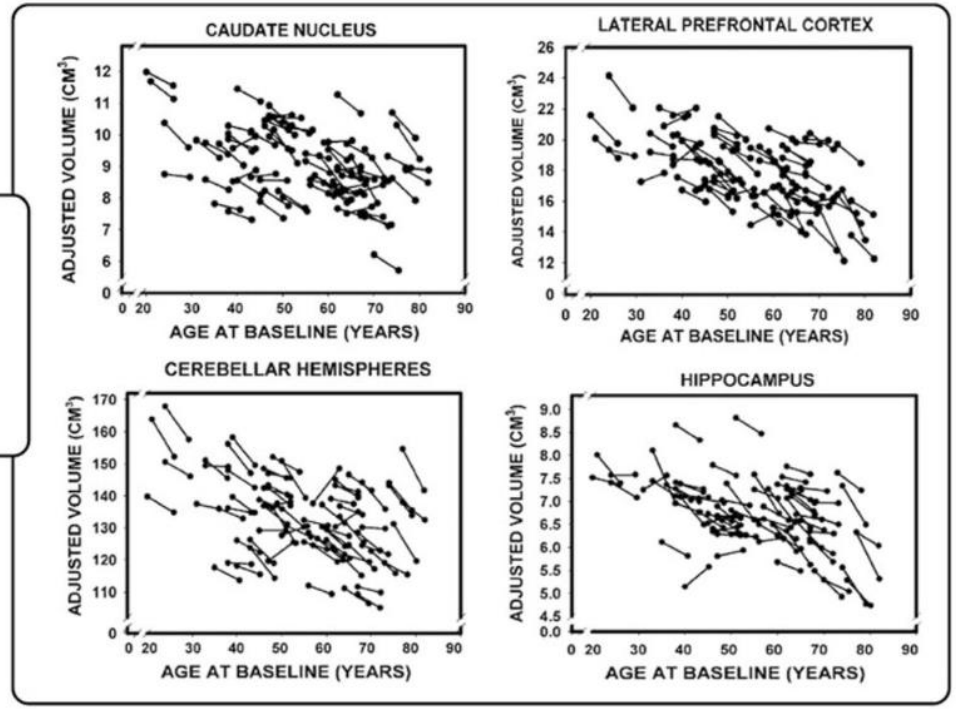
Imaging the Normally Aging Brain

- During aging of the “healthy brain”:
  - Brain volume diminishes, accelerating after age 50.
  - White matter hyperintensities increase.
  - Hippocampal volume decreases.
  - Cerebral microbleeds accumulate.
  - Cerebral amyloid angiopathy may underlie some age-related changes.

Chowdhury et al. J of Stroke and Cerebrovascular Diseases 2011;20(4):302-9; Emilien et al. Memory: Neuropsychological, Imaging and Psychopharmacological Perspectives. Psychological Press, 2004; Mattay et al. Biol Psychol. 2008;79:9-22.

Anatomy of the Aging Brain

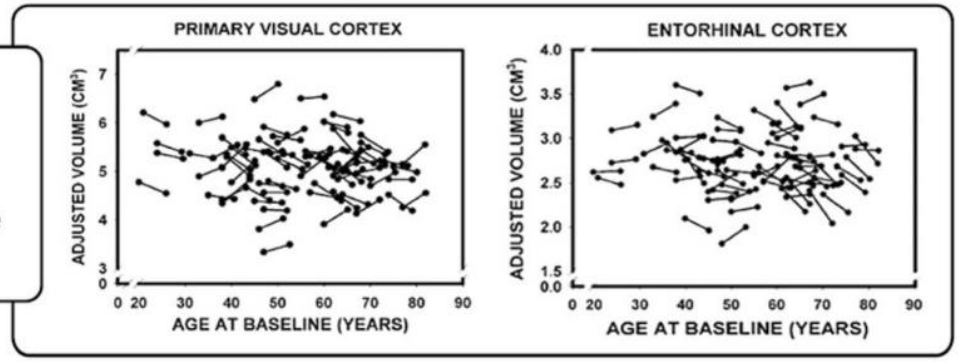
Brain regions that reduce in volume with age.



Executive function

Binding memory, speed and balance

Brain regions with minimal reduction or stable volume with age.



And perisylvian language area

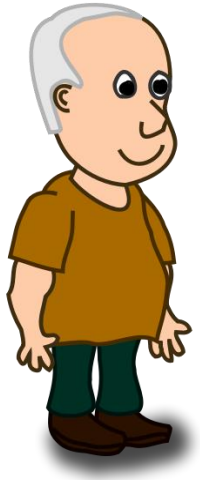
Park and Reuter-Lorenz. Ann Rev Psychol 2009;60:173-196.

Cognitive Reserve

- Greater level of education, higher socioeconomic status, higher baseline intelligence are associated with
  - Delay recognition of subjective decline
  - Preserve normal test performance despite pathology
  - Postpone transition to MCI or dementia.
- The physical bases of cognitive reserve include:
  - Neural reserve: pre-existing differences in cognitive networks
  - Neural compensation: recruitment of alternative networks or strategies in response to pathology.
  - Different from “brain reserve” = structural differences
- This helps explain how different levels of impairment can be associated with similar degrees of neurodegenerative pathology.

.Stern Y. Neuropsychologia. 2009 Aug;47(10):2015-28. doi: 10.1016/j.neuropsychologia.2009.03.004.

Subjective Cognitive Impairment/Decline (SCD)



Al (age 73)
"I'm really worried about my memory. I just don't feel as sharp as I used to!"

- Definition: Individual expresses awareness of memory difficulty (which may or may not be objectively present).
- Majority of individuals reporting SMI in community studies did not have MCI or dementia – Yet AD biomarkers may be positive.
- Common complaint in older adults (43% of age 65-74, 88% over age 85)
- **But Follow up is important!** *After 10 years of follow up, 75% of older adults who complained of SCD in 3 or 4 of their first annual visits had developed MCI or dementia (vs 25% for no initial SCD).*[2]

1. Iliffe and Pealing BMJ 2010;340:703-6; 3. Liew TM. Alzheimer's Research & Therapy 2020;12:135-147.

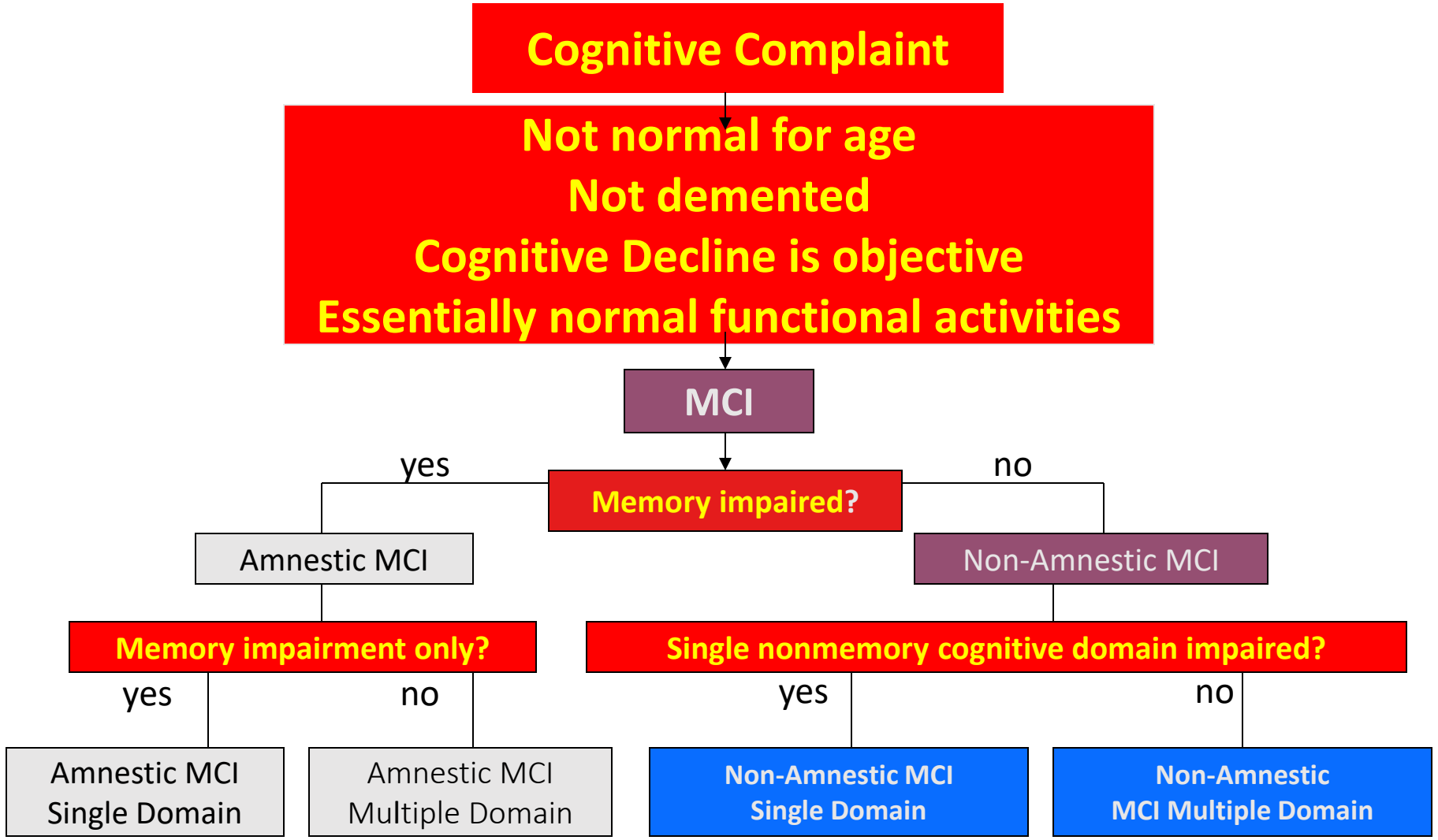
SCI/SCD: Differential Diagnosis Considerations[1,2]

- Rule out effects of:
  - Recent medical or psychosocial stressor (e.g. Long COVID, Loss)
  - Depression/Anxiety
  - Sleep disorder
  - Medications
  - Substances
- Consider whether prodrome of MiND / Dementia
- Attention to remediable factors may include referral for psychotherapy (CBT to address catastrophic thinking or identify stress sources)

1. Iliffe and Pealing BMJ 2010;340:703-6; 3. Liew TM. Alzheimer's Research & Therapy 2020;12:135-147.

Mild Cognitive Impairment (MCI)/ Mild Neurocognitive Disorder (MiND)

MCI: Evolution of Definition



Adapted from Petersen RC. Mild cognitive impairment. Continuum 2004;10:9-28.

DSM5TR Mild Neurocognitive Disorder

Betty (age 78)
My friends don't notice, but I have word-finding trouble, need lists, and depend on the GPS more. I need some help with my pills and bills.

A. Evidence of **modest cognitive decline** in one or more domains based on concern AND objective assessment.

B. Not sufficient to interfere with independence (**iADL preserved**) but may require greater effort and compensatory strategies

Exclusions: C) Not delirium, or D) another Axis I disorder.

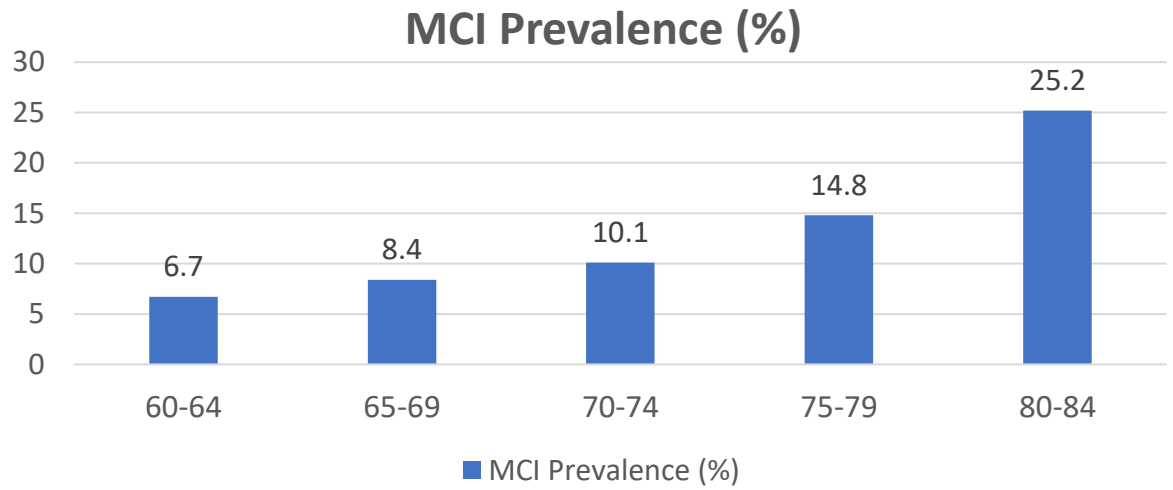
**Specify whether due to AD, FTLD, LBD, VD, TBI, SUD, HIV, prion, PD, HD, other, multiple, unspecified; with or without behavioral disturbance*

DOMAINS: New Learning/Memory, Complex Attention, Visuospatial, Executive Function, Language, Social Cognition

Adapted from: American Psychiatric Association (Ed.). (2022). Diagnostic and statistical manual of mental disorders: DSM-5-TR (Fifth edition, text revision). American Psychiatric Association Publishing.

Mild Neurocognitive Disorder Is Common Among Older Adults

- Annual prevalence: 12% to 19% in adults ≥ 60 years old[1-4]
- Prevalence increases with age:[5]
  - 6.7% (age 60-64)
  - 8.4% (age 65-69)
  - 10.1% (age 70-74)
  - 14.8% (age 75-79)
  - **25.2% (age 80-84)**
- Prevalence for men = prevalence for women[6]



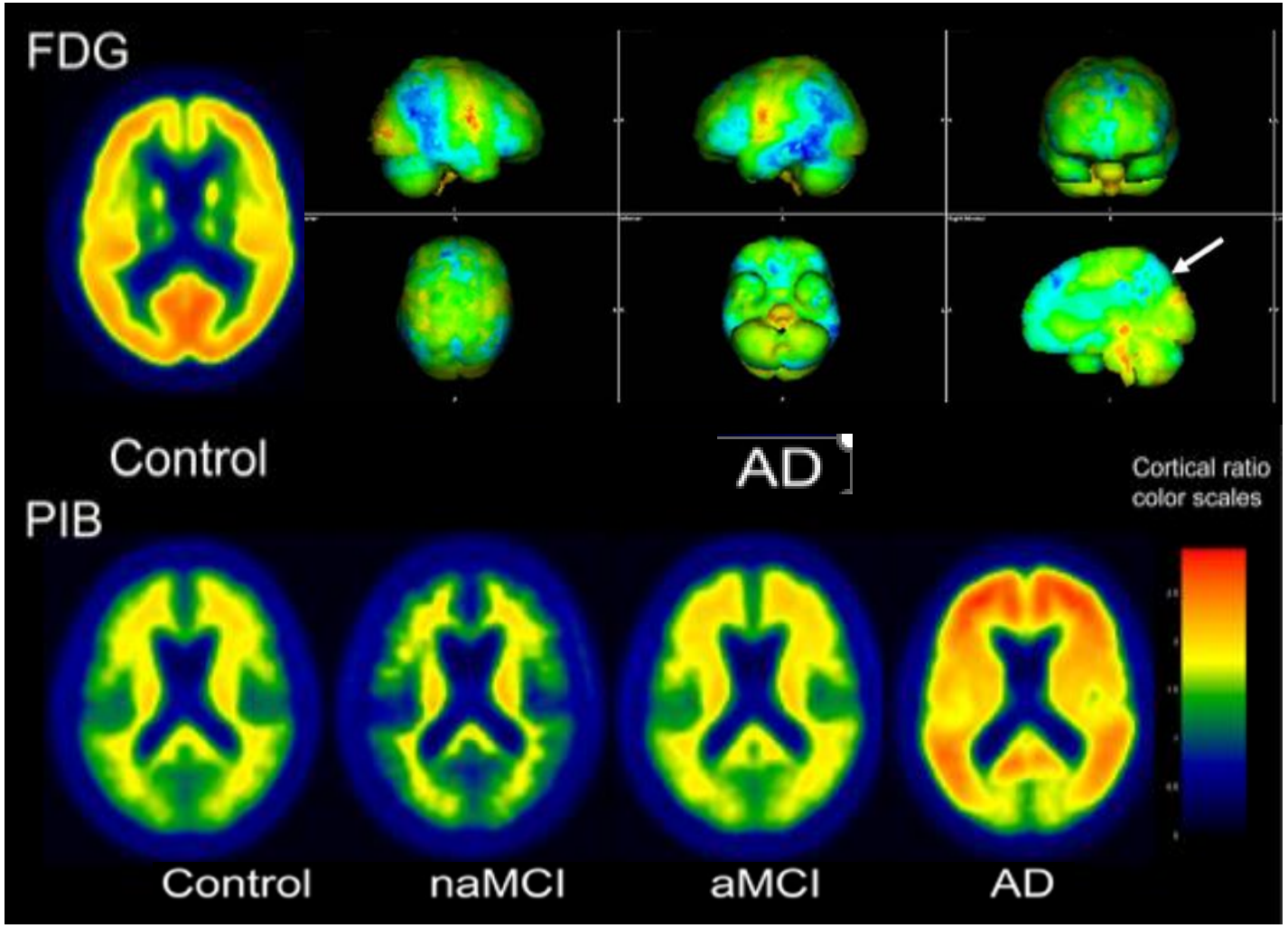
1. Busse et al. Neurology 2006;67:2176-85;2. DiCarlo et al. Neurology 2007;68:1909-16;3. Ganguli et al. 2010. Am J Geriatr Psychiatry 2010;18:674-83;4. Larrieu et al. Neurology 2002;59:1594-9; 5. Petersen et al. Neurology 2018;90:126-35; 6. Luck et al. Am J Geriatr Psychiatry 2017(4):328-339.

MCI Is Evidence Based

- **Volumetric hippocampal change[1,2]**
- **Functional neuroimaging[4]**
- **Blood and CSF biomarkers[3]**
- **Prognosis:[5]**
  - Rate of conversion to dementia greatly exceeds that in general population.

1. De Leon M.J. et al. Neurobiology of Aging 1997;18:1-11; MRI image is from Goulomb et al. 2001; 3. Parnettia L et al. J Alzheimer's Disease 2014;29:229–238; 4. Klunk et al: Annals of Neurology 2004;55:306-19; 5. Petersen et al. Arch Neurol 2001;58:1985-92.

MCI Is Evidence Based: PET Findings



FDG PET highlights metabolic activity.

Amyloid PET highlights plaque location.

PET-FDG image from Spano et al. PET Clin. 2023;18(1): 103–113. doi:10.1016/j.cpet.2022.09.006; PIB-PET image from Lowe et al. J Nuclear Med 2009;50:878-886,

MCI Is Evidence Based: Prognosis

MCI can be a prodrome to dementia:

*Cognitively healthy elders convert to AD at a low rate.

*4 year conversion rate of all MCI to dementia is 56%.[1]

*6 year conversion rate of all MCI to dementia is 80%.[2]

***14.4-38% "revert" to normal but remain at higher risk.[3]**

*Amnestic profile suggests MCI-AD

*Characteristic features can suggest MCI-LBD[4]

1. Petersen et al. Neurology 2018;90:126-35; 2. Rountree et al. Dement Geriatr Cogn Disord 2007;24:476-82;
3. Boyle et al. Neurology 2006;67:441-5; 4. Donaghy et al. Alzheimer's & Dementia 2023;19:3186-3202.

MCI Evaluation

Though Commonly Present in Primary Care Patients, MCI Often Goes Undiagnosed

- Among 3,242 non-demented GP patients aged 75-89, GP assessment of Global Deterioration Scale score was compared to psychometric interview data obtained by trained reviewers.[1]
  - GPs detected only 11-12% of MCI (lots of False Negatives).
  - Specificity was 93-94% (**few False Positives**).
  - Impressionistic assessment: Less reliable than formal screening.
  - Greater number of impairments was associated with true positives.
  - Middle to high level of education was associated with false negatives.
- **In Primary Care, a recent study estimated that only 8% of MCI diagnoses are made.[2]**

1. Hopman-Rock et al. Int J Ger Psychiatry 2001;16(4):406-14; 2. Liu et al. J Prev Alz Dis 2023 online at http://dx.dox.org/10.14283/jpad.2023.131R

Why Do We Miss Diagnosing MiND?

- No patient complaint (the majority of people with MCI are "anosognosic"[1])
- Other pressing priorities – lack of time/awareness
- Implicit bias
  - Ageism
  - Excessive focus on cognition=memory, miss other symptoms
  - Misleading effect of cognitive reserve
- No infallible/quick screening test for MCI/MiND
- Treatment limitations affect value of detection

1. Cova et al. Am J Alzheimer's Disease & Other Dementias 2017;32:401-7.

Collateral History: Informant AD8

1. Problems with judgment
2. Less interest in hobbies/activities
3. Repeats the same things
4. Trouble learning how to use tool/appliance gadget
5. Forgets month/year
6. Trouble with financial affairs
7. Trouble remembering appointments
8. Daily problems with thinking/memory

A score great than 1 suggests the need for further assessment.
Sensitivity > 84%, Specificity > 80%.

Usarel et al. Int Psychogeriatr 2019;31:223-9. doi: 10.1017/S1041610218000674. Epub 2018 Jun 20

Mini-COG

SCORE OF 0-2 is + SCREEN

Step 1: Three Word Registration

Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now." If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing).

The following and other word lists have been used in one or more clinical studies.[1-3] For repeated administrations, use of an alternative word list is recommended.

Version 1	Version 2	Version 3	Version 4	Version 5	Version 6
Banana	Leader	Village	River	Captain	Daughter
Sunrise	Season	Kitchen	Nation	Garden	Heaven
Chair	Table	Baby	Finger	Picture	Mountain

Step 2: Clock Drawing

Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11."

Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to Step 3 if the clock is not complete within three minutes.

Step 3: Three Word Recall

https://gwep.usc.edu/mini-cog-screening-for-cognitive-impairment-in-older-adults/

24-26 is + SCREEN for MCI

MMSE

- 5 pts: Orientation: year, season, month, date, day
- 5 pts: Orientation: country, province/state, city, building/street, floor/room
- 3 pts: Register 3 words for later recall
- 5 pts: Serial 7's / "WORLD" backwards
- 3 pts: Recall 3 words
- 2 pts: Name watch, pencil
- 1 pt: Repeat "No ifs ands or buts"
- 1 pt: Read and do: "Close your eyes"
- 1 pt: Write a sentence
- 3 pts: Take paper in non-dominant hand, fold in half, put on floor
- 1 pt: Copy intersecting pentagons

Heavy weighting of Orientation (attention and exec fx)

3 pt for delayed recall

https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/cogimp-smmse.pdf

SLUMS EXAMINATION

Questions about this assessment tool? E-mail aging@slu.edu

Name_____ Age_____

Is the patient alert?_____ Level of education_____

__/1 (1) 1. What day of the week is it?

__/1 (1) 2. What is the year?

__/1 (1) 3. What state are we in?

4. Please remember these five objects. I will ask you what they are later.
Apple Pen Tie House Car

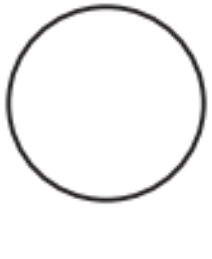
5. You have $100 and you go to the store and buy a dozen apples for $3 and a tricycle for $20.
(1) How much did you spend?
__/3 (2) How much do you have left?

6. Please name as many animals as you can in one minute.
__/3 (0) 0-4 animals (1) 5-9 animals (2) 10-14 animals (3) 15+ animals

__/5 7. What were the five objects I asked you to remember? 1 point for each one correct.

8. I am going to give you a series of numbers and I would like you to give them to me backwards. For example, if I say 42, you would say 24.
__/2 (0) 87 (1) 648 (1) 8537

9. This is a clock face. Please put in the hour markers and the time at ten minutes to eleven o'clock.
(2) Hour markers okay
__/4 (2) Time correct



(1) 10. Please place an X in the triangle.

__/2 (1) Which of the above figures is largest?

11. I am going to tell you a story. Please listen carefully because afterwards, I'm going to ask you some questions about it.

Jill was a very successful stockbroker. She made a lot of money on the stock market. She then met Jack, a devastatingly handsome man. She married him and had three children. They lived in Chicago. She then stopped work and stayed at home to bring up her children. When they were teenagers, she went back to work. She and Jack lived happily ever after.

(2) What was the female's name? (2) What work did she do?
__/8 (2) When did she go back to work? (2) What state did she live in?

Scoring is adjusted for educational level:

*Less than high school:
Normal=25-30
MCI=20-24
Dementia=01-19

*More than high school:
Normal=27-30
MCI=21-26
Dementia=01-20

Less focus on orientation, more on verbal and verbal contextual memory (13/30)

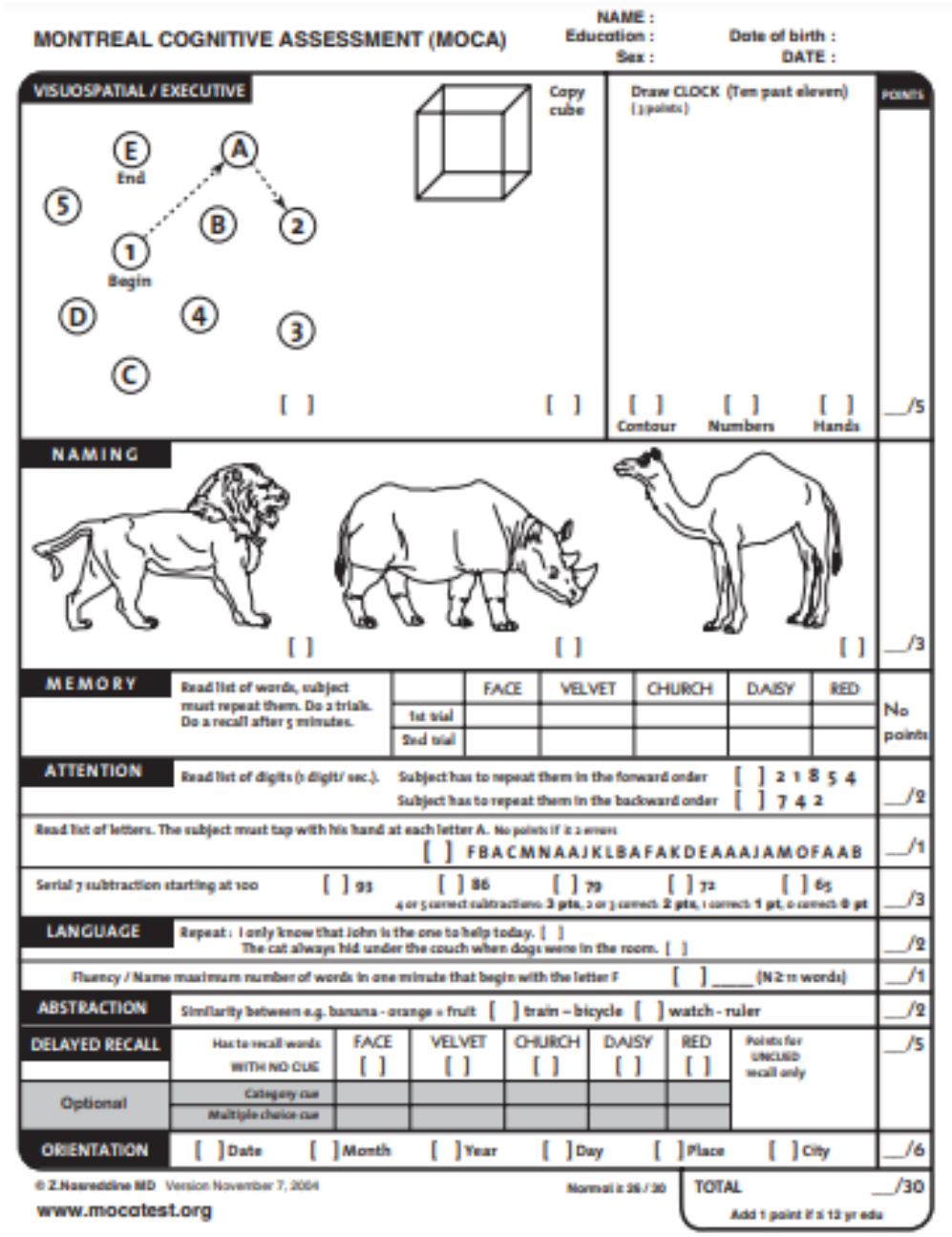
Tariq et al. Am J Geriatr Psychiatry 2006;14:900-910.

Montreal Cognitive Assessment (MoCA)

Multiple domains tested:

- Visuospatial
  - Copying
  - Clock
- Language:
  - Naming
  - Repetition
- Executive function:
  - Working Memory
  - Phonemic fluency
- Abstraction
- Memory:
  - Delayed recall (incorporates cues)
- Orientation

SCORE 18-25 is + SCREEN for MCI


MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — Copy cube — Draw CLOCK (Ten past eleven) — POINTS

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ] [ ] Contour [ ] Numbers [ ] Hands /5

NAMING

[ ] [ ] [ ] /3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4. Subject has to repeat them in the backward order [ ] 7 4 2 /2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B /1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65 — 4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt /3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ] /2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) /1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler /2

DELAYED RECALL	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City /6

© Z.Nasreddine MD Version November 7, 2004

Normal ≥ 26 / 30

TOTAL /30

Add 1 point if ≤ 12 yr edu

www.mocatest.org

Islam et al. Alzheimer's Dement 2023;19:3235-3243;
https://www.parkinsons.va.gov/resources/MOCA-Test-English.pdf

How Is Etiology of MCI/MiND Evaluated and Why Does It Matter?

Clinical History

Symptoms (6 domains, time course)

Informant needed

Medical / Psych/ Lifestyle factors

-Fluctuating cognition, visual hallucinations, RBD, Parkinsonism suggest MCI-LBD[1]

Exam

Physical

Cognitive screen

Further assessment as indicated (e.g. Neuropsych)

Labs

CBC,CMP,B12,Folate,TSH,RPR(?)

Specialized testing as indicated;

Biomarker blood tests are already available for specialist use

Neuroimaging

Structural imaging may be appropriate

Functional imaging = specialty care

DaT, Skin bx, PSG, MIBG findings can support dx of prodromal PD or LBD[1]

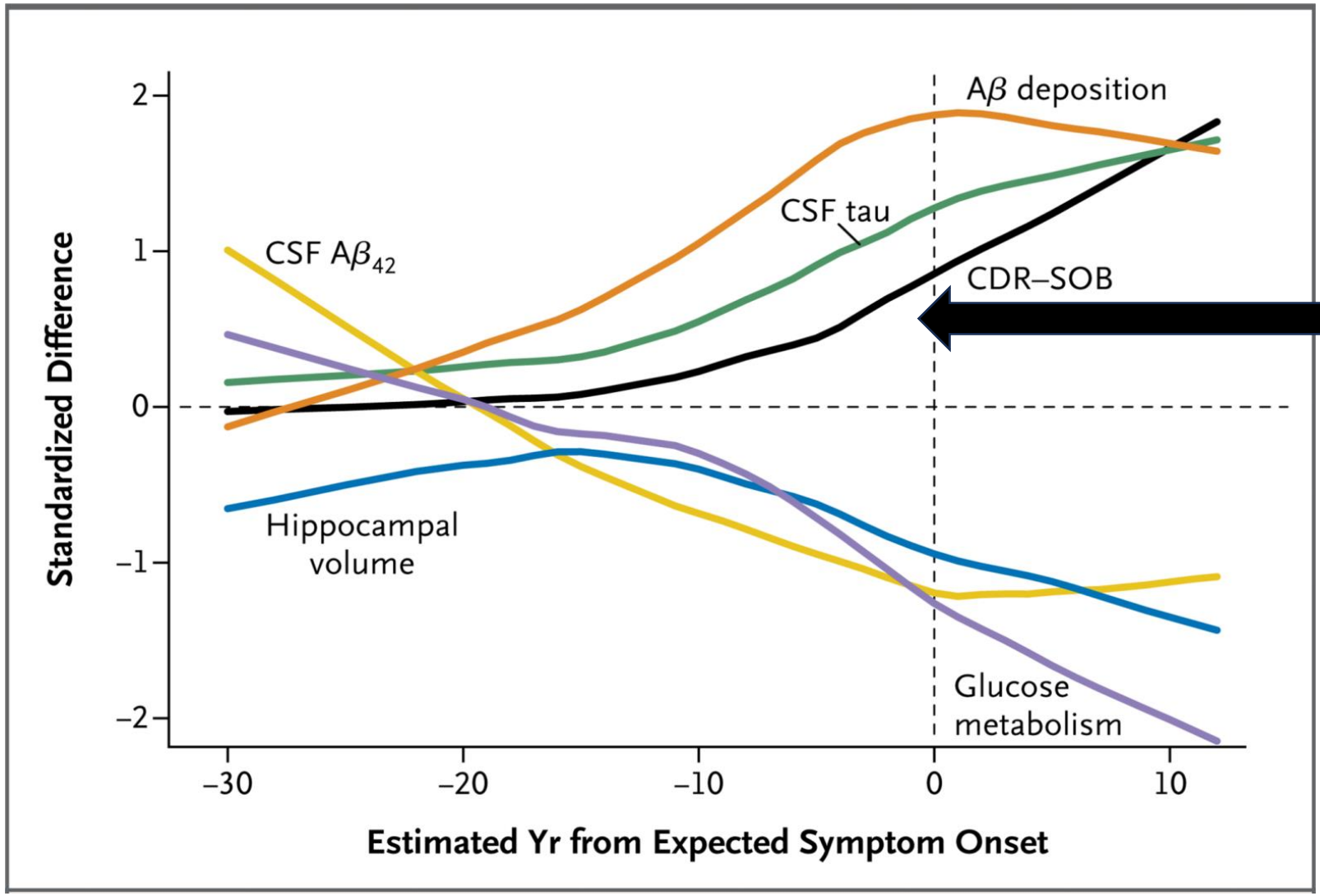
1. Donaghy et al. Alzheimer's & Dementia 2023;19:3186-3202.

Differential Dx of MCI: Many Possible Etiologies, *But aMCI is Often Preclinical Alzheimer's Disease*

- Other neurodegenerative disorders / neurological disorders
- Vascular MCI /Post-CVA cognitive impairment
- Brain injury
- Autoimmune or inflammatory disorders
- Cancer (paraneoplastic, chemotherapy,radiation)
- Intoxicants/medications/poisons
- Infectious (HIV, Lyme, syphilis, **COVID**)
- Nutritional deficiency
- NPH (normal pressure hydrocephalus)
- Sleep disorders
- Metabolic/endocrine (glucose, thyroid, electrolytes)
- POCD (Post-operative cognitive dysfunction)
- [Psychiatric (developmental, ADHD, depression, factitious)]

Guttierez et al. J Neuropsychiatry and Clin Neurosciences 1993;5:161-177.

Earlier Detection of AD, Increasingly Actionable, Is Aided by Testing of Biomarkers



Clinical Measure

Bateman et al. NEJM 2012;367:795-804.

AD Biomarkers as of 2024: $\underline{AT_1T_2}$NIVS

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ 42	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	p-tau217, p-tau181, p-tau231	
Core 2		
T_2 (AD tau proteinopathy)	MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments[a]	Tau PET

Jack CR et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimer's & Dementia 2024:1-27.

AD Biomarkers as of 2024: AT_1T_2NIVS

Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MRI, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD copathology		
V vascular brain injury		Infarction on MRI or CT, WMH
S α-synuclein	αSyn-SAA[a]	

Jack CR et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimer's & Dementia 2024:1-27.

New: Tests for Plasma Biomarkers

Biomarker	What it Reflects	Clinical Use	Evidence Highlights
Aβ42/40 Ratio	low toxic Aβ42 relative to Aβ40 in blood, sign of AD	Screen for AD; **not a diagnostic test**	Moderate diagnostic accuracy (70–90%); Better with APOE
Phosphorylated Tau (ptau181, ptau217)	**AD**	**Dx screening, confirmation; 217 better than 181**	**High specificity for AD (few false positives); cost can be a limitation**
Lumipulse G: pTau217/Aβ42	**AD**	**FDA approved but results may require confirmation**	**Sensitivity 90% Specificity 92%**
Precivity AD2: Aβ42/Aβ40 and ptau217/nptau217	**AD**	**Screening**	**88% sensitivity 89% specificity**
Labcorp ATN Profile: Aβ42/Aβ40,ptau181,NFL	**AD or Neurodegeneration**	**Screening**	**Sensivity/Specificity 80-90%**
Glial Fibrillary Acidic Protein (GFAP)	Astrocyte activation related to amyloid; neuroinflammation	Screening: c/w AD diagnosis	Elevated more in AD vs FTD
Neurofilament Light Chain (NfL)	Axonal damage and neurodegeneration	c/w with neurodegeneration	Elevated in all major dementias; Elevated more in FTD vs AD

The Era of Blood Biomarkers: Complex New Issue for Care Providers!

- **Cost to consumer**
- **Choice of subject and choice of test**
- **Interpretation**
  - Interpretation confounded by age, sex, race, comorbidities (e.g. **kidney disease**, CVA, MI associated with higher p-tau levels, higher BMI associated with lower p-tau, comorbidities higher in African Americans, Mexican Americans)
- **Disclosure/Communication/Implications**
- **And then…Next steps including access to specialty treatment**

1. Li Y et al. Neurology 2022;98(7):e688-e699.

Warning re False Plasma Biomarker Results

- Lumipulse G P (ptau217/Aβ42 Plasma Ratio) Thresholds Affect Predictive Value of Test[1]
  - Sensitivity nearly 100% but specificity varied 23% to85% depending on site of testing (high potential for false negatives)
  - False positive results with selected batches ➔ FDA recall; may require test validation for specific patients[2]
- Elecsys P-tau181 Plasma Immunoassay Predictive Value[3]
  - Very low false negative (high sensitivity)
  - False positive (lower specificity) rate requires follow up testing of positive results

1. Algeciras=Schimnich A et al. CTAD 2025. Abstract LB4;
2. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRes/res.cfm?ID=217941; 3. Hortsch S et al. CTAD 2025. Abstract OC32.

Diagnosis Disclosure

Why We Disclose

- Quality standard for treatment
- The majority of patients (without dementia) express wish to know[1,2,3]
- Avoids liability[3]
- Protects PWD's rights and autonomy
- Clarifies symptom etiology
- Strengthens clinician/patient relationship
- Opens discussion of early intervention options
- Promotes advance planning

1. Erde et al. 1988;The J of Fam Practice 1988;26:401-6;2. Holroyd et al. J Am Ger Soc 1996;44:400-3;
3. Carpenter et al. The Gerontologist 2004;44(2):149-58.

Stages of Disclosure: How Different With NCD?

- **Pre-Disclosure Preparation**: What do PWD and caregiver understand and what do they want? Who should be included? What supports are in place?
- **Disclosure**: An ongoing process, matched to patient's needs; use "teach back" to verify understanding, assess reaction and provide resources and follow-up plan. Expect limited retention of information.
- **Content**: Symptoms, differential, tests, etiology, certainty, prognosis, course, treatment options, planning ahead
- **Preserve appropriate hope**, emphasize what remains as well as what will be lost; acknowledge what treatment can provide.

Smith and Beattie The Canadian J of Neurol Sci 2001;28(suppl 1):S67-71; Lee and Weston. Canadian Family Physician 2011;57:851-2.

Life Decisions and Medicolegal Concerns

Cognitive Impairment Requires Caregiver and Patient to Plan

- Even mild cognitive/behavioral changes have significant implications for:
  - Employment/Work
  - Decision making capacity
  - Advance Directives
  - Financial affairs
  - Testamentary capacity
  - Driving
  - Where to live

Bejenaru and Ellison. J Geriatric Psychiatry and Neurology 2020 Sep 16;891988720957092. doi: 10.1177/0891988720957092.

Employment

- 10-20% of people with MCI or EOD are under age 65 and may be working.
- Cognitive difficulties interfere with work (distractibility, inflexibility, slower processing, executive dysfunction, apathy).
- “Premature retirement” is a major societal cost of dementia.
- Some need or prefer to continue employment.
- Accommodations (appropriate tasks and support) can promote retention of employees.

Silvaggi et al. Int J of Environmental Research and Public Health 2020;17:842-852.

Safety Concerns:

Undiagnosed People with **Dementia** Engage In Unsafe Activities

Activity	With No Dementia	Possible Dementia Without Diagnosis
Caregiving	21.0%	12.3%
Driving	84.2%	59.4%
Preparing Hot Meals	72.4%	64.8%
Managing Finances	74.8%	59.8%
Managing Medications	92.8%	72.5%
Visiting MD Alone	69.9%	51.6%
Living Alone	29.1%	35.8%

Amjad et al. J Am Geriatr Soc 2016;64:1223-1232.

Independent Decision-Making

- Valid decision-making is a prerequisite for autonomy.
- Medical decision making requires understanding, appreciation, reasoning, and choosing.[1]
- MCI alters capacity to understand options and weigh consequences. A MMSE score below 19 is very concerning.
- Informed consent and research participation may be affected.
- Capacity to choose surrogate decision-maker may be affected.

1. Appelbaum and Grisso. NEJM 1988;319:1635-1638.

Advance Directives

- Many older adults with mild cognitive symptoms have not engaged in advance care planning because they:[1]
  - don't know what to expect / can't envision their future wishes [2]
  - are losing ability to weigh options
  - believe others will take care of them
- A 2020 national poll found that only 46% of older adults had completed an Advance Directive.[3]
- But early designation of a surrogate decision maker can increase later realization of individual's wishes.

1. Fried et al. J Am Geriatr Soc 2021;69:932-937; 2. Porteri C. BMC Med Ethics 19, 9 (2018). https://doi.org/10.1186/s12910-018-0249-6;
3. https://www.healthyagingpoll.org/reports-more/report/older-adults-experiences-advance-care-planning.

Financial Decisional Capacity (FC)

- Comprises multiple cognitive domains and experience contributing to declarative knowledge, procedural knowledge, and judgment.[1]
- **In one study, more than ½ of Parkinson's Disease patients with MCI were mildly to moderately impaired on FC.[2]**
- **Scam vulnerability** is heightened with MCI.
- The Semi-Structured Clinical Interview for Financial Capacity guides assessment of 8 domains of financial knowledge.[3]

1. Marson et al. Arch Neurol 2000;57:877-884; 2. Martin et al. Parkinsonism Relat Disord 2013;19:986-990;
3. Marson et al. J Am Geratr Soc 2009;57:806-14.

Testamentary Capacity (TC)

- Ability to make or alter a valid will
- TC requires awareness of natural beneficiaries; understanding of the nature and extent of property, understanding the disposition being made, and making an orderly plan.[1]
- Distrust or even delusions may accompany mild cognitive changes.
- Assessment at or near the time of the writing of the will implies greater validity in supporting TC.

1. Lowder et al. Uniform Probate Code, in Encyclopedia of Aging and Public Health. Springer 2008.

Driving Capacity

- Driving's not a "right" but can define autonomy.
- Working memory assists adaptation to traffic environment.
- Left hand turns and lane control are particularly demanding.
- Evaluation is **mandated in many states**.
  - Massachusetts: RMV requires drivers to "self-report" a cognitive impairment. Health Care Providers are encouraged to report and have immunity for good faith reporting
  - Meaning of errors on MMSE/clock drawing is controversial.
  - Driver rehabilitation specialist is optimal for on-road testing.
  - MCI typically is evolving – Reassessment will be needed.

Bejenaru and Ellison. J Geriatr Psychiatry Neurol 2020. doi: 10.1177/0891988720957092.

Residential Decisions

- MCI is defined as “independent” – so why consider residence?
  - Adjustment, safety, care, food, social interaction, leisure activities
- Alternatives include:
  - In-home with supports as needed (family, friends, aide, home modification including technological aids)
  - Supported living environment
    - Senior housing
    - Assisted Living Facility (generally not nursing home)
  - Weigh disruption of move vs adjustment to new environment.

Anderson et al. Living with Mild Cognitive Impairment. Oxford University Press, 2012, pp 196-201.

Mild Cognitive Impairment: A Suicide Risk Factor in Later Life?

- Late life suicidal behavior can be classified as “early onset” vs “late onset”.
- Early onset suicidal behavior peaks around age 30 and late life suicidal behavior of early onset is associated with:
  - Childhood trauma
  - Impulsivity, borderline traits, interpersonal difficulties
- By contrast, late onset suicidal behavior is increased by cognitive impairment and by the personality trait of conscientiousness.
- New issue: Requests for physician assisted death related to biomarker disclosure.

Szanto et al. Am J Geriatr Psychiatry 2024;32:622-9.

Treatment

Treatment of MCI Cognitive/NonCognitive Symptoms

- Nonpharmacologic
  - Cognitive Rehabilitation
  - DICE (Describe/Investigate/Create/Evaluate)
  - Psychotherapy
- Pharmacologic?
  - Cognitive enhancers?
  - Disease Modifying Antibodies?
  - Supplements?
  - Behavioral meds?
- Prevention (will address diet, exercise, etc)

Cognitive Rehabilitation Therapy

- **Restorative** interventions aim to repair weak domains, often through rote tasks.
- **Compensatory** interventions teach strategies and aids to compensate for impairments – may be more successful.
- **Multicomponent interventions** combine complementary domains (e.g. activity, groups, cognitive training).
- The Finnish Geriatric Study to Prevent Cognitive Impairment and Disability supported multicomponent intervention. Confirmed by US Pointer Study.

Cohen et al. Delaware Journal of Public Health, in press 2021.

Psychotherapy in MCI

- Little is known about the efficacy of psychotherapy in people with MCI.
  - Mindfulness intervention reduced anxiety/stress symptoms in older adults with MCI.[1]
  - PST/ Problem Adaptation Therapy has been studied and was more efficacious than supportive therapy in reducing depression.[2,3]

1. Chouinard et al. Aging Ment Health 2019 ;23(9): 1246-1254. doi: 10.1080/13607863.2018.1484890.
2. Bingham et al. Curr Psychiatry Rep 2019;21(8):74. doi: 10.1007/s11920-019-1047-7; 3. Orgeta et al. Br J Psychiatry 2015;207(4):293-8.

Supplements: A 3.2 Billion Dollar Industry[1]

- Many are available – there is a high demand, but…
- OTC supplements can be sold without proof of safety or efficacy.
- Case example – Apoaequorin (Prevagen) (synthetic jellyfish protein)[2]
  - Questionable data: FDA monitoring avoided via GRAS designation
  - Significant cost
  - Significant adverse effects/should not be regarded as harmless

1. Hellmuth et al. JAMA 2019;321(6):543-4. 2. “Americans Took Prevagen for Years—as the FDA Questioned Its Safety”: https://www.wired.com/story/prevagen-made-millions-fda-questioned-safety/
Accessed 08/01/2021

Key Randomized/Controlled Trials of Cognitive Supplements

Supplement	Population	Design / N	Dose / Duration	Primary Outcome	Result (concise)	Key refs
Multivitamin (MVM)	Older adults without dementia	COSMOS-Mind/Web/Clinic; RCT; n>3,000	Daily MVM; 2–3 y	Global cognition/episodic memory	Small but significant benefits vs placebo (esp. in CVD subgroup); cocoa extract null	Alzheimers Dement 2023; AJCN 2024
Omega-3 (DHA/EPA)	Elderly w/ memory complaints	MAPT; factorial RCT; n=1,680	PUFA 800 mg/d; 3 y	Cognitive composite (MAPT)	No significant effect of Ω-3 alone or w/ multidomain intervention	Lancet Neurol 2017
B vitamins (B6/B12/folate)	MCI with high homocysteine	VITACOG; single-center RCT; n=271	FA 0.8 mg + B12 0.5 mg + B6 20 mg; 2 y	Brain atrophy (primary); cognition secondary	Atrophy slowed; cognitive benefit mainly when homocysteine high; no dementia prevention shown	PLoS One 2010
Ginkgo biloba	Older adults ± MCI	GEM; multicenter RCT; n=3,069; ~6 y	120 mg BID	Dementia incidence; cognitive decline	No benefit on dementia prevention or cognitive decline vs placebo	JAMA 2008; 2009
Souvenaid (Fortasyn Connect)	Prodromal AD / MCI due to AD	LipiDiDiet; RCT; n=311 (24 m); ext 36 m	Daily multinutrient drink; 24–36 m	NTB cognitive composite (24 m)	Primary not met at 24 m; less brain atrophy; post-hoc at 36 m suggests less clinical decline	Lancet Neurol 2017; Alz Dement 2021
Curcumin (Theracurmin)	Non-demented older adults (some MCI)	DB-RCT; n=40; 18 m	Theracurmin 90 mg BID; 18 m	Memory/attention; FDDNP-PET	Improved memory/attention; ↓PET binding; small study—needs replication	Am J Geriatr Psychiatry 2018
Berry/ anthocyanins	Older adults ± MCI	Multiple small RCTs; n≈35–100; 12–24 w	Freeze-dried blueberry / extracts	Exec. function & episodic memory tasks	Task-specific modest improvements; heterogeneous/short-term	Sci Rep 2022 review
Cocoa flavanols	Older adults without dementia	COSMOS substudy RCTs	Cocoa extract 500–600 mg flavanols/d; 2–3 y	Global cognition/memory	No consistent cognitive benefit in RCTs	Alzheimers Dement 2023

Supplement Clinical Takeaways

- No OTC supplement demonstrates robust, consistent improvements in memory or prevention of dementia in healthy older adults or unselected MCI.
- Best evidence signal: daily multivitamin in COSMOS substudies (small effect sizes on global/episodic memory over 2–3 years).
- Neutral: Omega-3 PUFA in MAPT; Cocoa flavanols in COSMOS substudy RCTs.
- Negative: Ginkgo biloba (GEM) for dementia prevention and cognitive decline.
- Conditional: B-vitamin therapy can slow brain atrophy in MCI with elevated homocysteine (VITACOG); cognitive/clinical benefits remain uncertain.
- Specialized medical foods: Souvenaid showed structural benefits; cognitive primary endpoint negative at 24 months; post-hoc signals at 36 months.
- Small/early signals needing replication: curcumin (Theracurmin), berry/anthocyanins (task-specific).
- Counsel on lifestyle/risk-factor control as first-line (physical activity, BP/lipids, sleep, hearing, depression), and address deficiencies (B12, D, folate, thyroid).

What About Lithium?

- Aging lithium-deficient AD-predisposed mice treated developed increased amyloid-β deposition and ptau accumulation that was revered with lithium orotate replacement.[1]
- Population studies correlating trace lithium exposure to reduced dementia risk have reported mixed findings.[2,3] Neuroprotective benefits have been suggested in population studies (mood/bipolar>non-bipolar) for standard treatment doses.[4]
- Microdose li (300 mcg/d) vs placebo delayed MMSE decline in non-bipolar AD. [5]
- RCT in amnestic MCI targeting low serum levels (0.25-0.5 nmol/L) reported less cognitive decline and reduced CSF ptau vs placebo.[6] Cognitive benefits were sustained over 4 years of follow up.[7]
- In one published MCI trial, low dose Li (mean 0.17 mEq/L) failed to outperform placebo on 6 measured outcomes (cognitive and imaging).[8]

1. Aron et al. Nature 2025;645:doi: 10.1038/s41586-025-09335; 2. Gerhard et al. Br J Psychiatry 2015;207:46-51; 3. Duthie et al. Int J Geriatric Psychiatry 2023;e5890. doi.org/10.1002/gps.5890; 4. Mauer et al. Australian & New Zealand J Psychiatry 2014;48:809-818; 5. Nunes et al. Current Alz Research 2013;10:104-7; 6. Forlenza et al. Br J Psychiatry 2011;198:351-6; 7. Forlenza et al. Br J Psychiatry 2019;215:668-74; 8. Gildengers et al. JAMA Neurology 2026; Published Online: March 2, 2026 doi: 10.1001/jamaneurol.2026.0072.

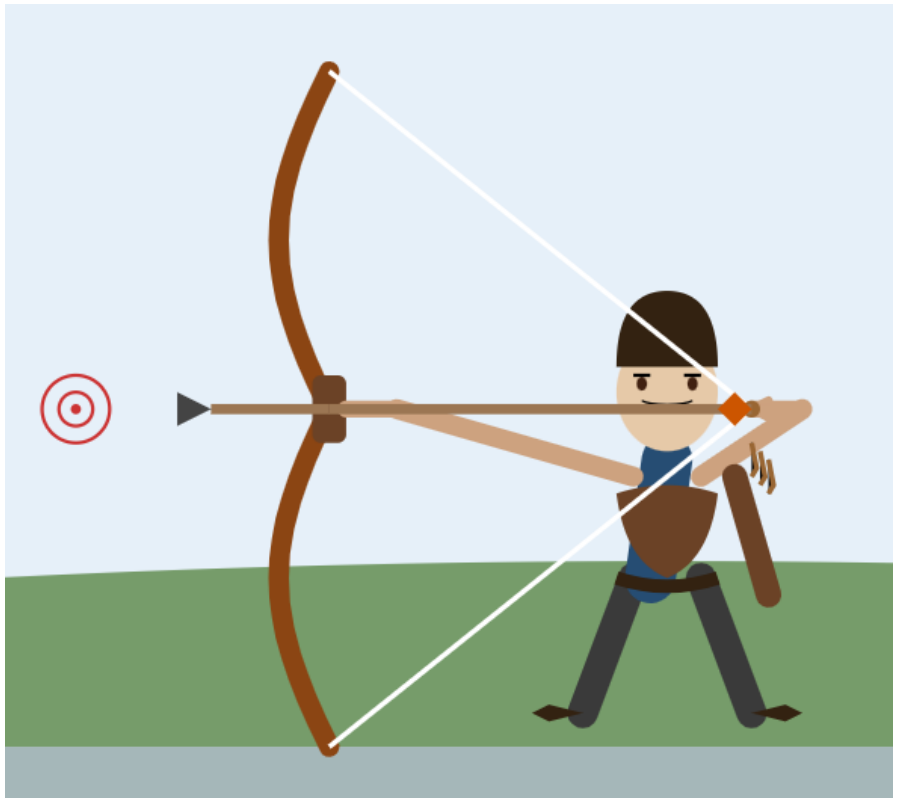
These Cognitive Enhancers Have Not Been Shown Effective In Treating MBI/MCI

And yet, in one large US study, use of cholinesterase inhibitors was noted in 24% and memantine use was noted in 6% of subjects with MCI[1]

Donepezil[1,2]	**3 credible studies**	**3 years of treatment with donepezil 10 mg/d did not reduce progression from MCI to AD.**
Galantamine[3,4]	2 credible studies	2 years of treatment did not reduce progression from MCI to dementia.
Rivastigmine[3,4]	1 credible study	4 years of treatment did not reduce progression from MCI to dementia.
Memantine	no studies	

These studies done in pre-biomarker era: 1. Petersen et al. New England Journal of Medicine 2005;352(23):2379–2388. https://doi.org/10.1056/NEJMoa050151; 2. Peterson et al. Neurology 2018;90(3):126-35; 3. Knopman. Curr Neurol Neurosci Rep 2006;6(5):365-71; 4. Matsunaga et al. J Alzheimers Dis 2019;71(2):513-523. doi: 10.3233/JAD-190546

Targeted Treatment of MCI-AD



“MAbs” – Who Should Be Screened?

- Lecanemab and donanemab are approved, others will follow
- Expert consensus group has suggested:
  - Verify presence of amyloid prior to treatment.
  - Recognize adverse events great with high dose (ARIA)
  - Include genotyping because APOEε4 confers higher risk.
  - Match treatment population to clinical trial population
    - Age 50-85, MCI or mild AD, MMSE 21-30, MoCA 17-30, stable condition with respect to cardiovascular/medical/psychiatric health, not on anticoagulant or with hx of acute or subacute hemorrhage including larger lacunar infarction (>1.5 cm) or diffuse WMD, should have adequate support, adequate consent.
- Additional Exclusion Suggestions in 2022: hx of bleeding disorder, seizures, CVA, TIA, autoimmune/inflammatory condition)/ Monitoring with more frequent MRI scans (AAIC 2022)

Cummings et al. Aducanumab: Appropriate Use Recommendations. J Prev Alzheimers Dis 2021;8(4):398-410. https://doi.org/10.14283/jpad.2021.41

Anti-Amyloid Monoclonal Antibodies:
Specificity for Various Aβ Aggregation States

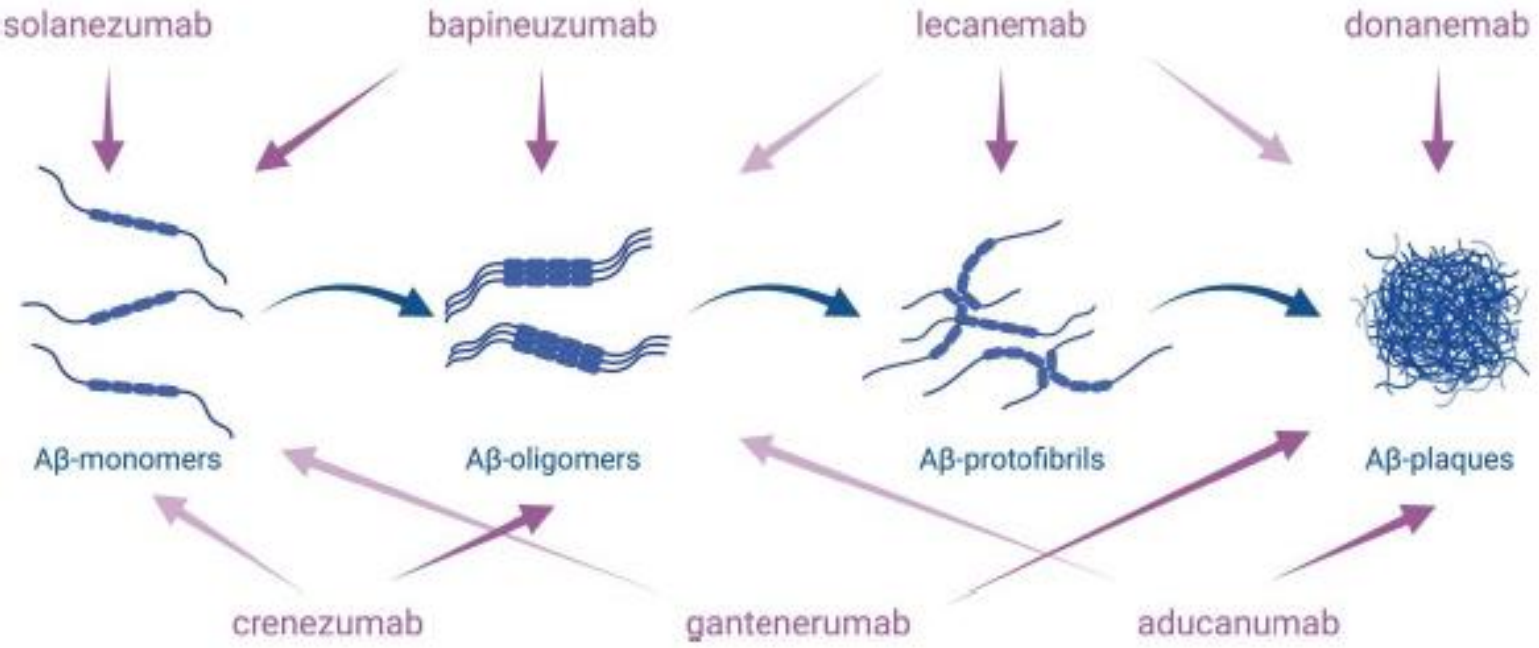


Figure 2 Schematic comparison of different antibodies directed against different aggregation states of Aβ. Source: Developer data

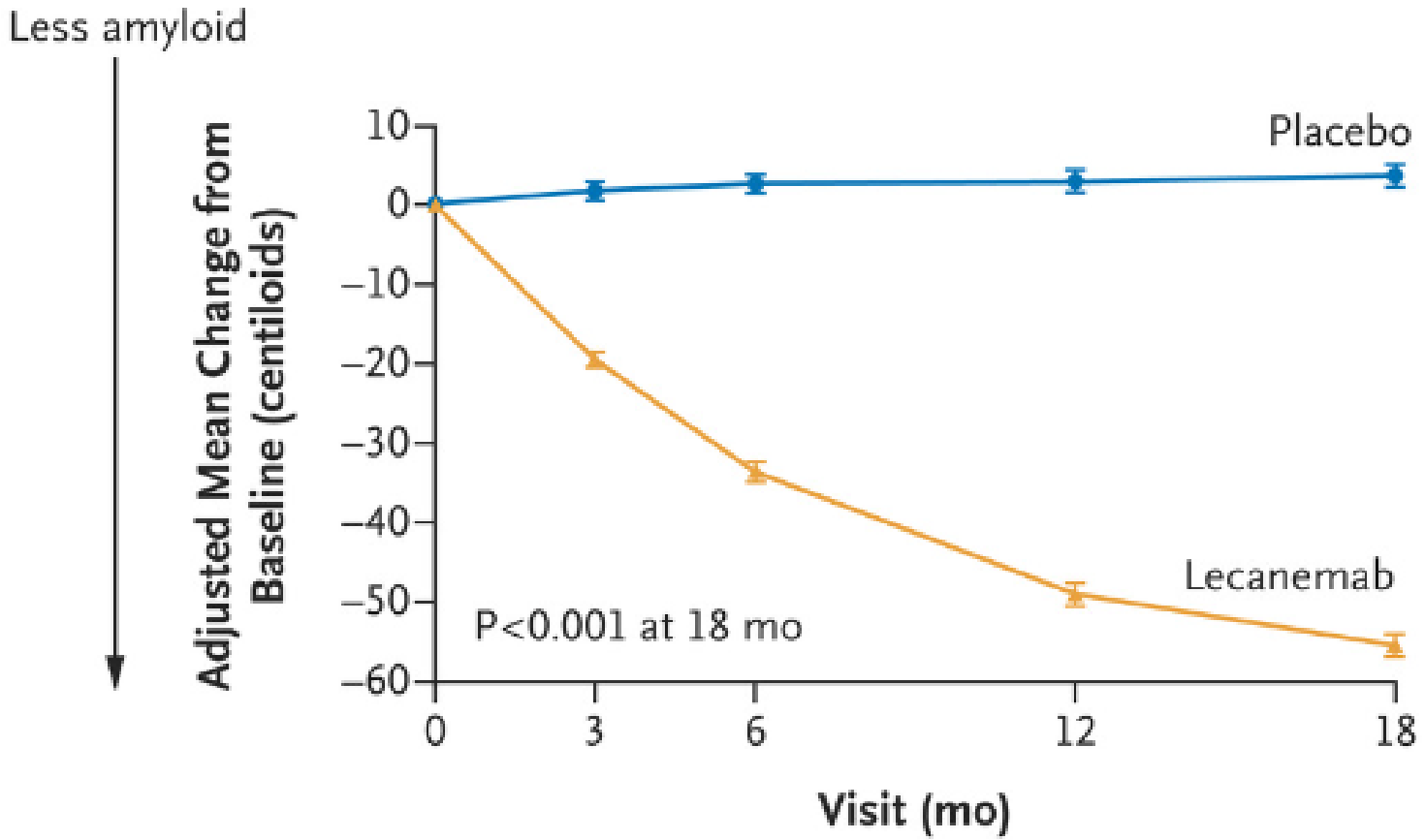
Perneczky et al. Brain 2023;146:842-9.

Lecanemab: First traditionally FDA-Approved MAb for AD

- Primary analysis population (n=1795) were individuals with clinical symptoms of Alzheimer's disease **and demonstrated levels of beta amyloid in brain**.
- Treatment course was 18 mo.
- Primary and secondary endpoints measuring cognitive and functional decline were met.
- Lecanemab vs placebo slowed decline in ADL by %27.

Van Dyck et al. NEJM 2023;388(1):9-21; https://clinicaltrials.gov/study/NCT03887455

Lecanemab Effect on Amyloid Burden

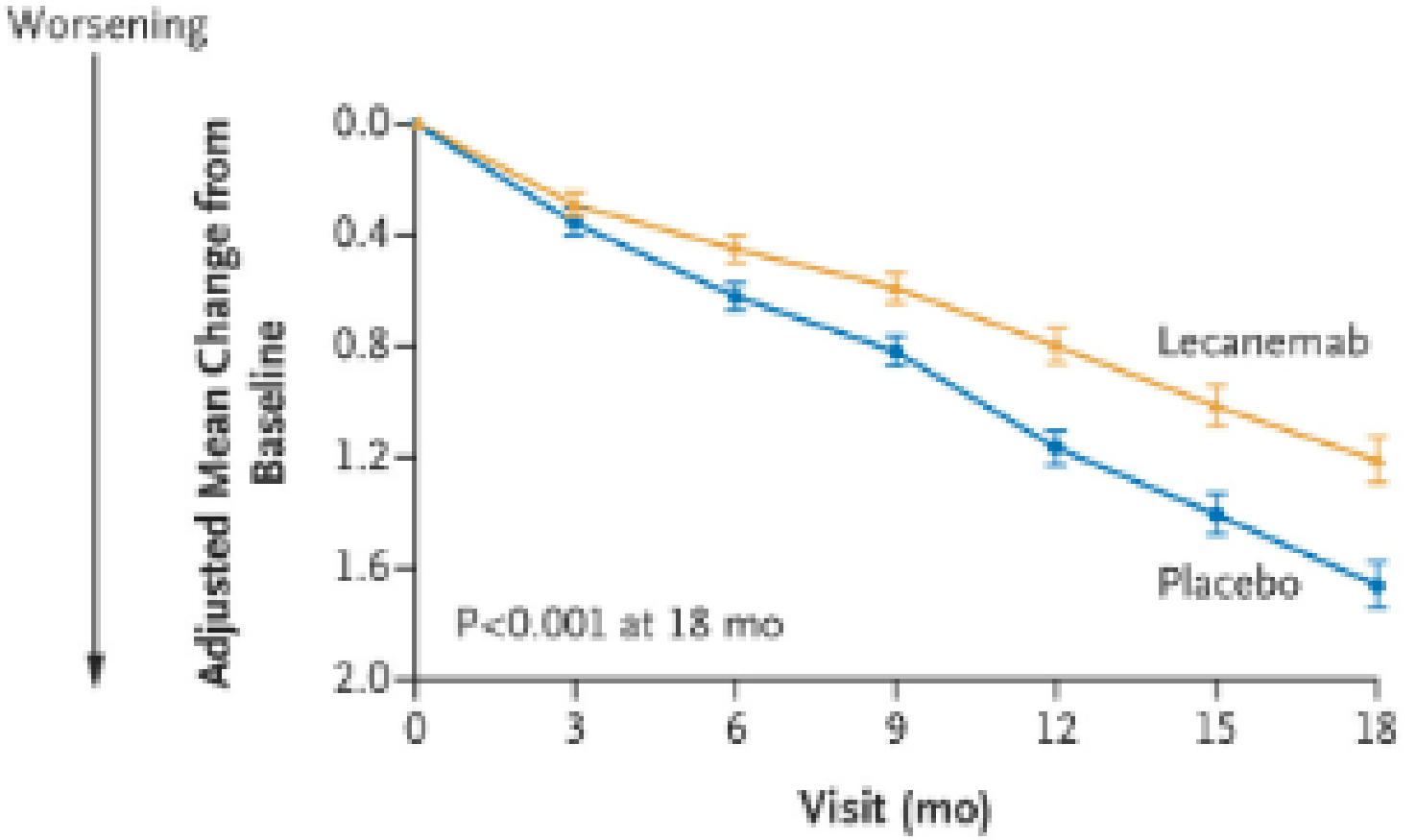


No. of Participants					
Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

Note: Lecanemab
Also lowers p-tau

Van Dyck et al. N Engl J Med 2023; 388:9-21;DOI: 10.1056/NEJMoa2212948

Lecanemab CDR-SB Score: Significant



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

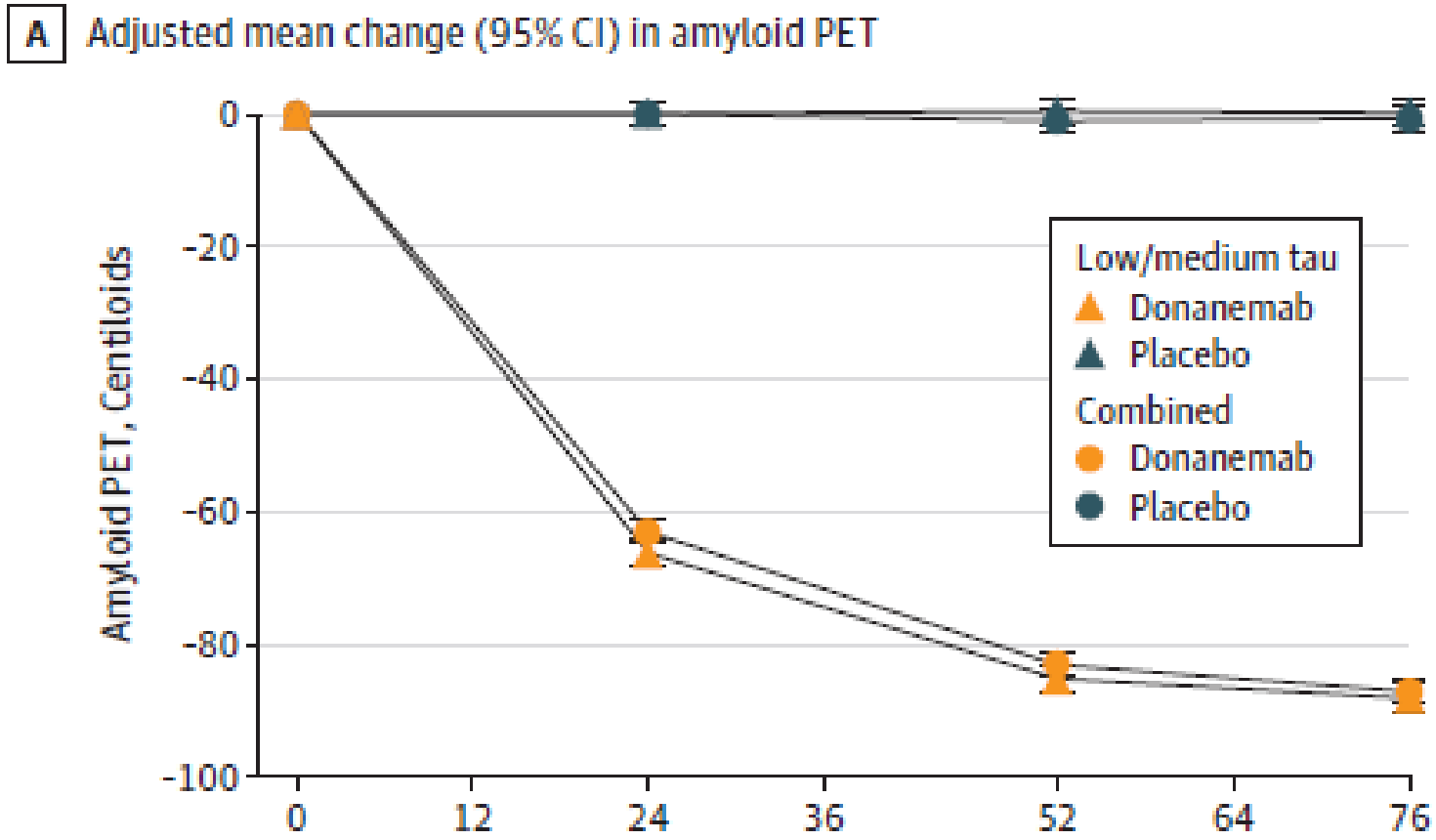
Van Dyck et al. N Engl J Med 2023; 388:9-21;DOI: 10.1056/NEJMoa2212948

Donanemab: Second Traditionally FDA-Approved MAb for AD

- Primary analysis population (n=1182) were individuals with clinical symptoms of Alzheimer's disease **and intermediate levels of tau**.
- Treatment course was "completed" (plaque clearance achieved) by:
  - 52% of subjects at 1 year
  - 72% of subjects at 18 months
- Primary endpoint and all secondary endpoints measuring cognitive and functional decline were met.
- Donanemab vs placebo slowed decline in ADL by 40%
- **Nearly half (47%) of donanemab subjects (vs 29% on placebo)=NNT 4.5 showed no clinical progression on CDR-SB over 1 year study period.**

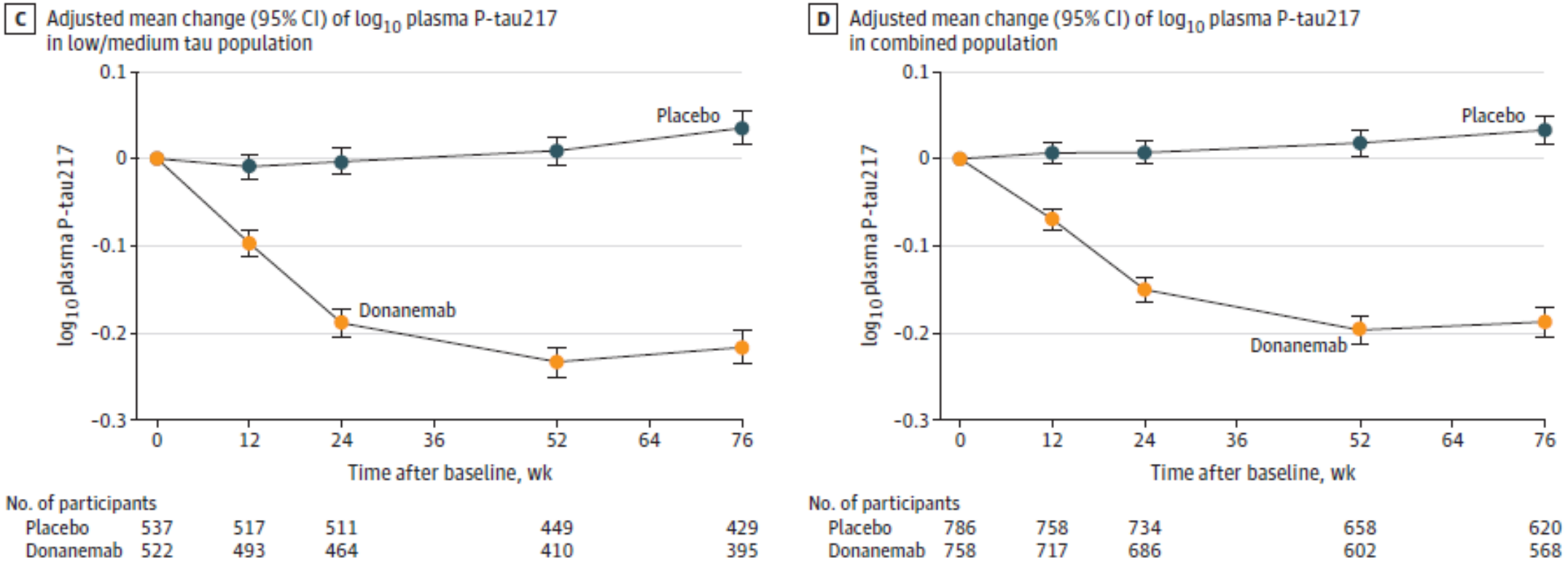
Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA. 2023;330(6):512-527. doi:10.1001/jama.2023.13239.

Significant Amyloid PET Change from Baseline Through 76 Weeks: Aggregate Data on Low/Med Tau vs All



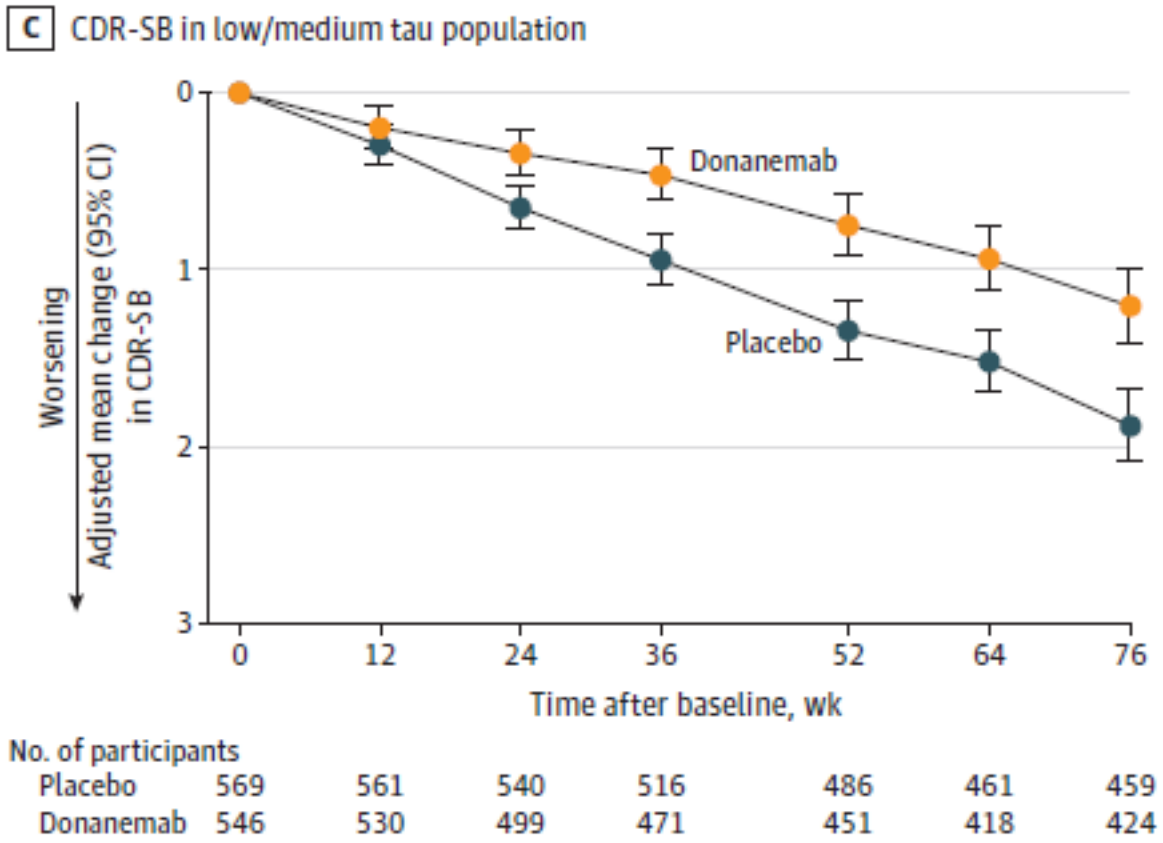
Sims et al. JAMA 2023;330:512-27.

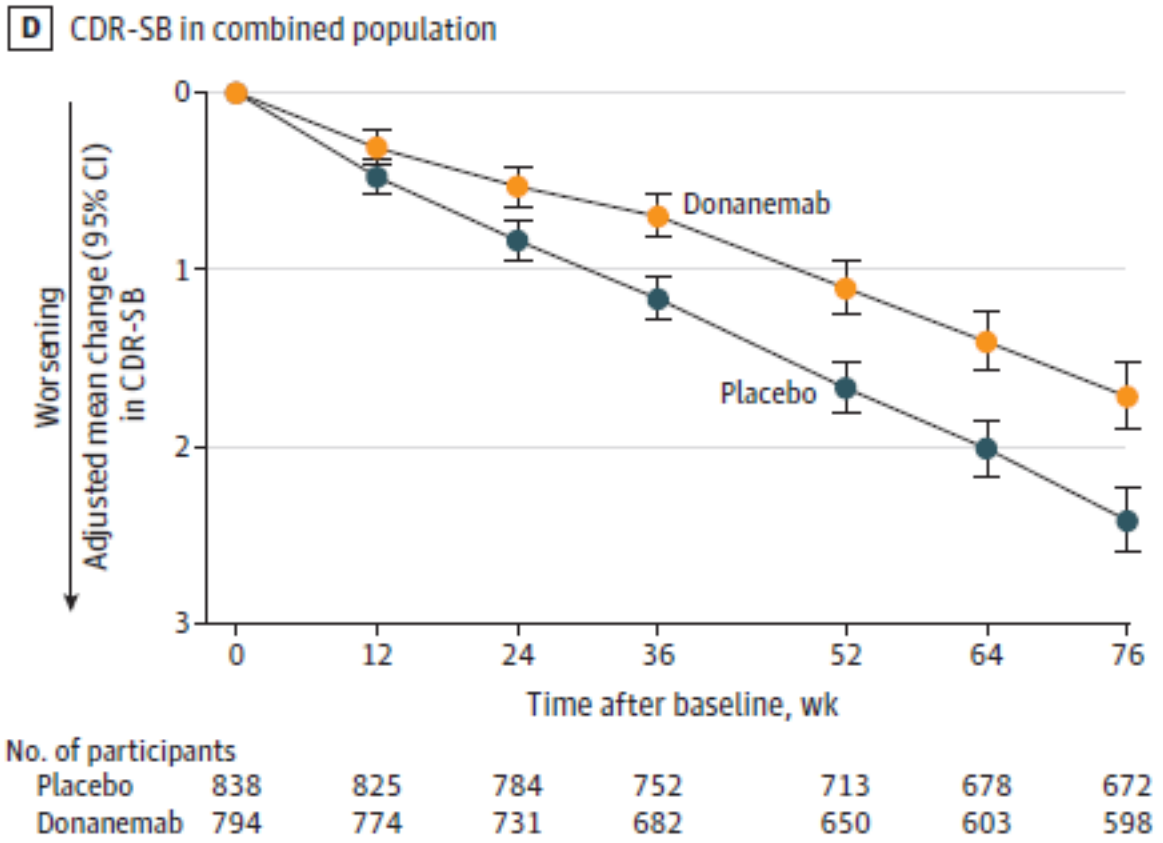
P-tau 217 Was Also Lowered by Donanemab: Change From Baseline Through 76 Weeks: Low/Med Tau vs All



Sims et al. JAMA 2023;330:512-27.

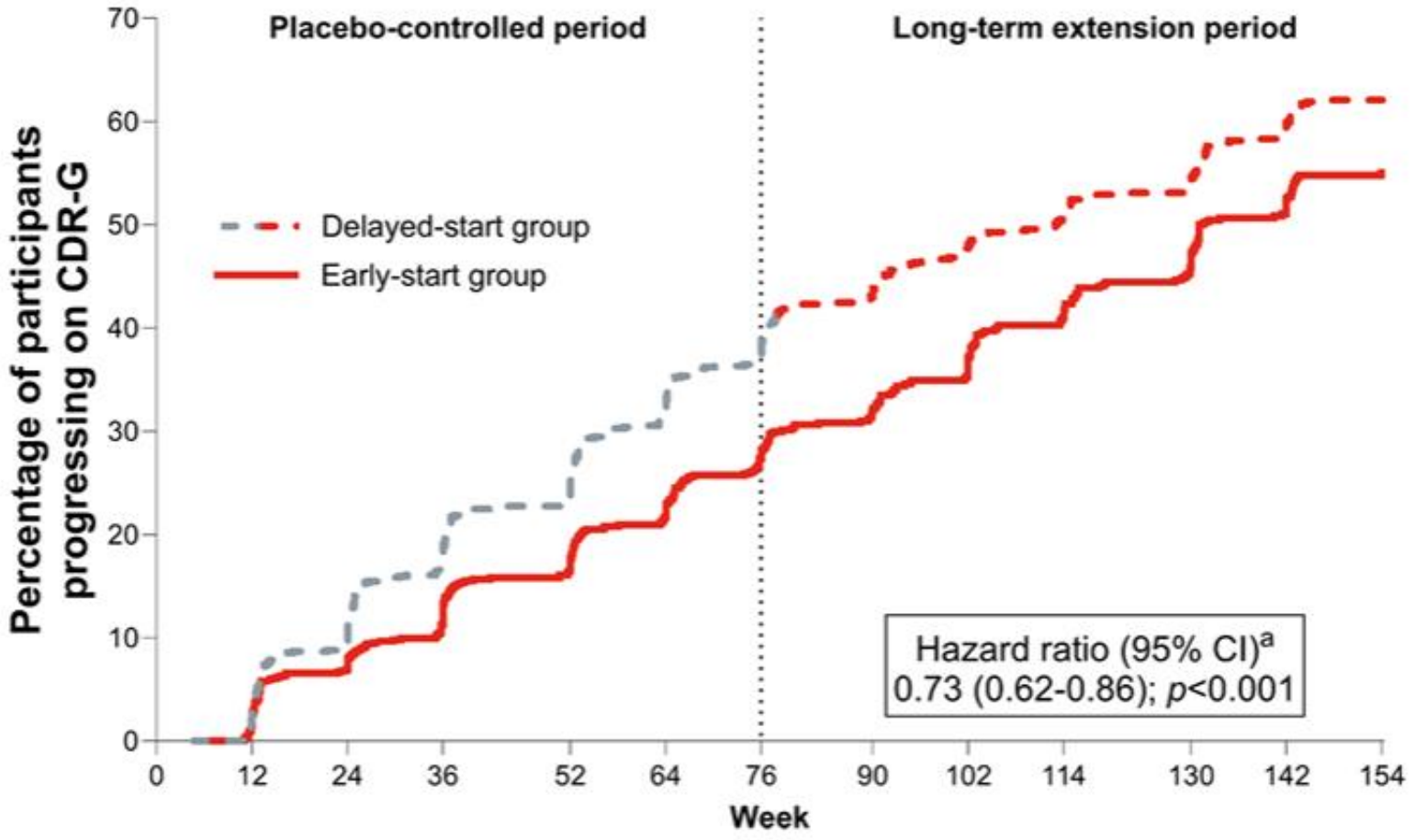
Clinical Benefit: CDR-SB Change from Baseline Through 76 Weeks: Low/Med Tau vs All





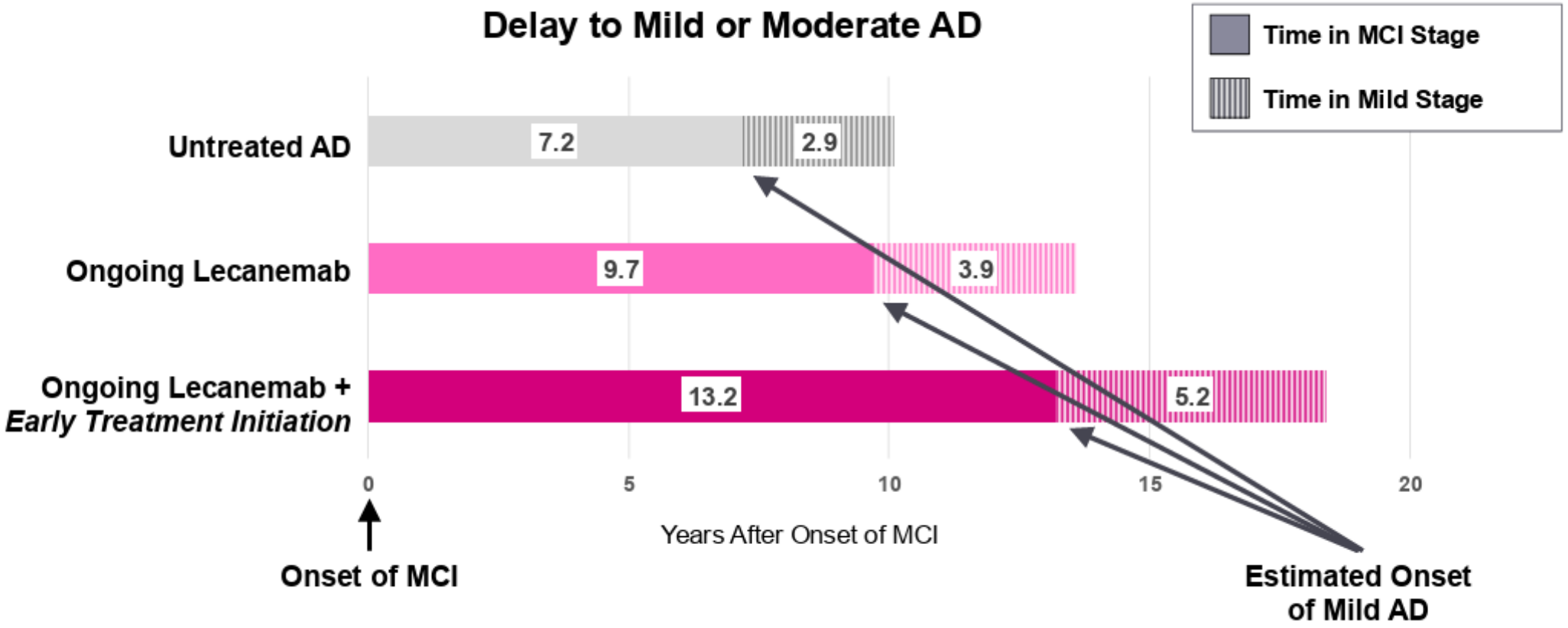
Sims et al. JAMA 2023;330:512-27.

Real World Longterm Donanemab Results from the TRAILBLAZER-ALZ 2 Long Term Extension



Zimmer J et al. J Prev Alzheimers Dis 2026;13:100446. doi: 10.1016/j.tjpad.2025.100446

Estimated Progression in CDR-SB from MCI to Moderate Dementia for Lecanemab in Clarity AD Low-Amyloid Group

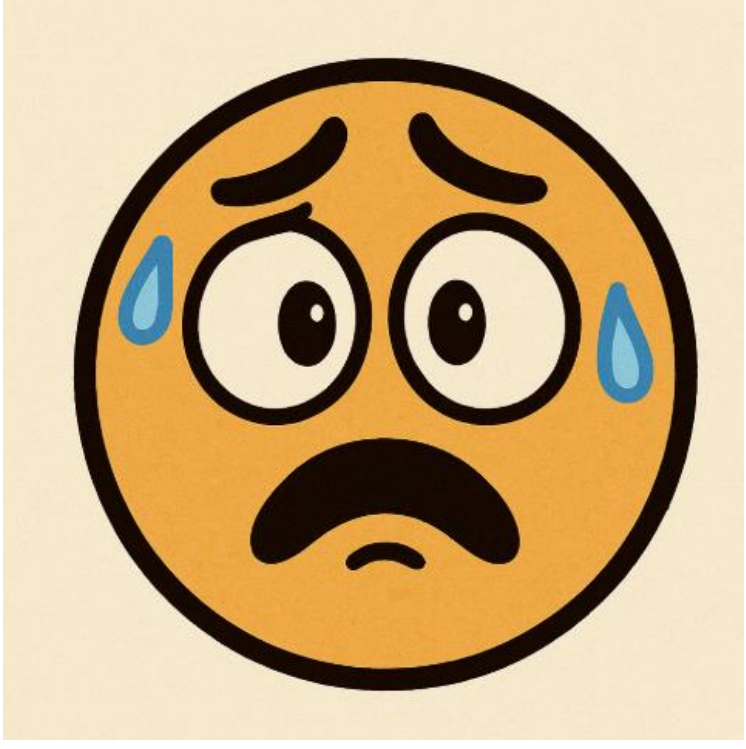


Whetten J et al. CTAD 2025:https://www.mayvillemedical.com/

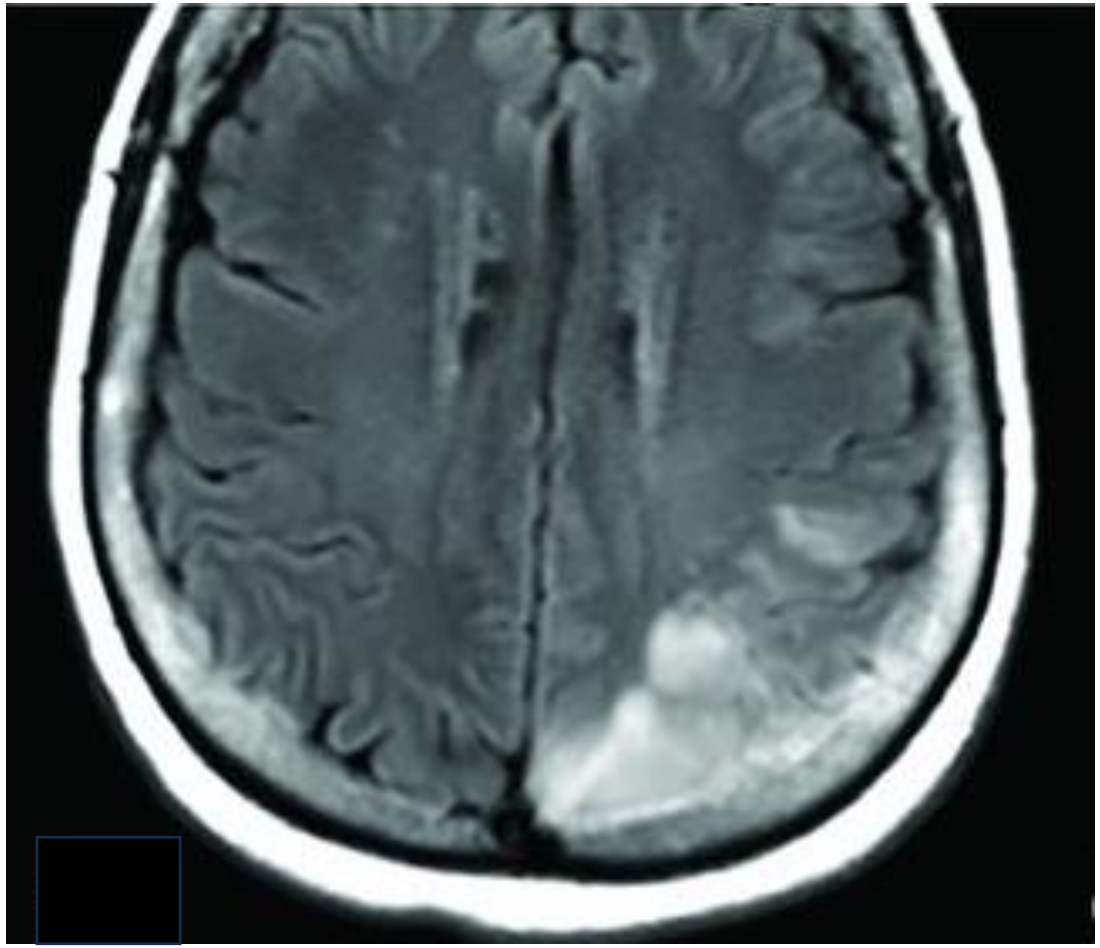
New: SubQ Lecanemab

- Appears to be as safe and effective as intravenous infusions.
- Now available for mid treatment switch or treatment initiation.
- First 2 injections are directly observe for a healthcare provider.
- Proper biohazard waste disposal precautions must be taken.

Adverse Effects: Mobilization of Amyloid Solves One Problem And Creates Others



ARIA-E: Edema, Sulcal Effusion



Cogswell et al. Am J Neuroradiol 2022;43:E19-35.

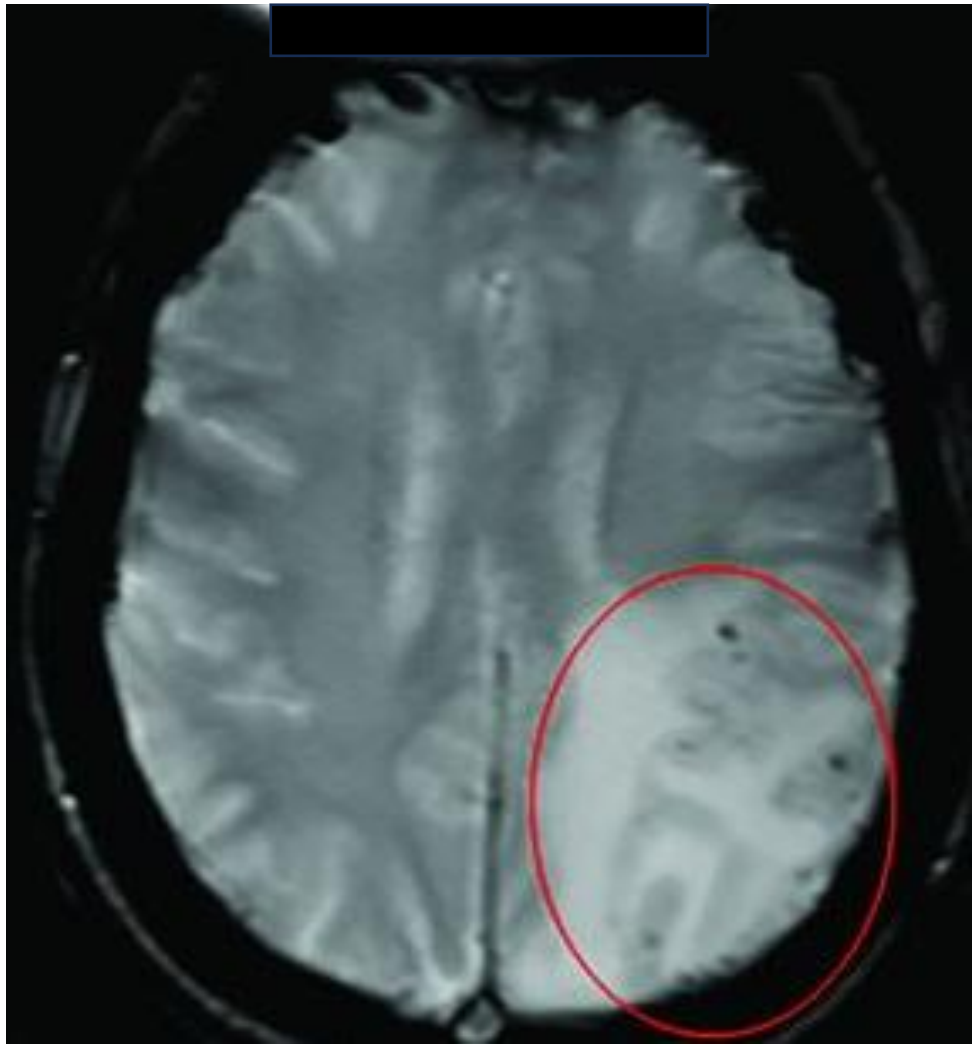
Increased permeability of blood vessels due to the clearing of amyloid plaques from vessel walls

Mild: 1 location; <5 cm

Moderate:1 location; 5-10 cm
OR >1 location,<10 cm

Severe: ≥1 location, >10 cm

ARIA-H: Leakage of Blood Products



Cogswell et al. Am J Neuroradiol 2022;43:E19-35.

Mild: 1 focal superficial siderosis AND/OR ≤4 microhemorrhages

Moderate: 2 focal SS AND/OR 5-9 microhemorrhages

Severe: >2 SS AND/OR >10 microhemorrhages

Lecanemab Adverse Events

Event	Lecanemab (N=898)	Placebo (N=897)
Overall — no. (%)		
Any adverse event	798 (88.9)	735 (81.9)
Adverse event related to lecanemab or placebo†	401 (44.7)	197 (22.0)
Serious adverse event	126 (14.0)	101 (11.3)
Death	6 (0.7)	7 (0.8)
Adverse event leading to discontinuation of the trial agent	62 (6.9)	26 (2.9)
Adverse event that occurred in ≥5% of participants in either group		
Infusion-related reaction	237 (26.4)	66 (7.4)
ARIA with microhemorrhages or hemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)

Van Dyck et al. N Engl J Med 2023; 388:9-21;DOI: 10.1056/NEJMoa2212948

Donanemab Adverse Effects

Event	Donanemab (%)	Placebo (%)
Death related to treatment	0.4	0.1
D/C due to AE	13.1	4.3
ARIA-E	24	1.9
ARIA-H	19.7	7.4
Infusion-related reaction	8.7	0.5
Headache	14	9.8
Dizziness	6.2	5.5

Data from Sims et al. JAMA 2023;330:512-27.

Symptoms of ARIA Mimic Acute Stroke, PRES, SAH

Mild ARIA

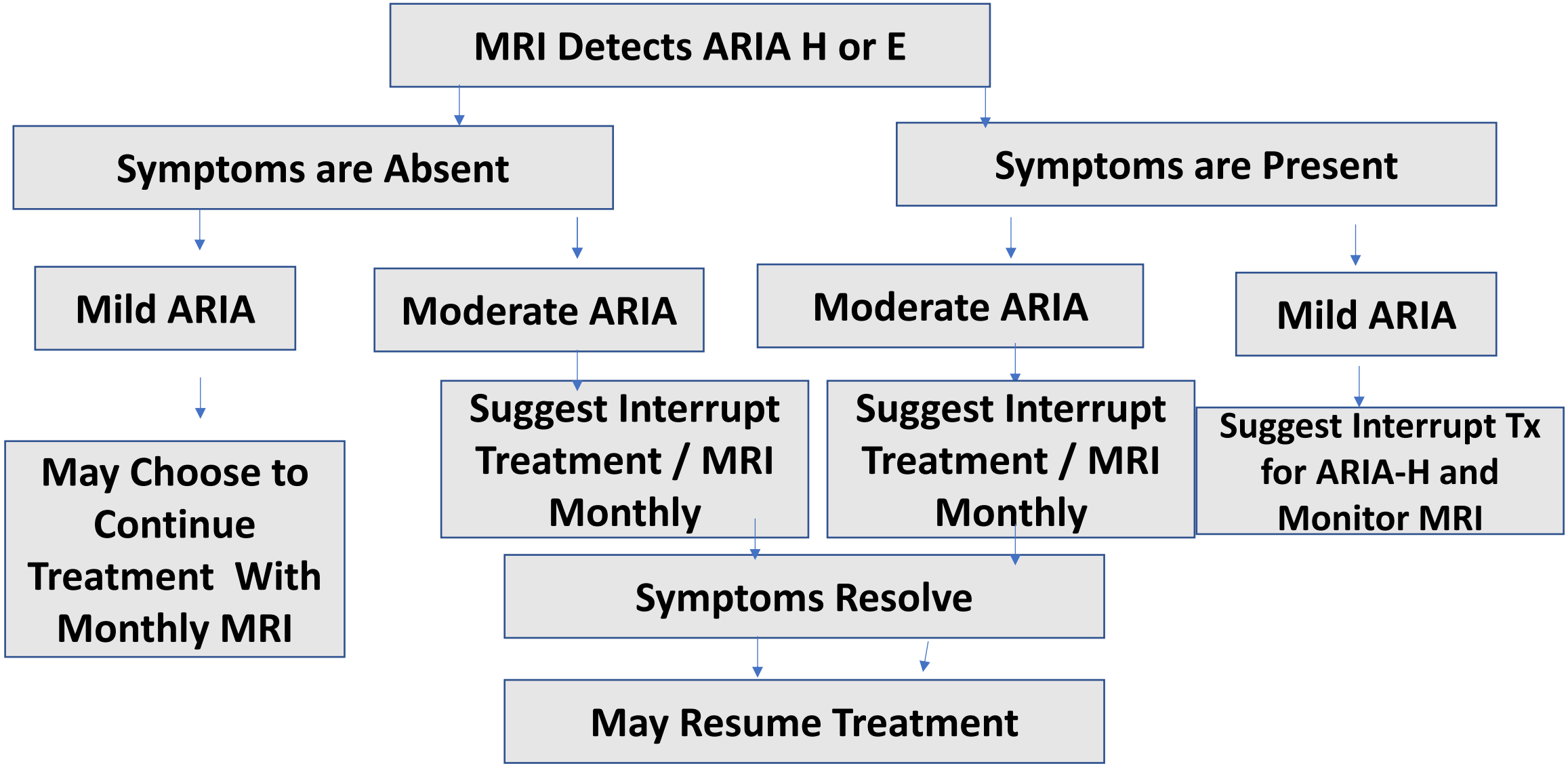
- Headache
- Confusion/Altered Mental Status
- Dizziness
- Nausea/Vomiting
- Gait disturbance
- Visual Disturbance

Severe ARIA

- Focal neurological deficits
- Seizures
- Status epilepticus
- Encephalopathy
- Stupor

Salloway et al. JAMA Neurol 2022;79:13-21; https://www.alz.org/media/Documents/lecanemab-toolkit.pdf

Suggested Management of Mild/Moderate ARIA



Leqembi (lecanemab) Prescribing Information, Eisai Inc., 2023; Rabinovici et al. J Prev Alz Dis 2025;12:1-18

Treating Severe ARIA

- Severe cases require
  - **Stop** monoclonal antibody infusions
  - High dose glucocorticoid
    - IV methylprednisone followed by oral prednisone
    - Taper over weeks to months
  - Seizures:
    - EEG
    - Anticonvulsant treatment
  - Notify/Coordinate with prescriber of MAb
  - Inpatient care may be indicated
  - Reporting to regulatory agency

Cummings et al. J Prev Alzheimers Disease 2023;10:362-77.

Inclusion Criteria for Monoclonal Antibody Treatment

1. **Ages 50- 90 years;** case-by judgement under 50 or over 90 years.
2. Diagnosis of **MCI or mild probable AD with (MMSE ≥ 22 or MOCA ≥ 17 for lecanemab, MMSE ≥ 20 for donanemab)**
3. **Positive biomarkers** for Alzheimer's disease as defined by
    - **Aβ PET** scan with elevated amyloid deposition
    - **CSF** analysis at a CLIA approved lab with biomarker profile consistent with underlying AD pathology
4. **Brain MRI** inclusive of FLAIR, DWI, and heme sequences (SWI preferred, but GRE acceptable) performed within 12 months prior to expected time of treatment initiation
5. Eligible and **willing to receive requisite safety MRIs** during at least the first year of treatment
6. **Labs:** INR/PT, aPTT, and complete blood count including platelet count within the normal range of the resulting CLIA approved lab within 3 months prior to treatment
7. **Able to understand the risks** and provide ongoing informed consent for treatment
8. Has a **care partner** who routinely interacts with patient

Adapted from Rosenbloom MH, O'Donohue T, Zhou-Clark D, et al. CNS Drugs 2024;38:493-505.

Exclusion Criteria for Monoclonal Antibody Treatment

- **Not sufficiently impaired** (e.g. Subjective Cognitive Decline) or excessively impaired
- **Non-AD** neurodegenerative disorder
- **Exclusionary MRI findings**: Acute or subacute **hemorrhage or infarction**, More than 4 microhemorrhages of 10mm or less at greatest diameter, 1 or more macro hemorrhage, defined as 10mm or larger at greatest diameter, One or more regions of superficial siderosis, 1 or more cortical infarctions, 2 or more lacunar infarctions, Evidence of **substantial white matter changes** concerning for ischemic microvascular disease including irregular periventricular white matter T2 hyperintensities extending into deep white matter and beginning confluence, large confluent areas of deep white matter T2 hyperintensities (Fazika score>2), large confluent areas of deep white matter T2 hyperintensities, **Intraparenchymal lesion** that is concerning for malignancy or likely to increase the risk of herniation in the event of ARIA-E or ICH, Other evidence of active neuroinflammatory disease
- **Anticoagulants** or non-aspirin antiplatelet medications; Nonaspirin antiplatelets (clopidogrel, ticagrelor, etc. and aspirin up to 325 mg PO daily permitted)
- **Any medical co-morbid medical condition** that might pose a safety risk to treatment initiation including but not excluded to CVA in the preceding 12 months, **uncontrolled hypertension** or endocrine disorder; seizure disorder; active **autoimmune or inflammatory** disease; **recent cancer diagnosis not in remission** (excluding skin cancers, localized prostate cancer), **uncontrolled HIV** with development of AIDS, **bleeding disorders**, **amyloid angiopathy** (relative), major depression, pregnancy**, immunomodulatory drugs including systemic corticosteroids**, parenteral immunoglobulin, blood products, plasma derivatives, plasma exchange, and plasmapheresis. Systemic immunosuppressive drugs are not permitted for 3 months before starting anti-amyloid therapy, but may be considered on a case-by-case basis after starting therapy, use of another anti-amyloid antibody therapy in the last 6 months or history of hypersensitivity to monoclonal antibodies or active participation in an Alzheimer's-related clinical trial
- APOE Genotype now considered important for risk stratification and informed consent.

Adapted from Rosenbloom MH, O'Donohue T, Zhou-Clark D, et al. CNS Drugs 2024;38:493-505.

Concurrent Treatment Monitoring

- Screen for:
  - New antithrombotic use
  - Recent CVA
  - New or changed headaches
  - Nausea,vomiting
  - Tremor
  - Cognitive deterioration
  - Gait change
  - Change in alertness
  - Seizure
- Neuroimaging monitoring

ISTAART Mild Behavioral Impairment Criteria

Carl (age 76)

He is getting more frustrated lately. He never used to have such an irritable temper. He is distrustful, anxious and depressed.

- Changes from baseline behavior/personality, ≥ 6 months in duration, age ≥ 50: motivations, impulse control, social appropriateness, perception/thought content, social or occupational or independent functioning.
- At least minimal impairment from behaviors
- Not dementia, not other psychiatric/medical or substance or medication-related disorder.

Adapted from Ismail et al. Alzheimers Dement 2016;12:195-202.

Medications for NCBS in MCI

- Apathy
- Depression
- Anxiety
- Psychosis
- Agitation
- What to Avoid

Behavioral Syndromes Treated By Evidence and/or Analogy ("Off-Label")

Symptoms	Prevalence in MCI	Potential Treatments	Adverse Effects
Apathy[1]	30-40%	ChEI/methylphenidate/stimulating antidepressant	Agitation, anxiety, psychosis, cardiac
Depression/ Anxiety[1,3,4]	40-50%	Antidepressants (1 study) Avoid benzodiazepines, avoid antipsychotics **(For PBA, consider quinidine/dextromethorphan)**	QTc, Na, motivation, sleep, eating
Delusions/ Hallucination[1]	3-14%	SSRI, ChEI, antipsychotics	FDA boxed warning re mortality Metabolic, cardiac, neurological effects
Agitation/ Disinhibition[1]	4-35%	Brexpiprazole* **has FDA approval** for AD Agitation Good research evidence for SRIs Some evidence for trazodone ChEI not effective usually, avoid benzodiazepines	

1. Gallagher et al. The Canadian Journal of Psychiatry 2017;62(3):161-169;2. Devanand et al. Int J of Geriatric Psychiatry 2003;18:123-30;3. Tannenbaum et al. Drugs Aging 2012;29(8):639-58.

*may be suitable for LTCF use

Apathy

- In 30-40% of people with MCI
- Not “depression” - lacks negative cognitions and dysphoria
- Can precede and presage cognitive symptoms
- Attributed to disruption of circuits associated with reward processing and complex planning (prefrontal cortex, basal ganglia, anterior cingulate)
- Treat first with activation, exercise.
- ChEI/methylphenidate may treat apathy in AD, not proven in MCI.

Gallagher et al. The Canadian Journal of Psychiatry 2017;62(3):161-169.

Medications: Stimulants

Syndromes	Specific Agents	Evidence Says	Suggested Use
Apathy Depression	Methylphenidate	Modest benefit in apathy in AD, not proven in MCI	5 mg/d up to 10 mg bid with monitoring
	Potential Adverse Effects: Agitation, Insomnia, Psychosis, Anxiety, Anorexia, Elevated HR/BP		

Gallagher et al. The Canadian Journal of Psychiatry 2017;62(3):161-169; Padala et al Am J Psychiatry 2018; 175:159-68; Landes et al. J Am Geriatr Soc. 2001;49:1700-7; Galynker et al. J Neuropsychiatry Clin Neurosci 1997;9:231-9. Rosenberg et al. J Clin Psychiatry 2013;74:810-6 (ADMET trial).

Depression/Anxiety

- 40-50% of people with MCI
- In older adults, cognitive decline is predicted by
  - New onset depression
  - Persisting cognitive impairment after depression treatment
- Attributed to poor self-care, but also hypercortisolemia, reduced hippocampal volume, disruption of corticostriatal tracts, increased deposition of beta-amyloid protein, inflammation, oxidative stress.
- Tx with antidepressant is hoped to prevent secondary effects.

Gallagher et al. The Canadian Journal of Psychiatry 2017;62(3):161-169.

Antidepressants for Depression/Anxiety in MCI/MiND: One Study

- Only one study has addressed antidepressant treatment of subjects with MCI and depression:
  - N=26 completers, open trial, dose sertraline 200 mg/d x 12 weeks
  - 17 mood responders, 9 non-responders
  - Responders improved in digit symbol substitution test while non-responders declined.
  - Other neuropsych measures were not associated with response.
  - Suggestion that lack of cognitive improvement portends cognitive decline at follow up.

Devanand et al. Int J of Geriatric Psychiatry 2003;18:123-30.

What Harm Can Antidepressants Do?

- SRIs are associated with adverse effects:
  - QTc prolongation (citalopram, escitalopram)
  - Agitation, Insomnia, nightmares, sedation
  - Hyponatremia
  - Loss of appetite, increased appetite
  - Bruising/bleeding
  - EPS, apathy
  - Syncope

Delusions/Hallucinations

- 3-14% of people with MCI show psychotic symptoms.[1]
- Late life psychotic sx increase risk of dementia 8-11X
- Delusions more than hallucinations (except in LBD)
- Often persecutory or misidentification
- Attributed to frontal dysfunction
- Consider first treating with SSRI or ChEI.[2]
- Antipsychotic medication use carries risks - be cautious!

1. Gallagher et al. The Canadian Journal of Psychiatry 2017;62(3):161-169; 2. Cummings et al. Am J Ger Psychiatry 2006;14(7):605-12.

Medications: Atypical Antipsychotics Modest Effects, Significant Drawbacks

Syndromes	Usual Agents	Evidence for Use in Dementia, not in MCI	Suggested Use
Psychosis Agitation Aggression	Aripiprazole	May have modest benefit for agitation/psychosis	Begin with 2 mg/d Increase as high as10 mg/d
	Risperidone (approved in Europe, not US)		Begin with 0.25 mg/d Increase as high as 2 mg/d
	Olanzapine	Possible benefit	Begin with 2.5 mg/d Increase as high as 15 mg/d
	Quetiapine	Questionable	Begin with 12.5 mg/d Increase as high as 200 mg/d
	Brexpiprazole	**FDA INDICATED 7/23 for Agitation in AD**	0.5-2 mg/d in testing
	Clozapine	Inadequate data	Begin with 6.25 mg/d Increase up to 300 mg/d

Yunusa et al. JAMA Network Open 2019;2(3):e190828.doi:10.1001/jamanetworkopen.2019.0828

What Harm Can Antipsychotics Do?

- Somnolence, orthostatic hypotension, gait disturbance[1]
- Extrapyramidal symptoms including tardive dyskinesia[1]
- Metabolic effects, ADA warning for risk of diabetes with all atypical antipsychotics[2]
- FDA warning of increased CVAEs and increased mortality in elderly patients with dementia[3,4]

1. McDonald WM. J Clin Psychiatry. 2000;61(suppl 13):3-11; 2. American Diabetes Association, et al. Diabetes Care. 2004;27:596-601; 3. Wang et al. N Engl J Med. 2005;353:2335-2341; 4. Schneider et al. JAMA. 2005;294:1934-1943.

Agitation/Disinhibition

- 4-35% of people with MCI
- Can accompany even very mild cognitive symptoms
- Agitation predicts cognitive decline
- Attributed to changes in frontal cortex, amygdala, anterior cingulate cortex: impaired threat appraisal and fear regulation
- ChEI not effective, antidepressants may be, antipsychotics may be needed but are risky.
- Brexpiprazole, though with antipsychotic warnings, approved by FDA for treatment of agitation in AD.

Gallagher et al. The Canadian Journal of Psychiatry 2017;62(3):161-169.

Pharmacology Pearl: Re-Evaluate Current Regimen Before Adding New Meds

- Are current treatments evidence-supported?
- Are they matched with target symptom?
- Are doses appropriate? Have trials been adequate?
- Are there drug/drug interactions or adverse effects?
- Are there multiple drugs from same class?
- Are multiple providers collaborating/communicating?
- Is there excessive anticholinergic burden?
- ***Removing a medication may be better than adding one!***

What Can Be Removed?
Beers List of "Potentially Inappropriate Medications": Some Psychiatric Meds Are Included

- Anticholinergics
- Antihistamines
- Antidepressants with anticholinergic effects
- Serotonergic antidepressants
- Antipsychotics
- Benzodiazepines (with or without opioids)
- Z-drugs (non-benzo benzo-receptor agonists)
- Analgesics

American Geriatrics Society. JAGS 2023;71:2052-2081.

Prevention

An Estimated 45% of Cases of Cognitive Decline Can Be Delayed or Prevented through Lifestyle Modification.

Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission.
www.thelancet.com Published online July 31, 2024 https://doi.org/10.1016/S0140-6736(24)01296-0

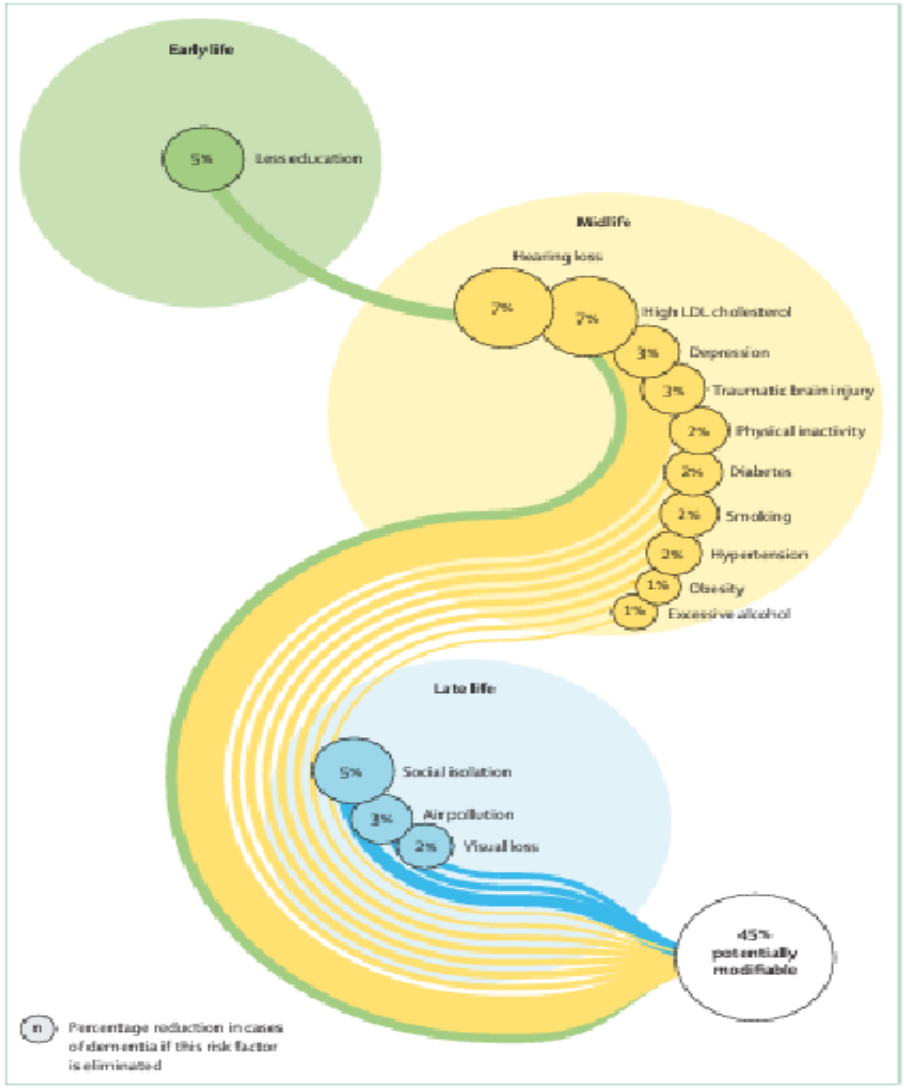
Prevention and PAR: The Latest from The Lancet

Hearing Loss 7%
Visual Loss 2%

High LDL 7%
Diabetes 2%
Smoking 2%
HTN 2%

Depression 3%
Inactivity 2%
Social isolation 5%

Less education 5%
TBI 3%



Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission.
www.thelancet.com Published online July 31, 2024 https://doi.org/10.1016/S0140-6736(24)01296-0

Keys to Optimal Cognitive Aging: Evidence-Based Interventions

- **D**isease Management
- **A**ctivity
- **N**utrition
- **C**ognitive Stimulation
- **E**ngagement with others and sense of purpose
- **R**elaxation
- **S**uccessful Sleep / **S**ensory Deficit Correction

Caregiver

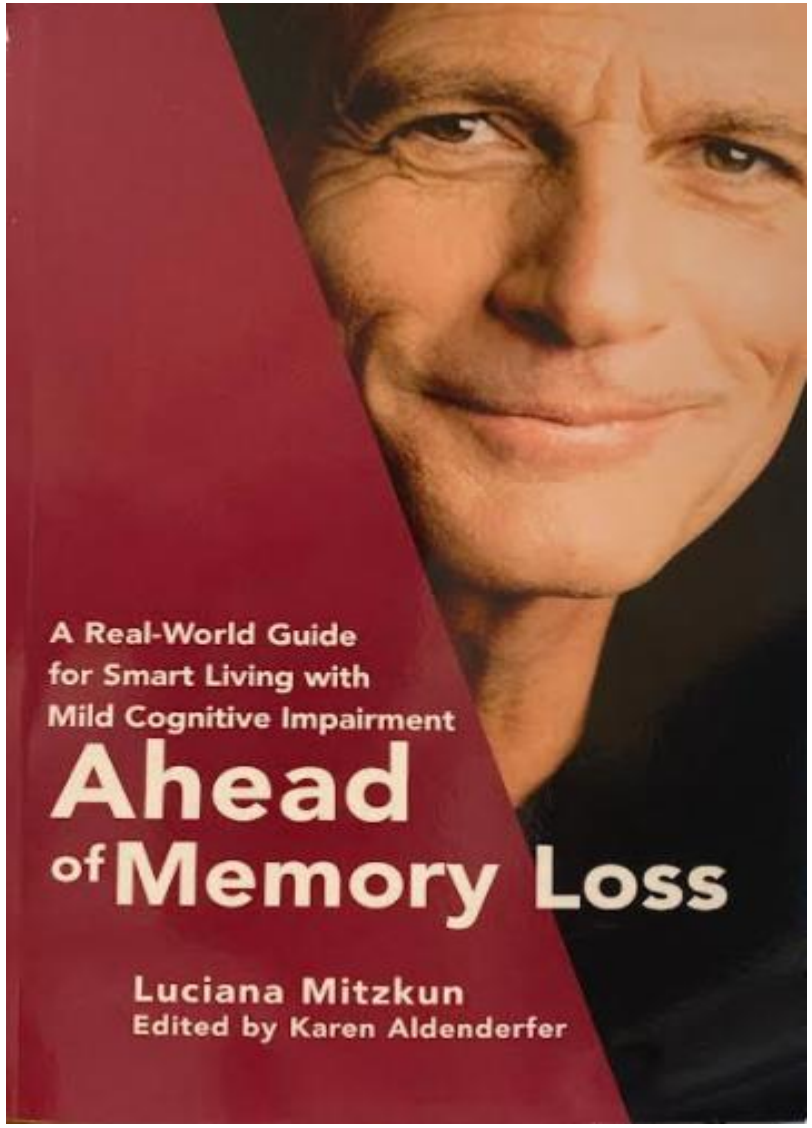
What Is The “Caregiver Burden” Of MCI?

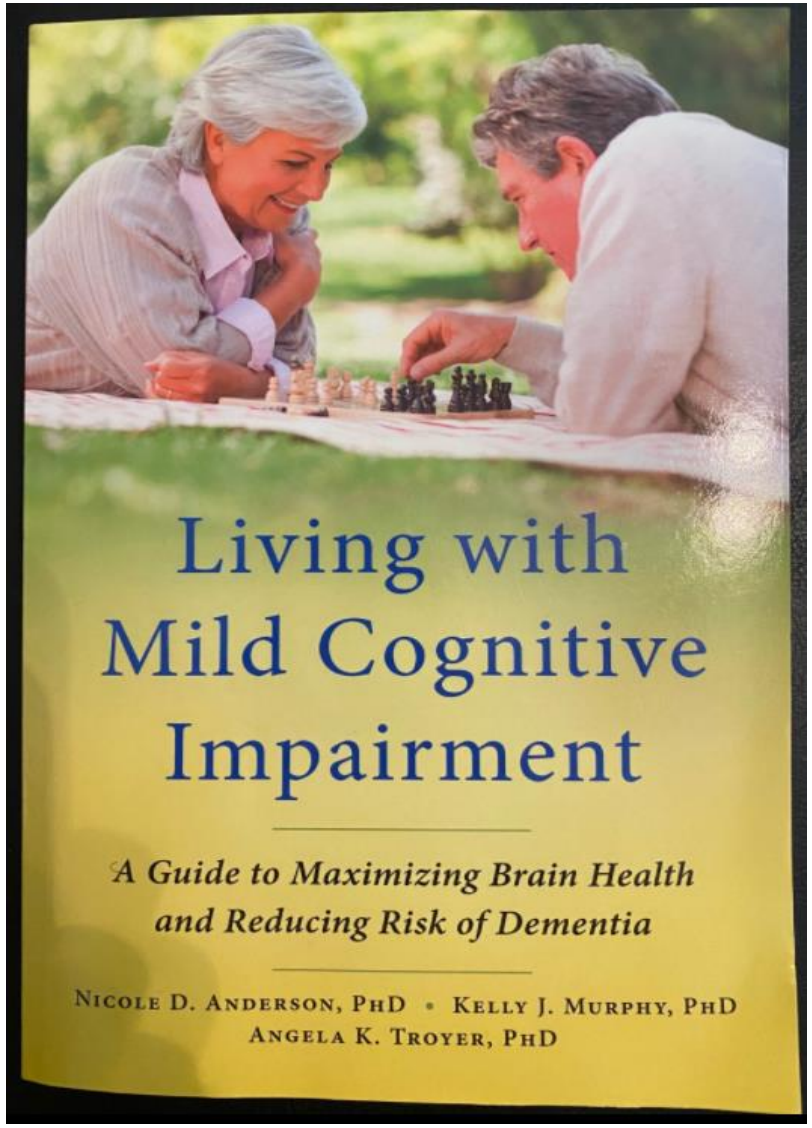
- About 1/3 of caregivers of people with MCI experience significant “burden”.[1,2]
  - Important contributors are[1]:
    - Higher levels of neuropsychiatric symptoms (e.g. depression)
    - Lower functional ability
    - Lack of driving
    - Caregiver employment
    - Changing nature of relationship: less intimacy, asymmetrical relationship, “absent presence”[3]

1. Connors et al. Am J of Geriatric Psychiatry 2019;27(11):1206-1215; 2. Paradise et al Aging & Mental Health 2015;19(1):72-8; 3. Barak et al. Family Relations 2024;73:2730-44.

What can we offer caregivers?

- Education/Information resources
- Encouragement of respite/ self-care
- Peer support groups
- Depression/anxiety treatment if needed
- Help in preparing for future





Additional Resources

Key Points

- Key Points:
  - MCI/MiND is highly prevalent in the aging population.
  - Lifestyle interventions can reduce the risk of cognitive decline.
  - MCI/MiND warrants:
    - Detection
    - Evaluation
    - Treatment
    - Advance Planning
  - Non-pharmacologic interventions are prioritized.
  - Better pharmacologic interventions are coming soon!

Next Best Steps

- Become proficient in detection of neurocognitive disorders at an earlier stage.
- Consider etiologic diagnosis when evaluating for cognitive impairment before implementing treatment.
- Practice diagnosis disclosure.
- Employ full range of nonpharmacologic and pharmacologic interventions for both behavioral and cognitive symptoms.
- Support community-based care programs (e.g. GUIDE).
- Develop referral process for MAb treatment.

National Resources for AD Support

1. **Alzheimer's Association:** alz.org
    1. Helpline: 1-800-272-3900
    2. The Alzheimer's Association offers a wide range of services, including support groups, educational programs, and a 24/7 helpline.
2. **Alzheimer's Foundation of America (AFA)**: alzfdn.org
    1. Helpline: 1-866-232-8484
    2. The AFA offers support services, educational materials, and a helpline for individuals living with Alzheimer's disease and their caregivers.
3. **National Institute on Aging (NIA)**: nia.nih.gov
    1. The NIA is part of the National Institutes of Health and provides information on Alzheimer's disease research, clinical trials, and resources for caregivers.
4. **Administration for Community Living (ACL)**: acl.gov
    1. The ACL provides resources and support for older adults and people with disabilities, including programs for Alzheimer's patients and their caregivers.
5. **Eldercare Locator**: eldercare.acl.gov
    1. Helpline: 1-800-677-1116
    2. The Eldercare Locator helps connect older adults and their caregivers with local services, including those for Alzheimer's disease.

6. UCLA Caregiver Videos: https://www.uclahealth.org/medical-services/geriatrics/dementia/caregiver-education/caregiver-training-videos

THANK YOU

QUESTIONS & DISCUSSION

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