Optum Health Education™

Dementia: Screening, Diagnosis, and Initial Management for the PCP

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Disclosures

Dr. Naomi Lin received personal compensation in the range of $500 to $4999 for serving as a consultant for Ventegra.

Off-label use of melatonin, trazodone, citalopram, sertraline, and antipsychotics will be discussed.

Objectives

At the conclusion of the presentation participants will:

1. Define dementia, as well as its various types and stages and modifiable risk factors.
2. Identify strategies to evaluate patients for dementia.
3. Describe the amyloid hypothesis and its role in the pathophysiology of dementia.
4. Review management strategies for dementia, including current and emerging treatments targeting amyloid plaques.

Understanding Dementia

Iadecola, Costantino, AAN Plenary Lecture 2023

-Dementia cause is complex with admixture of genes, environmental and exposures (Continuum (Minneap Minn) 2024:30(6, Dementia):1584-1613, 1761-1789.

-Neurodegeneration and neurovascular pathogenic overlap

Systemic conditions:

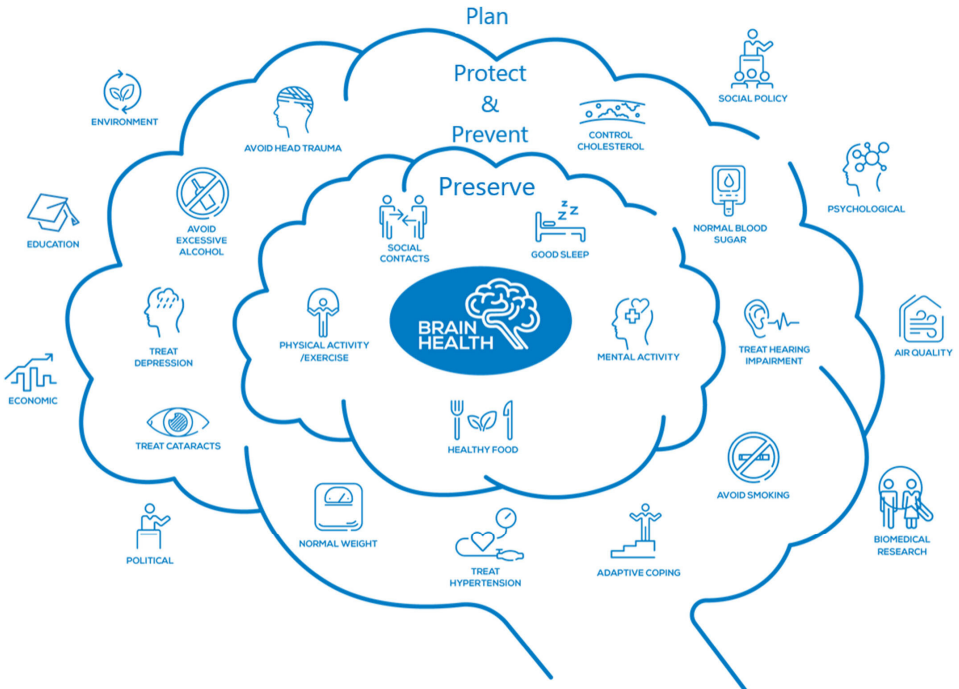
-Liver-heart-brain axis (atrophy, microvascular)

-Kidney-brain axis (eGFR)

-Gut-brain axis (microbiome)

-Lung-brain axis (microbiome)

-COVID (long-COVID)



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Neurocognitive disorders (NCDs) defined

A group of disorders in which the primary clinical deficit is in cognitive function and is acquired rather than developmental.

Mild neurocognitive disorder (mild cognitive impairment)

An intermediate state between normal cognition and dementia in which there are objective cognitive impairments but no decline in overall level of function.

Major neurocognitive disorder (dementia)

Acquired disorder characterized by a decline in cognition involving one or more cognitive domains. The deficits must represent a **decline from previous level of function** and be severe enough **to interfere with daily function and independence.**

**Early onset <age 65; late onset >age 65

Cognitive domains:

Learning and memory
Social cognition
Perceptual-motor function
Complex attention
Executive function
Language

(Larson EB, 2024; APA, 2022)

Major NCD (dementia) prevalence

Affects an estimated **2.4 to 5.5 million** people in the U.S.

3.2%
of persons aged
65 to 74 years

9.9%
of persons aged
75 to 84 years

29.3%
of those
older than 85 years

Alzheimer's disease accounts for **60-80% of dementia cases** in older adults.

(USPSTF, 2020; Larson, 2024)

Types of Dementia (clinically and pathologically overlap)

Continuum (Minneap Minn) 2024:30(6, Dementia)

Alzheimer dementia

Most common

Marked episodic memory impairment

Lewy Body dementia/Parkinson's Disease Dementia

Second most common but hard to diagnose (definitive diagnosis - autopsy Lewy bodies but 80% have "mixed" Alzheimer pathology)

Parkinsonism (bradykinesia, rigidity, postural instability/falls), visual hallucinations, REM sleep behavioral disorder

Fluctuation – confusion, inattention, hypersomnolence and "normal" days

No FDA approved treatment for LBD; can use cholinesterase inhibitors for PDD

Frontotemporal dementia/Primary Progressive Aphasia

Behavioral changes (disinhibition, apathy/inertia, loss of sympathy/empathy, stereotyped or ritualistic behavior, impulsiveness, hyperorality), or language deficits (difficulty with speech production, comprehension)

No disease modifying therapy

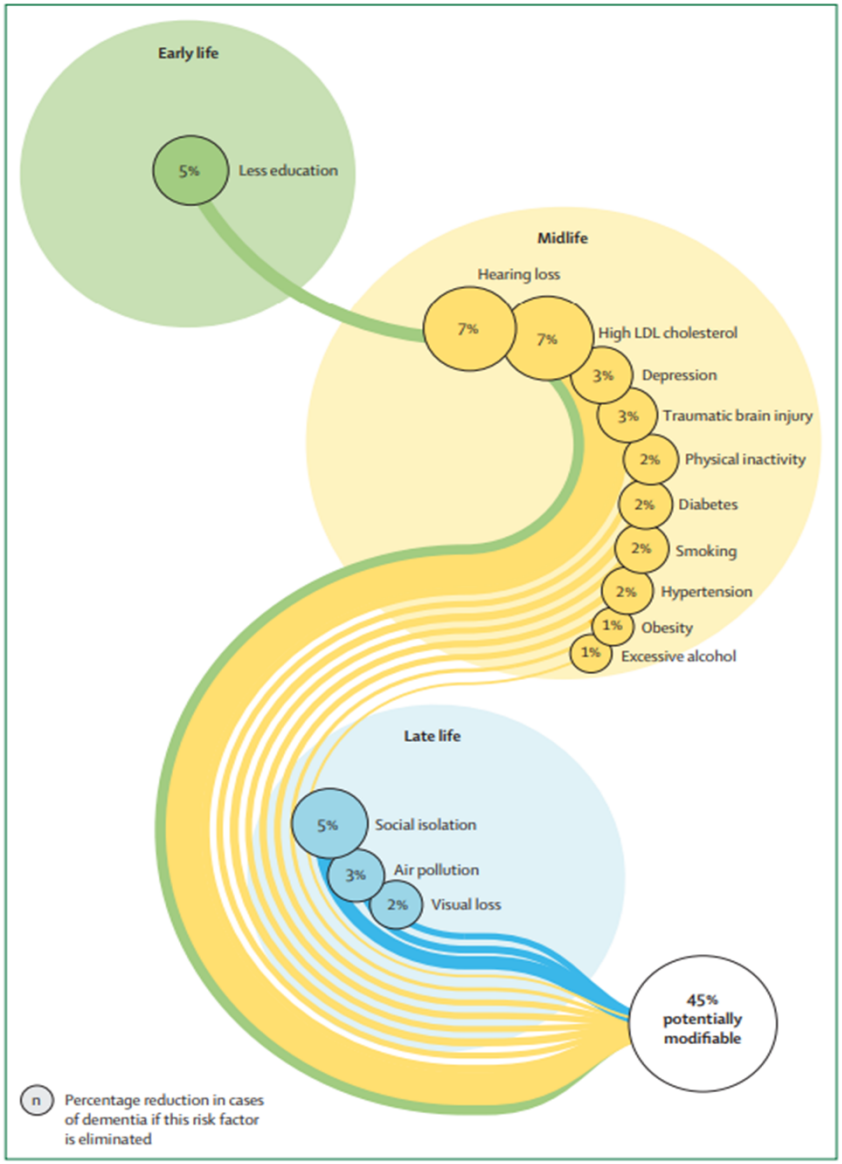
No FDA approved treatment

Others:

- Chronic traumatic encephalopathy
- Substance/medication-induced
- HIV infection
- Prion disease
- Huntington's disease

Population attributable fraction of potentially modifiable risk factors for dementia –

Borrowed with permission from Lancet 2024; 404: 572–628.



Initial Evaluation for Dementia

Optum Forum for Evidence-Based Medicine 9/2023.

1. Thorough History
   -progressive decline over time?
   -living situation – identify care partner
   -Who is managing meds, finances?
   -Is patient driving?
   -alcohol, smoking
   -review of medications
2. Exam: PHQ9 screen for depression
3. Cognitive assessment tool
4. FAST to assess daily functioning and independence
5. Workup - CMP, TSH, B12, (HIV, RPR) – CBC/UA

Ascertain Dementia 8 Questionnaire

Continuum (Minneap Minn) 2024:30(6, Dementia):1584-1613.

Ask “informant” to rate change

No time limit

Sensitivity > 84%

Specificity > 80%

PPV > 85%

NPV > 80%

If answer is “yes” to 2 or more likely to have cognitive impairment.

AD8 Dementia Screening Interview

Patient ID#:_____

CS ID#:_____

Date:_____

Remember, “Yes, a change” indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems.	YES, A change	NO, No change	N/A, Don’t know
1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking)			
2. Less interest in hobbies/activities			
3. Repeats the same things over and over (questions, stories, or statements)			
4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)			
5. Forgets correct month or year			
6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)			
7. Trouble remembering appointments			
8. **Daily** problems with thinking and/or memory			
TOTAL AD8 SCORE			

Adapted from Galvin JE et al, The AD8, a brief informant interview to detect dementia, Neurology 2005:65:559-564

Cognitive assessment screening tools

Mental status assessments	Time to perform	Dementia sensitivity %	Dementia specificity %	Comments
Mini-Mental State Examination (MMSE)	< 15 min	81	89	Good for identifying mild to moderate AD dementia. Does not directly assess executive function resulting in poor results for assessing MCI. Copyrighted with costs for use.
Mini-Cog	< 5 min	76-100	54-85	High sensitivity for dementia.
Montreal Cognitive Assessment (MoCA)	< 15 min	91	81	High sensitivity for detecting MCI due to the broader range of cognitive domains assessed than MMSE. Mandatory training and a fee-based certification is required.
Saint Louis University Mental Status Examination (SLUMS)	< 15 min	84-100	87-100	Superior to MMSE in its ability to identify individuals with MCI due to its more direct measure on executive function. Free annual training video required.
General Practitioner Assessment of Cognition (GP-Cog)	< 4 min	85%	86%	Consists of a four-component patient assessment and a brief informant interview (six questions). Available to use for free.

(Mendez M, 2024; MoCA Test; SLU; Mormino EC, 2018; Seeher KM, 2017; Falk N, 2018)

FAST Dementia Staging

CMS.gov

Normal	Stage #1: No difficulty, either subjectively or objectively
Normal	Stage #2: Complains of forgetting location of objects; subjective work difficulties
Early	Stage #3: Decreased job functioning evident to coworkers; difficulty in traveling to new locations
Mild	Stage #4: Decreased ability to perform complex tasks (e.g., planning dinner for guests; handling finances)
Moderate	Stage #5: Requires assistance in choosing proper clothing
Mod-Severe	Stage #6: Decreased ability to dress, bathe, and toilet independently: Sub-stage 6a: Difficulty putting clothing on properly Sub-stage 6b: Unable to bathe properly; may develop fear of bathing Sub-stage 6c: Inability to handle mechanics of toileting (i.e., forgets to flush, does not wipe properly) Sub-stage 6d: Urinary incontinence Sub-stage 6e: Fecal incontinence
Severe	Stage #7: Loss of speech, locomotion, and consciousness: Sub-stage 7a: Ability to speak limited (1 to 5 words a day) Sub-stage 7b: All intelligible vocabulary lost Sub-stage 7c: Non-ambulatory Sub-stage 7d: Unable to sit up independently Sub-stage 7e: Unable to smile Sub-stage 7f: Unable to hold head up

Assessing severity

Dementia Severity Rating Scale (DSRS)

About the assessment:

- 5 minutes to administer
- Twelve multiple choice questions
- Assesses twelve functional abilities (e.g., speech and language, recognition of family members)
- Can be completed via e-mail, phone, or in person
- Completed by family/caregiver
- Requires minimal staff training

DSRS practice utility:

- Accurate documentation
- Educate and inform patient and caregivers regarding disease progression

Scores:

Each section of the DSRS receives a score.

Points are added together.

Total points indicate a patient's dementia may be at a mild, moderate, or severe stage.

Mild 0-18

Moderate 19-36

Severe 37-54

(Moelter ST, 2015)

Amyloid Cascade Hypothesis (Alzheimer disease)

Optum Forum for Evidence-Based Medicine 9/2023.
Continuum (Minneap Minn) 2024:30(6, Dementia):1584-1613.

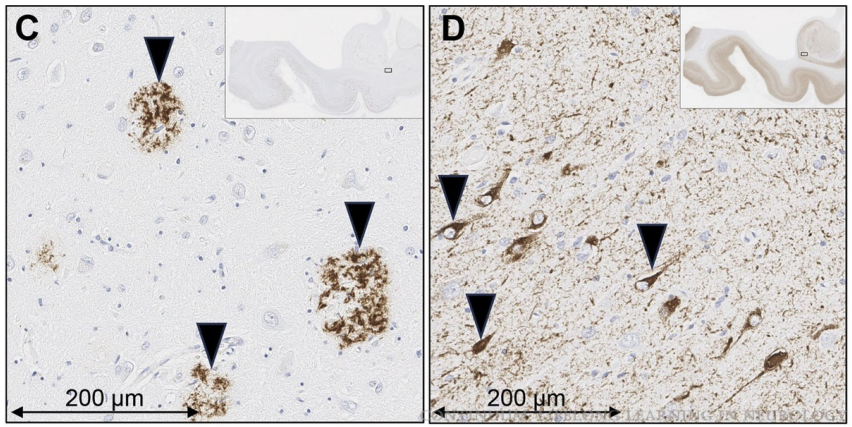
- Amyloid-beta - normal byproducts of cerebral metabolism
- Amyloid Hypothesis: Amyloid-ß aggregation and accumulation is the primary cause of Alzheimer disease

Problems:

-Genome-wide association studies have implicated risk genes that are not involved in amyloid-ß processing.

-Many older adults have brain amyloid-ß that fulfills Alzheimer's disease criteria but have no symptoms.

-Lowering amyloid burden does not clearly correlate with improved clinical outcomes.



Amyloid plaques (extracellular) Tau neurofibrillary tangles (intracellular)

Why Genetic Tests are Not Widely Done

Continuum (Minneap Minn) 2024:30(6, Dementia):1584-1613, 1761-1789.

-Limited clinical utility

-Poor predictive value

-Genome wide association studies with over 40 Alzheimer risk genes (Iadecola, Costantino, AAN Plenary Lecture 2023)

1-5% of patients with genetic variants associated with development of Alzheimer:

- Presenilin – PSEN1, PSEN2
- Amyloid Precursor Protein – APP
- Apolipoprotein E – APOE

APOE – APOE epsilon 4 alleles carriers have increased risk of Alzheimer, normal epsilon 3, protective effect epsilon 2 – apolipoprotein E role in lipid shuttling and clearance of amyloid beta; epsilon 4 isoforms associated with reduced clearance and enhanced aggregation of amyloid beta in brain; may accumulate tau at lower amyloid levels

- APOE is neither necessary nor sufficient to cause Alzheimer
  - May be justified for risk stratification for monoclonal antibody treatment
  - APOE epsilon 4 increased risk bleeding/edema

Trisomy 21 associated with development of Alzheimer at a young age

Why Serum Biomarkers are not Widely Used

Hansson et al, Alzheimer's and Dementia, 2022.

-Need to be validated in diverse ethnic, socioeconomic population in real world clinics

-Need accurate reference standards

-Need tools for interpretation of results

-Confounders – race, ethnicity, high BMI, peripheral neuropathies, other diseases, kidney disease – need large cohort

-Biological variation – intra-day, between day variations in individuals with various conditions

-Need prospective longitudinal study of serum biomarkers in real world memory clinics

-Need prospective studies in the PCP clinic with representative and diverse populations (heterogeneous causes: renal, cardiovascular, diabetes, depression)

-Should only be used in specialist clinics and confirmed with CSF or PET

Expert opinion Dr. Clifford Jack. *Neurology Today* 9/2024: "We are specifically recommending to NOT test cognitively unimpaired individuals… do not do it, because there are no approved treatments for people without clinical symptoms."

Anti-Amyloid therapy for Alzheimer 2025

	Lecanemab[77]	Donanemab[80]
Efficacy measure		
Clinical Rating Scale-Sum of Boxes (CDR-SB) % slowing	27%	29%
CDR-SB points difference	0.45	0.67
Mean baseline amyloid (centiloids)	78	104
Mean amyloid clearance (centiloids)	52	86
Centiloid reduction	66%	83%
Patients amyloid negative at 18 months	68%	76%
Safety measures		
Net amyloid-related imaging abnormalities due to hemorrhage (ARIA-H) (treated-placebo)	8%	12%
Net amyloid-related imaging abnormalities due to cerebral edema or effusion (ARIA-E) (treated-placebo)	11%	22%
ARIA-E by genotype (raw)		
ε3/ε3	5%	15%
ε3/ε4	11%	21%
ε4/ε4	33%	36%
ARIA-H by genotype (raw)		
ε3/ε3	12%	19%
ε3/ε4	14%	32%
ε4/ε4	40%	50%

Lecanemab Considerations

Lecanemab Appropriate Use Considerations. Alzheimer Association, 2023.

Inclusion:

- Mild Alzheimer Disease
- BMI >17, <35
- Have partner/family

ARIA rates reported for the CLARITY AD trial of lecanemab			
	APOE4 Noncarrier Lecanemab (N=278)	*APOE4* Heterozygote Lecanemab (N=479)	*APOE4* Homozygote Lecanemab (N=141)
ARIA-E	5.4%	10.9%	32.6%
Symptomatic ARIA-E	1.4%	1.7%	9.2%
Serious event with ARIA-E	0.7%	0.4%	2.1%
Total ARIA-H (Concurrent & Isolated)	11.9%	14.0%	39.0%

Exclusion:

- Microhemorrhages on MRI
- Stroke, TIA, seizure last 1 year
- Psychiatric illness, hallucinations that can interfere with participation
- GDS>8
- Immunologic disease requiring immunosuppressants, IVIG, monoclonal antibodies
- Bleeding disorders, anticoagulants, tPA/TNK (patients cannot get tPA/TNK in future for stroke or atrial fibrillation when on therapy)
- Unstable medical conditions (cardiac, respiratory, renal, GI disease), life limiting conditions (metastatic cancer)

Alzheimer Monoclonal Antibody Therapies

Medicine for Early Dementia Treatment Optum 2024

Candidates:

Low genetic risk for side effects

Have not had a recent stroke

Not on blood thinners

Not taking immunosuppressants or immunomodulating drugs

No other life-limiting conditions (like cancer spread throughout the body)

Considerations:

If patients will notice a 3% change in thinking “grade” by adding monoclonal antibodies to usual care. Meaningful change to clinicians is about 6-11%.

If lessening this protein buildup in the brain is enough to slow the illness down.

If people taking monoclonal antibodies are able live at home safely for longer.

If you need to keep taking monoclonal antibodies past 18 months.

How Black/African American people may respond (under-represented in data).

Alzheimer Disease Medications

Continuum (Minneap Minn) 2024;30(6, Dementia):1823-1844.

FDA approved medications for Alzheimer:

-Acetylcholinesterase inhibitors: delay in decline in daily function and nursing home placement, reduced mortality, decreased delusions and mood disturbances. Unclear role in severe Alzheimer.

-FDA approved for mild, moderate, advanced Alzheimer

-Side effects: GI, weight loss, bradycardia, syncope, falls, vivid dreams

-Donepezil 5 mg daily for 1 month, then 10 mg daily

-Galantamine transdermal patch 4.6 mg daily for 1 month, then 9.4 mg to 13.3 mg daily

-NMDA receptor modulator (memantine): less decline in cognition, improved daily and global function, decreased agitation. When added to donepezil in moderate Alzheimer, cognitive scores stabilize, less decline. Unclear role in mild Alzheimer.

-FDA approved for moderate, advanced Alzheimer

-Side effects: dizziness

-Memantine 5 mg daily for 1 week, then 5 mg bid for 1 week, then 5 mg in AM and 10 mg in PM for 1 week, then 10 mg bid

-Brexipiprazole – agitation related to Alzheimer disease; Black box warning antipsychotic

Symptomatic and Supportive Treatment

Continuum (Minneap Minn) 2022; 28(3, Dementia): 885-900.
Continuum (Minneap Minn) 2024;30(6, Dementia):1823-1844.

Off-label medications:

-Insomnia – melatonin 10 mg qhs, trazodone 50 mg qhs

-Agitation – citalopram, sertraline, antipsychotics (quetiapine, risperidone)

-Treat comorbid medical problems: depression/anxiety disorders, hearing loss, pain, alcohol misuse

-Obstructive sleep apnea most common primary sleep disturbance in older adults – CPAP helpful

-Deprescribe meds with cognitive side effects if possible (polypharmacy)

-Engage patients early about advanced care planning

-Identification of educational, supportive, and resource needs of the patient and caregivers - PT/OT/ST, social workers, meal delivery, driving assessment, local transportation, day care, SNF, Alzheimer Association (https://www.alz.org/alzheimers-dementia/what-is-dementia), local Area Agency on Aging (eldercare.acl.gov/Public/About/Aging_Network/AAA.aspx)

Management: Resources

- Advanced care planning
- Aging in place vs assisted living
- Home and social safety
- Driving safety
- Legal and financial planning

National and community resources:

Optimal Care Website – Dementia:
Xyleme Syndicate Portal

Advanced Care Planning:
https://optum.bravais.com/s/WlaAnKi2l5RTWgFUyclJ

Dementia and driving:
https://www.alz.org/help-support/caregiving/safety/dementia-driving

National senior transportation resources:
https://www.alz.org/media/Documents/national-senior-transportation-resources.pdf

Additional transportation links:
https://eldercare.acl.gov/Public/Resources/LearnMoreAbout/Transportation.aspx

Community resource finder:
https://www.communityresourcefinder.org

Bias

African Americans are less represented in clinical trials on antiamyloid therapy

African Americans and Hispanics have higher incidence of Alzheimer disease than Caucasians

African Americans usually present later in dementia stage when therapy no longer effective

There is bias in screening tools against people with less education and less verbal skills

Summary

Dementia etiology is still unclear, but likely multifactorial with genetic, environmental, and exposures.

Antiamyloid therapy have demonstrated statistically significant decrease in cognitive decline in individuals with mild Alzheimer disease, but have significant side effects, costs, and burden of time (frequency of infusions, scans) with unclear long term clinical significance.

Anticholinergic medications, NMDA modulators, symptomatic therapy can be offered with community resources for care partners.

It is important to promote healthy living and treat modifiable risk factors in early life (less education), midlife (hearing loss, LDL, depression, traumatic brain injury, sedentary lifestyle, diabetes, smoking, hypertension, obesity, excessive alcohol) and late life (social isolation, air pollution, visual loss) to decrease dementia risk.

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Appendix

Aducanumab

AAN Guidelines 2022, FDA Update 2021, Optum Forum for Evidence-Based Medicine 9/2023.

Class II studies:

ENGAGE – no clinical efficacy; EMERGE – unclear efficacy

-Decreased amyloid deposition in the brain on amyloid-PET scan at 1 year vs placebo

-Efficacy varied on dose and outcome but had no effect versus less worsening (vs placebo) of unclear clinical significance

-Adverse reactions

ARIA-E 35% of the treatment versus 3% placebo

ARIA-H, microhemorhage 19% versus 7%

ARIA-H, siderosis 15% versus 2%

. -Monthly infusion dose titrated to 10 mg/kg over 6 months

-Study duration 1.5 years but unknown duration of therapy in real world

-Studies excluded: dementia due to other causes, younger patients, underrepresented minority groups, prior stroke, brain bleed, antiplatelet therapy, psychiatric conditions that might contribute to cognitive impairment, cardiovascular disease, CKD, age>85

- Analysis of 2.87 million Medicare beneficiaries with symptomatic AD in 2021 - 91% of patients diagnosed with AD dementia and 86% of patients with MCI met at least 1 exclusion criterion

Lecanemab

Clarity – NEJM 11/2022

Age 50-90 MCI due to AD or mild AD, positive amyloid in PET or spinal tap

Less worsening in cognitive scores (CDR-SB) at 1.5 years, edema/effusions

Infusion 10 mg/kg every 2 weeks

**2 deaths after trial open label (stroke, cerebral hemorrhage – both on anticoagulation)

4.5 percent Black and 22.5 percent Hispanic participants, comorbidities including hypertension, diabetes, heart disease, obesity, and renal disease

ICER 3/2023 – promising but inconclusive if lecanemab provides net health benefit to supportive care with risk of ARIA 21% with effusion, hemorrhage, or both

JAMA letter 5/2023 – lecanemab high cost can possibly lead to beneficiary premium increases; Medicare spending may increase by $2 billion to $5 billion

Neurology letter 8/2023 – donepezil outperformed lecanemab in CDR-SB (0.53 vs 0.45) and in ADAS-Cog (2.37 slowing vs 1.44 slowing) therefore symptomatic benefits are very small; amyloid present in patients who are asymptomatic; multi-focal hemorrhage in patient given tPA for stroke who was on lecanemab; elderly patients may develop a fib, stroke requiring thrombolysis in future; giving lecanemab to all MCI, mild Alzheimer patients would cost $120 billion per year

Donanemab

Optum Forum for Evidence-Based Medicine 9/2023.

-Phase 2 clinical trial enrolled 257 patients with MCI or mild dementia attributed to early Alzheimer's disease.

-Primary outcome was change in the Integrated Alzheimer's Disease Rating Scale (iADRS) at 76 weeks.

-Positive significant change in iADRS (-6.86 with treatment and -10.06 with placebo, p=0.004).

-Clinically meaningful change on the iADRS has been estimated at 5 points for MCI, but 9 points for mild dementia.

-Phase 3 trial - low, medium, high tau pathology based on PET

-Positive significant change iADRS (-3.25 in the low/medium tau cohorts; -2.92 in the combined population) and the CDR-SB (-0.67 in the low/medium tau cohorts; -0.7 in the combined population).

- -Brain amyloid decreased significantly.

-ARIA-E 24% in treatment versus 1.9% placebo group

-ARIA-H in 19.7% versus 7.4%

Clinically meaningful change on the iADRS has been estimated at 5 points for MCI, but 9 points for mild dementia (Optum Forum for Evidence-Based Medicine 9/2023).

Serum Biomarker Candidates:

Hansson et al, Alzheimer's and Dementia, 2022.

Currently used in clinical trials only:

--Amyloid beta 42/40 – small change between positive and negative individuals due to peripheral production

--Serum phosphorylated tau - related to density of amyloid beta plaques and tau tangles - screening in clinical trials

--Neurofilament light chains - axonal damage (nonspecific)

--Glial fibrillary acidic protein – astrocyte activation to clear amyloid beta - higher in brain astrocytes than peripheral macrophages – need additional study to validate

Validated Testing for Alzheimer Disease Pathology
Hasson et al, Alzheimer's and Dementia, 2022.

Beta Amyloid PET scan – deposition of beta amyloid in plaques

CSF amyloid beta 42/40 ratio – low ratio reflects depletion of Amyloid beta 42 due to growing plaques

-Can be used in symptomatic patients to determine AD vs non-AD

Plasma phosphorylated Tau 217
Ashton et al, JAMA Neurology 2024

Certain plasma p-tau – associated with neurofibrillary tangle pathology

pTau- 217 (phosphorylated tau at threonine 217) - high performance in differentiating AD from other neurodegenerative disorders, and in detecting AD pathology in patients with MCI

- Associated with longitudinal trajectory associated with brain atrophy and declining cognitive performance in people with amyloid beta pathology
- Preclinical population with lower prevalence of amyloid beta abnormalities – plasma p-tau can help with diagnosis and prognosis longitudinal change (increase with amyloid beta only, and with amyloid beta and pTau)
- Anti amyloid therapies may be less effective in patient with advanced tau pathology
- Related to density of amyloid beta plaques and tau tangles