NOVELLO SPECIALTY CLINIC
Healthcare Reimagined.

Alzheimer's Disease and Its connection to Traumatic Brain Injury

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10/17/2024

WHAT IS COGNITION

What is a behavioral neurologist?

Behavioral Neurology

The intersection of cognition and behavior:

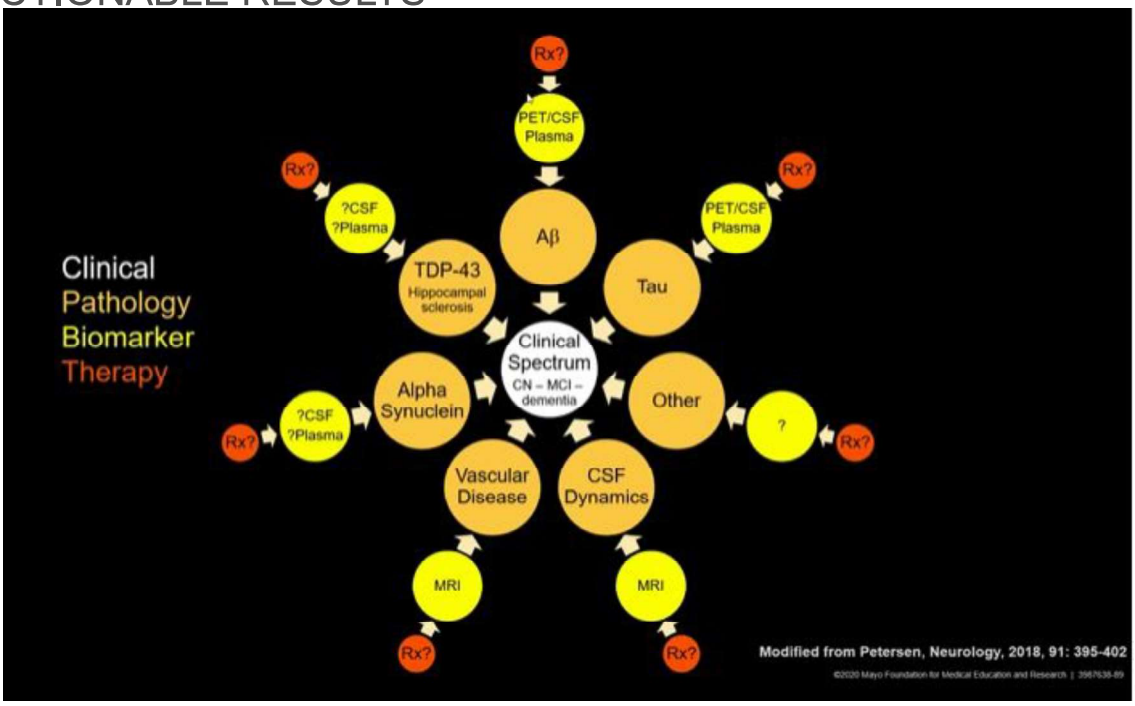
1) diffuse and multifocal brain disorders affecting cognition and behavior (e.g. delirium and dementia)

2) neurobehavioral syndromes associated with focal brain lesions (e.g. aphasia, amnesia, agnosia, apraxia)

3) neuropsychiatric manifestations of neurological disorders (e.g. depression, mania, psychoses, anxiety, personality changes, or obsessive-compulsive disorders, which may accompany diseases such as epilepsy, cerebrovascular disease, traumatic brain injury, or multiple sclerosis).

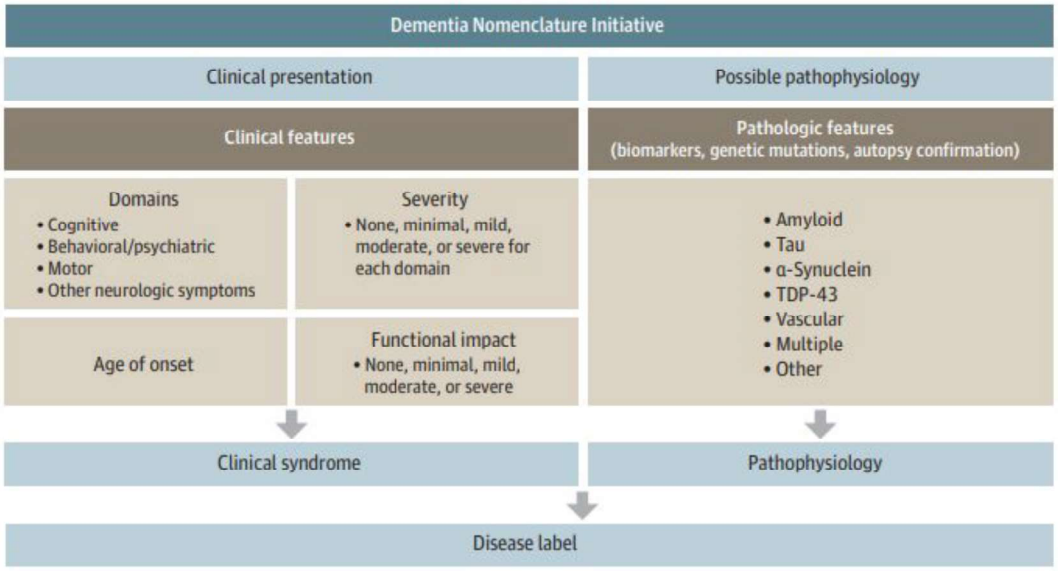
WHY SHOULD WE MAKE A DIAGNOSIS?

1. ACTIONABLE RESULTS



Marrying pathophysiology and symptoms

Figure. Dementia Nomenclature Initiative

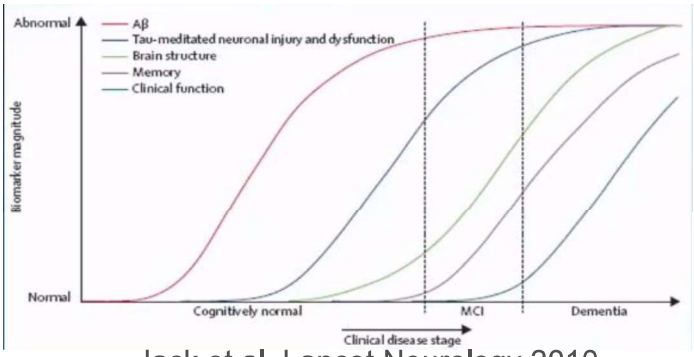


Petersen RC, Weintraub S, Sabbagh M, et al. A New Framework for Dementia Nomenclature. *JAMA Neurol.* 2023;80(12):1364–1370. doi:10.1001/jamaneurol.2023.3664

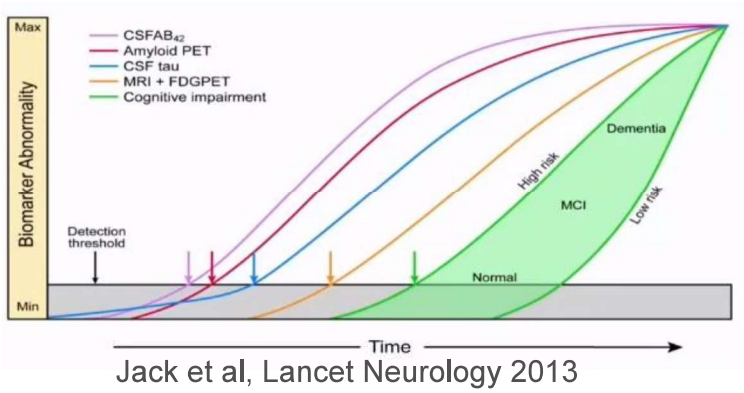
Revised Diagnostic Criteria for AD

- Prior workgroups for conceptualization of AD in 2011, 2012, 2018
  - Separating Syndrome from Biology
  - AD is a biological process detected by Core biomarkers
  - There is a continuum, beginning with abnormal biomarkers while patients are asymptomatic – progressing with appearance/progression of symptoms as pathologic burden increases.
  - n-terminal p-tau fragments 9217, 181, 231) become abnormal at the same time as amyloid pet (before tau PET).

Dr Clifford Jack, Jr.



Jack et al, Lancet Neurology 2010



Jack et al, Lancet Neurology 2013

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-tau 217, p-tau 181, p-tau 231	
Core 2		
T_2 (AD tau proteinopathy)	MTBR-tau243, other phosphorylated tau forms (e.g., p-tau 205, non-phosphorylated mid-region tau fragments*)	Tau PET
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*	

	Initial-stage biomarkers	Early-stage biomarkers	Intermediate-stage biomarkers	Advanced-stage biomarkers
	(A)	**(B)**	**(C)**	**(D)**
PET	amyloid PET	tau PET medial temporal region	tau PET moderate neocortical uptake	tau PET high neocortical uptake
	$A+T_{2}-$	$A+T_{2MTL}+$	$A+T_{2MOD}+$	$A+T_{2HIGH}+$
Core 1 fluid	CSF Aβ 42/40, p-tau 181/Aβ 42, t-tau/Aβ 42, and accurate* Core 1 plasma assays can establish that an individual is in biological stage A or higher, but cannot discriminate between PET stages A–D at present.			

Staging may be accomplished by 1) a combination amyloid PET and tau PET, or 2) a combination of Core 1 fluid biomarkers (which would establish biological stage A or higher), plus tau PET (which would be used to discriminate among stages).

Stage 0 Asymptomatic, deterministic gene

No evidence of clinical change. Biomarkers still in normal range

Stage 1 Asymptomatic, biomarker evidence only

Performance within expected range on objective cognitive tests.

No evidence of recent cognitive decline or new symptoms

Stage 2 Transitional decline: Mild detectable change, but minimal impact on daily function

Normal performance within expected range on objective cognitive tests.

Decline from previous level of cognitive or neurobehavioral function, that represents a change from individual baseline within past 1-3 years, and has been persistent for at least 6 months.

- May be documented by evidence of subtle decline on longitudinal cognitive testing which may involve memory or other cognitive domains but performance still within normal range
- May be documented through subjective report of cognitive decline (SCD)
- May be documented with recent onset change in mood, anxiety, motivation not explained by life events

Remains fully independent with no or minimal functional impact on daily life activities (ADL)

Stage 3 Cognitive impairment with early functional impact

Performance in the impaired/abnormal range on objective cognitive tests

Evidence of decline from baseline, documented by the individual's report or by observer (e.g. study partner) report or by change on longitudinal cognitive testing or neurobehavioral behavioral assessments.

Performs daily life activities independently but cognitive difficulty may result in detectable functional impact on complex activities of daily life, i.e., may take more time or be less efficient but still can complete, either self-reported or corroborated by observer.

Stage 4 Dementia with mild functional impairment

Progressive cognitive and mild functional impairment on instrumental ADL with independence in basic ADL

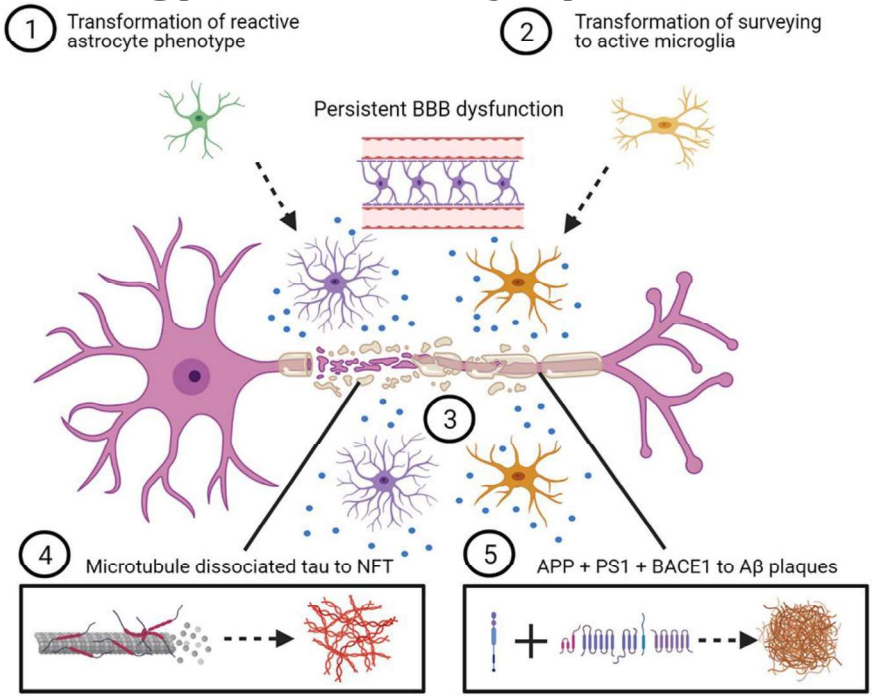
Stage 5 Dementia with moderate functional impairment

Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance

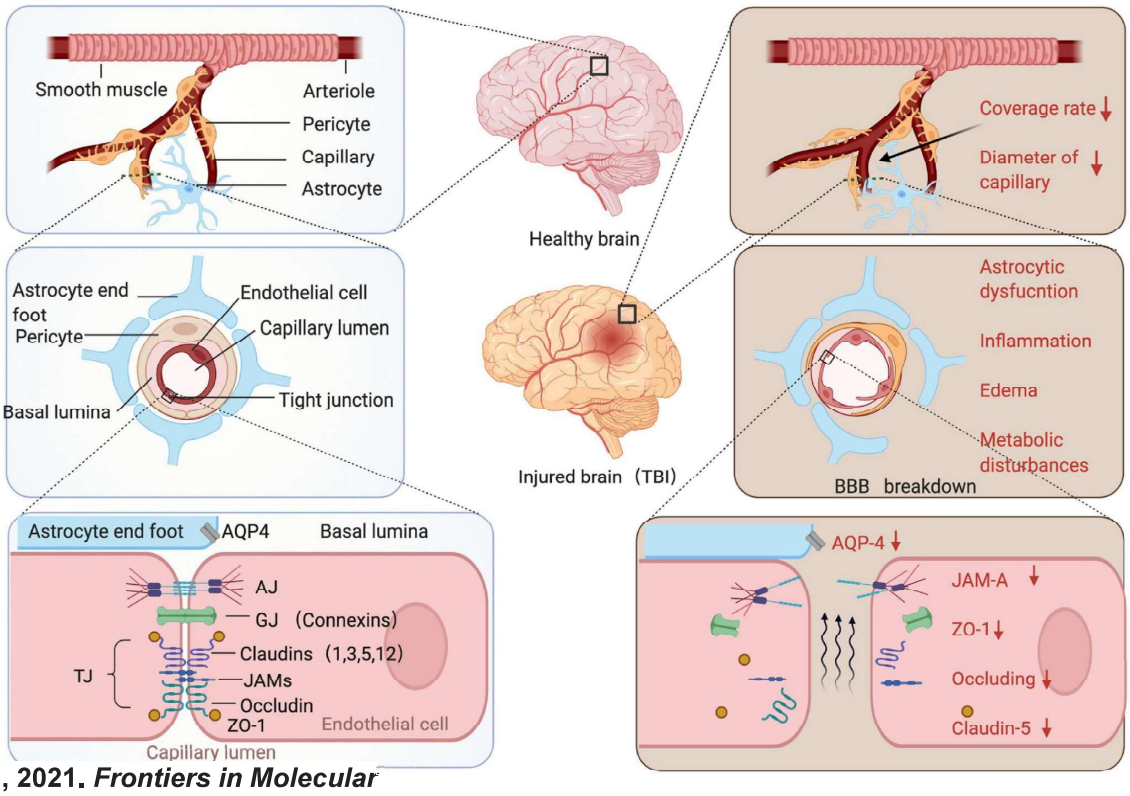
Stage 6 Dementia with severe functional impairment

Progressive cognitive and severe functional impairment on dependence for basic ADLs

Pathophysiology of Brain Injury



Brett, et al., 2022. Traumatic brain injury and risk of neurodegenerative disorder.
***Biological psychiatry*, *91*(5), pp.498-507.**



Glymphatic system dysfunction → secondary injury

Hu, Y. and Tao, W., 2021. *Frontiers in Molecular Neuroscience*, *14*, p.750810.

Chronic Effects of TBI

- Behavioral Disorders
- Mild cognitive impairment
- Parkinsonism
- Chronic migraine
- Dementias
- ALS
- CTE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neurodegenerative Disease Mortality among Former Professional Soccer Players

Authors: Daniel F. Mackay, Ph.D., Emma R. Russell, M.Sc., Katy Stewart, Ph.D., John A. MacLean, M.B., Ch.B., Jill P. Pell, M.D., and William Stewart, M.B., Ch.B., Ph.D.
Author Info & Affiliations

Published October 21, 2019 | N Engl J Med 2019;381:1801-1808
DOI: 10.1056/NEJMoa1908483 | VOL. 381 NO. 19 | Copyright © 2019

- 7676 pro soccer players & 23,028 matched controls
- 3.5x higher risk of death due to neurodegenerative disease.
  - Alzheimer's: 5x higher risk
  - Motor neuron disease: 4x higher risk
  - Parkinson's Disease: 2x higher risk

- Position dependent risk:
  - Outfielders: 4x higher risk
  - Defenders: 5x higher risk
  - Forwards: 3x higher risk

J Neurotrauma. 2023 Jul;40(13-14):1423-1435. doi: 10.1089/neu.2022.0360. Epub 2023 Jan 27.

Lifetime Traumatic Brain Injury and Cognitive Domain Deficits in Late Life: The PROTECT-TBI Cohort Study

Matthew J Lennon [1 2], Helen Brooker [3], Byron Creese [3], Tony Thayanandan [1], Grant Rigney [1 4], Dag Aarsland [5 6], Adam Hampshire [7], Clive Ballard [3], Anne Corbett [3], Vanessa Raymont [1]

- 15,752 patients greater than age 50
- 36.3% had > or = 1 mTBI

- If > or = 1 mTBI → poorer attention
- 3 mTBI → poorer executive function + attention
- >3 mTBI → poorer processing speed, working memory, attention.

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

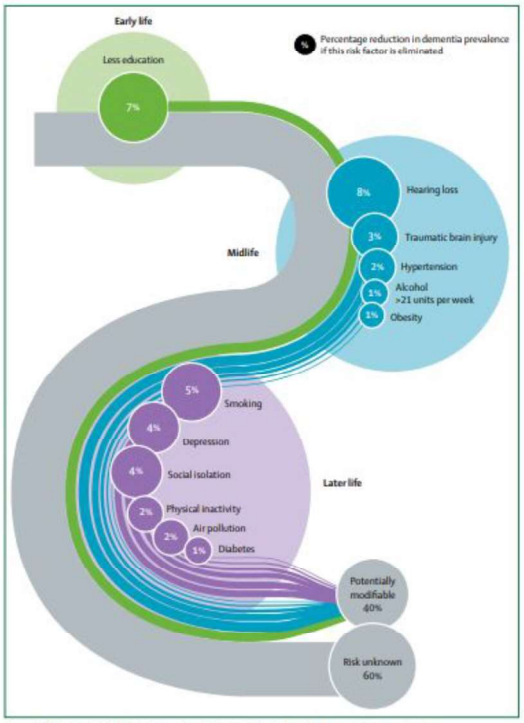
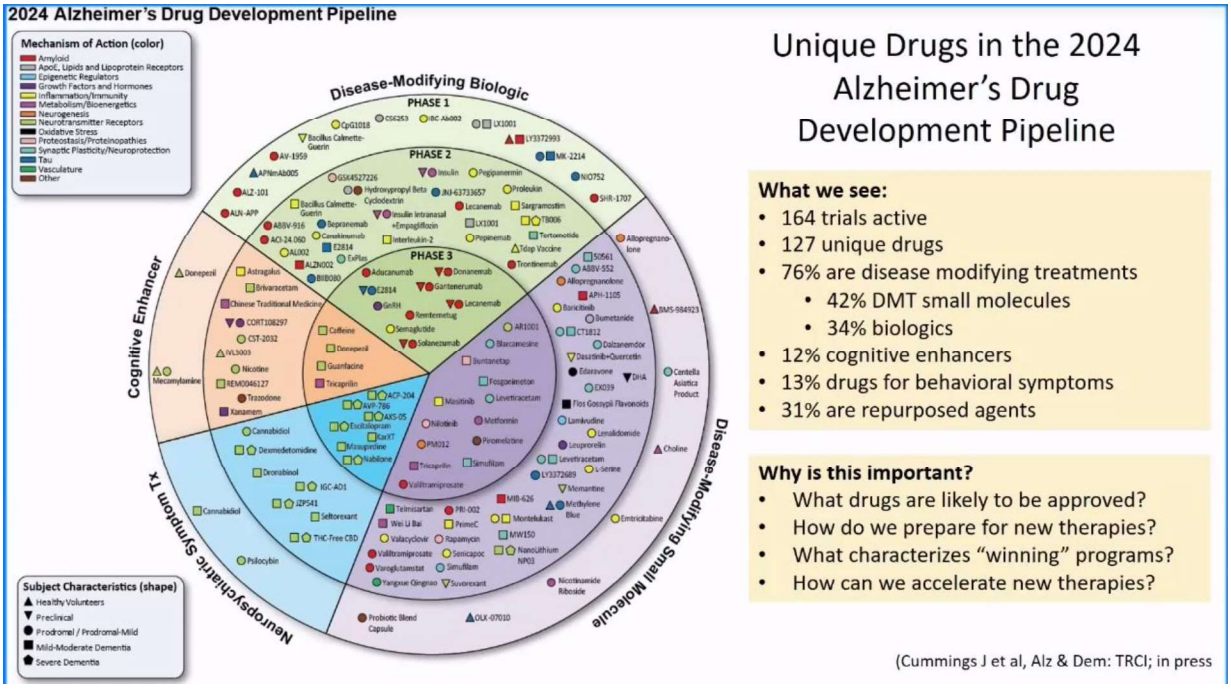


Figure 7: Population attributable fraction of potentially modifiable risk factors for dementia

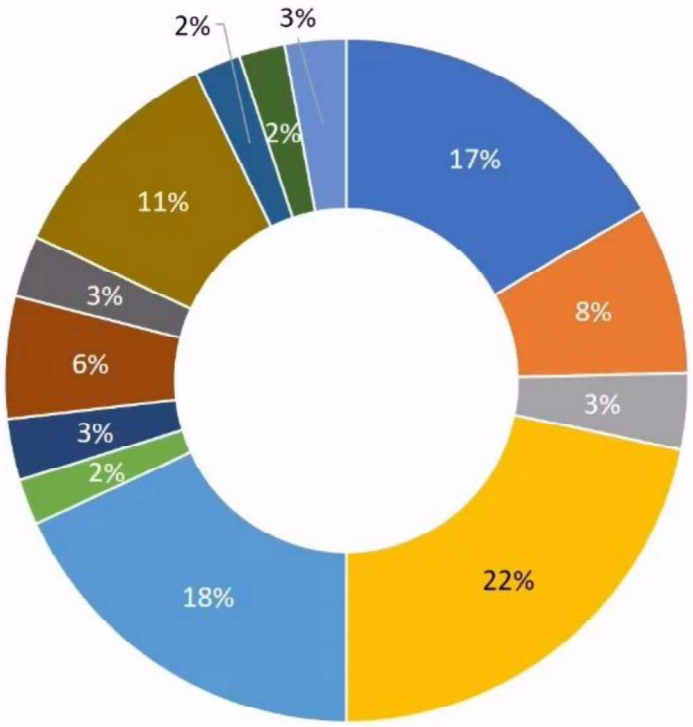
AD Treatment Updates

AD Treatment Updates



Jeffrey L. Cummings, MD, ScD
Cleveland Clinic Lou Ruvo Center for Brain Health

2024 AD Drug Development Pipeline: Targets



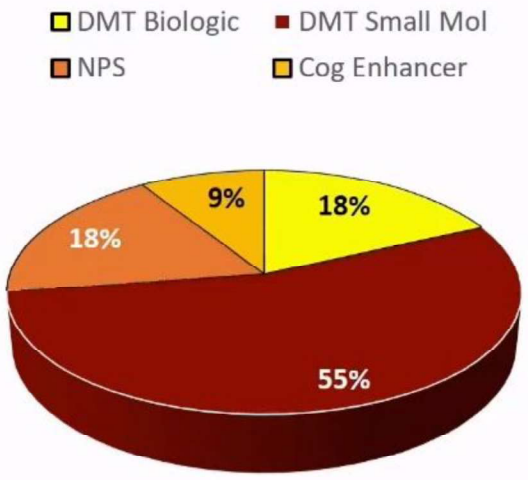
- Canonical targets A,T – 25%
  - Amyloid – 18%
  - Tau – 7%
- Transmitters – 22%
- Inflammation – 20%
- Synaptic plasticity – 12%
- Bioenergetics – 6%
- APOE and related – 4%
- 15 target categories represented
- Nealy all mechanisms for engaging targets are unique

*"Other" – 1-2 agents for the target

Cummings J et al, Alz & Dem: TRCI; in press

Therapeutic Purpose	Agent	Mechanism
DMT small molecule	Buntanetap (posiphen)	Proteostasis
DMT small molecule	Piromelatine (Neu-P11)	Melatonin and serotonin receptor agonist
DMT small molecule	Valitramiprosate (ALZ-801)	Amyloid aggregation inhibitor
DMT small molecule	Blarcamesine (Anavex 2-73)	Sigma-1 receptor agonist; M2 autoreceptor antagonist
DMT small molecule	Fosgonimeton (ATH-1017)	Hepatocyte growth factor receptor system activators
DMT small molecule	Simufilam (PTI-125)	Stabilizes Aβ-nicotinic effect on filamin A to decrease tau phosphorylation
DMT biologic	Semaglutide	GLP-1 agonist (CSF biomarker study)
DMT biologic	Donanemab	Anti-amyloid MAB (dose study)
Anti-agitation agent	AVP-786	NMDA receptor antagonist (2 trials)*
Anti-agitation agent	Escitalopram	Selective serotonin reuptake inhibitor
Cognitive enhancer	Caffeine	Adenosine antagonist; PDE inhibitor

2024: Phase 3 Readouts (12 Trials)



Cog – Cognitive; DMT – disease modifying therapy; Small mol – small molecule; NPS – Neuropsychiatric Symptoms
*Readout as negative after report Index Date (1/1/2024)

33 • New

37 • Completed

1 • Suspended

10 • Terminated

4 • Withdrawn

7 • Unknown

2024: Trials Coming and Going

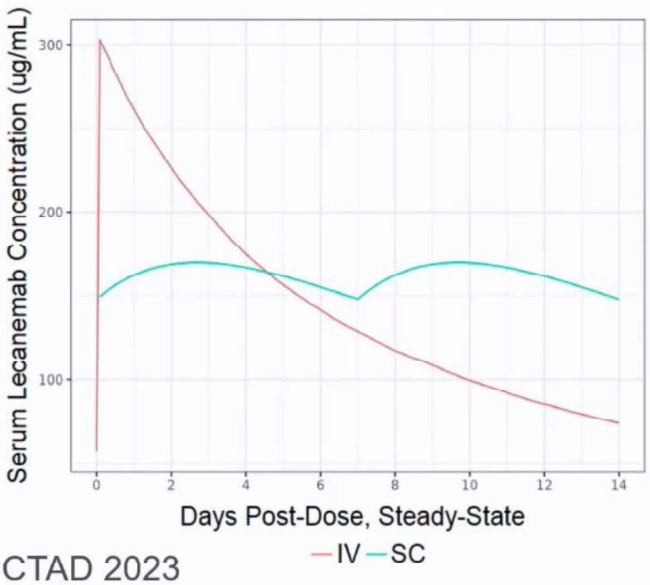
164 trials

- 129 trials continued from last year
- 33 new trials
- 59 trials left the pipeline

"Unknown" – no update on Clinicaltrials.gov ≥ 2 years

What therapies are coming?

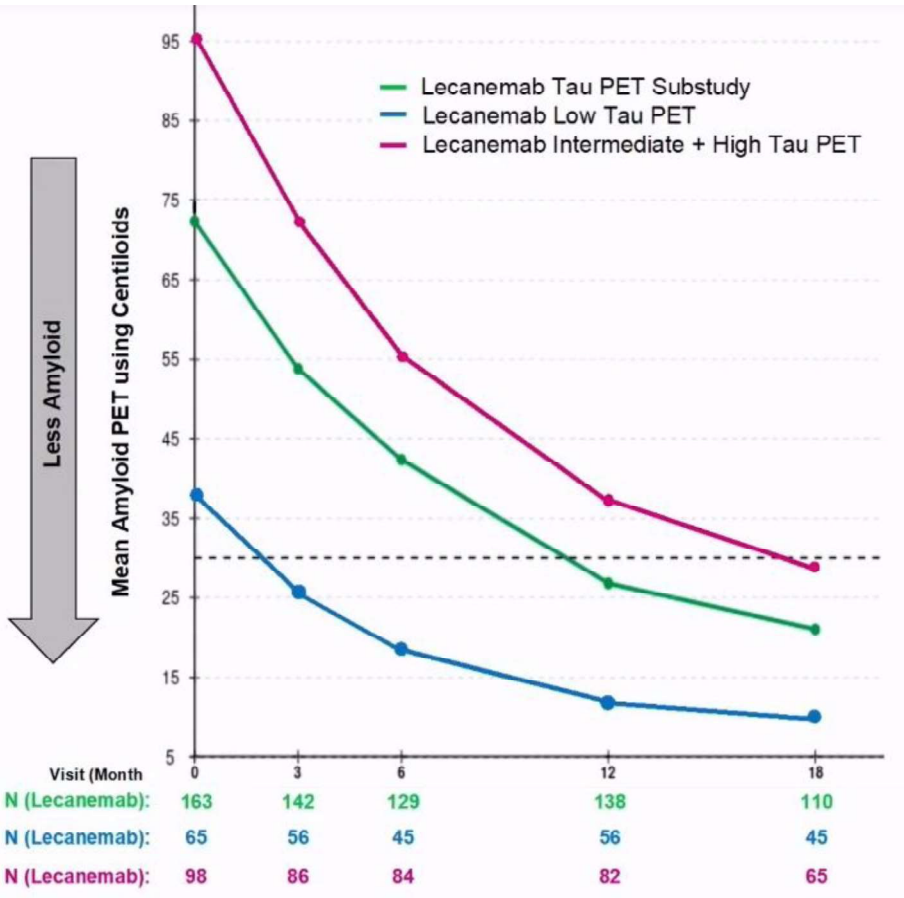
Subcutaneous formulation of lecanumab



Data presented at CTAD 2023

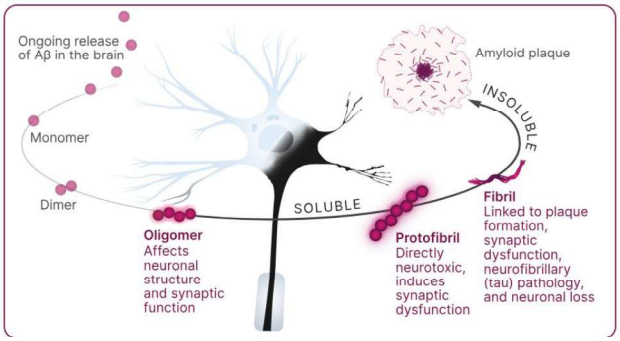
Philip Scheltens, MD PhD

Treat earlier



Data presented at CTAD 2023

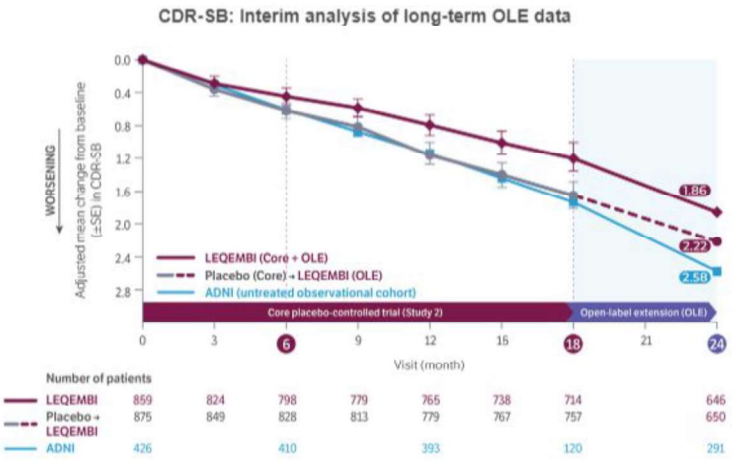
Lecanemab



CLARITY AD :
- Double-blind RCT of 1765 patients with MCI or Mild AD with confirmed pathology.
-Primary endpoint CDR-SB
-Secondary endpoint: change at 18 months of ADCS MCI-ADL(function),
ADAS-Cog14(cognition), amyloid PET

Open Label Extension: up to 48 months

Different rates of progression were observed through 24 months[4,7]

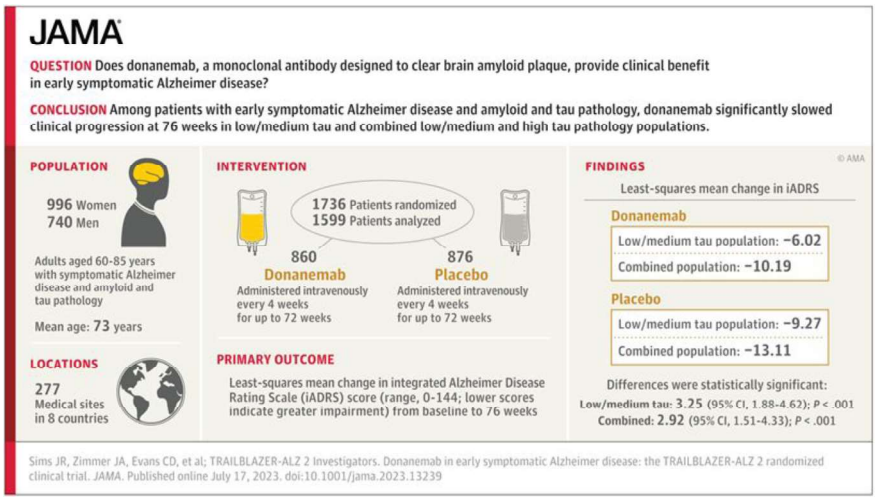


Donanemab

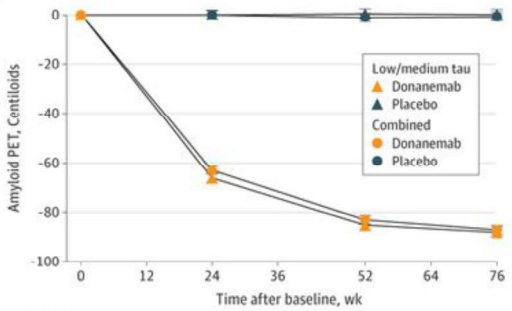
Mechanism: Immunoglobulin G1 monoclonal antibody directed against insoluble, modified, N-terminal truncated form of β-amyloid present only in **brain amyloid plaques**. Donanemab binds to N-terminal truncated form of β-amyloid and aids plaque removal through microglial-mediated phagocytosis.

Trailblazer 2:

- 1736 participants with MCI or mild dementia
- Tau PET scan's to differentiate
  - Low/intermediate tau group versus high tau group
- Every 4 weeks for 72 weeks.
- If dose completion criteria was met, switched to receive Placebo.
- integrated Alzheimer Disease Rating Scale (range 0-144; lower = greater impairment)
- Secondary outcomes included CDR-SB

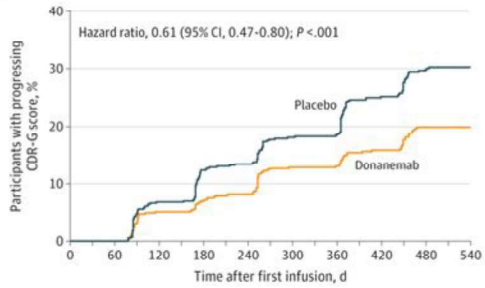


A Adjusted mean change (95% CI) in amyloid PET



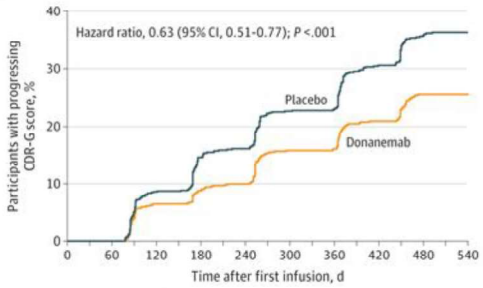
No. of participants					76-wk value, Centiloids	Difference from baseline %
Low/medium tau						
Donanemab	525	521	463	433	-88.0	-85.5
Placebo	556	552	498	470	0.2	0.2
Combined						
Donanemab	765	760	670	614	-87.0	-83.7
Placebo	812	805	729	690	-0.7	-0.7

E CDR-G score in low/medium tau population



No. of participants at risk						
Treatment	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



No. of participants at risk						
Treatment	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

How to differentiate between TBI versus AD symptomatology?

Where can we improve NOW in our community?

1) limitations of studies due to reliance on diagnostic codes that lack specificity

ACTION ITEM: Be specific in your documentation - premorbid TBI versus repetitive versus NO KNOWN HX.

2) Cognitive protection and recommendations are not universally accepted.

ACTION ITEM: Continue to encourage cognitive-protective habits and lifestyle

3) Policies and guidelines around sports related injuries are inconsistent and unenforced.

ACTION ITEM: Speak up in your community groups about preventing brain injury

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Healthy Brain Tips

Cognition:

1. Exercise the brain daily with puzzles, games, reading, learning, picking up new hobbies, etc
2. Maintain healthy, regular socialization

Nutrition & Supplements:

Follow a Mediterranean diet:

1. Eat a handful of nuts daily (almonds & walnuts are particularly good)
2. Eat fatty fish like salmon or halibut three times per week
3. Eat recipes with curcumin i.e. curry spice, olive oil, whole grains, beans
4. Focus on antioxidant rich foods like berries, grapes, leafy greens, green tea
5. Limit red meat and poultry
6. Take one B-complex Vitamin and 500mg of Vitamin C per day. If Vit D is low, take Vit d3 (consult your primary care doctor first).
7. Limit neuro-toxic substances like alcohol, nicotine, THC, etc

Daily Habits:

1. Treat hypertension for a goal blood pressure of <130/90 mmHg
2. Treat high cholesterol with an LDL goal of <100 mg/dL
3. Maintain a fasting glucose under 100 mg/dl
4. Target body mass index is less than 27
5. Moderate aerobic exercise with pulse >100 beats per minute for 150 minutes per week. Aim for 10,000 steps per day.

Optimize:

1. Hearing - treat if hearing loss is present
2. Mood - Depression and anxiety can significantly impact cognition
3. Sleep - consult your doctor if you have snoring, gasping, or episodes of decreased breathing
4. Dental health - Keep up regular visits with your dentist and good oral hygiene
5. Avoid medications that worsen memory - e.g. Benadryl, Tylenol PM, Ditropan, Ambien, Benzodiazepines

QUESTIONS & ANSWERS

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