Treatment Interventions in Alzheimer's Disease

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1

Learning Objectives

NONPHARMACOLOGICAL TREATMENTS

PHARMCOLOGICAL TREATMENTS

2

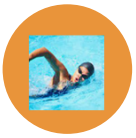
Nonpharmacological Treatments

American Academy of Neurology: Practice Guidelines in Mild Cognitive Impairment[1]

Multi-domain Treatment Approach

Grade B Recommendations

Modification of reversible causes



Aerobic exercise

Future Planning

Treatment of behavioral symptoms

Grade C Recommendations

Cognitive Interventions

Participation in clinical trials

-The most recent practice guidelines written by the American Academy for Mild Cognitive Impairment include the recommendations listed here, which have been endorsed by the Alzheimer's Disease Association

-Unfortunately, no cures are available, so most of our treatment recommendations are Graded B and C non-pharmacological interventions

- The one Grade-A recommendation is informing and prescribing patients off-labeled cholinesterase inhibitors, such as donepezil

-Grade B recommendations include:

1) Modify reversible causes of cognitive impairment, including medication side effects, general medical conditions, sleep disturbance, and depression
2) Aerobic Exercise: Originally, prior studies showed that exercising twice a week over a six-month period could benefit those with MCI; however, studies now endorse that we should engage in thirty-minutes of aerobic exercise of moderate intensity daily
3) Future planning: Though clinicians cannot predict the progression of the disease, we do recommend that families discuss long-term plans early in the course of the disease so that patients can actively participate in discussions that involve advance directives, driving safety, finances, and estates
4) Treatment of behavioral symptoms:
Behavioral/psychiatric symptoms are common in MCI, and it is important to treat these symptoms as they are associated with greater functional impairment[2] and an increased risk of progression from MCI to dementia[3].
Grade C recommendations include:
1) Participation in clinical trials as this provides an opportunity for interested patients to participate in new treatment options that are not available to the general public.
2) Cognitive interventions: There are no specific modalities that have shown to be significantly beneficial, however

patients should have daily cognitive stimulation in an activity of interest.
-Now, from a conglomeration of different non-pharmacological clinical trials, including the landmark study the FINGER Trial, we do endorse a multidomain approach that has shown significant improvements in cognition and delay in progression by implementation of aerobic exercise, Mediterranean diet, and cognitive stimulation and socialization.

"A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomized controlled trial."[4]

- **Study Aim:** Determine the effects of a multidomain approach of diet, exercise, cognitive training, and vascular risk monitoring in preventing cognitive decline in an elderly population at risk for dementia

- **Characteristics of Study Participants:**
  - Aged 60–77 years-old
  - Cognitive status: Normal – Mild Cognitive Impairment
  - CAIDE (Cardiovascular Risk Factors, Aging And Dementia) Risk Score: 6

	Participants with information available	Intervention group (n=591)	Control group (n=599)
Demographic characteristics			
Age at the baseline visit, years	1190	69·5 (4·6)	69·2 (4·7)
Number of women	1190	267/591 (45%)	284/599 (47%)
Education, years	1179	10·0 (3·4)	10·0 (3·4)
Married or cohabiting	1189	436/590 (74%)	454/599 (76%)
Vascular factors			
Systolic blood pressure, mm Hg	1179	140·1 (16·7)	139·8 (15·7)
Diastolic blood pressure, mm Hg	1179	80·5 (9·6)	80·1 (9·3)
Serum total cholesterol, mmol/L	1186	5·2 (1·0)	5·2 (1·0)
Fasting plasma glucose, mmol/L	1188	6·1 (0·8)	6·1 (1·0)
2 h oral glucose tolerance test, mmol/L	1031	7·0 (2·1)	7·0 (2·2)
Body-mass index, kg/m²	1179	28·1 (4·5)	28·1 (4·9)
Lifestyle factors			
Physical activity two or more times per week	1180	410/585 (70%)	427/595 (72%)
Current smokers	1186	58/588 (10%)	48/598 (8%)
Alcohol drinking at least once per week	1182	265/588 (45%)	265/594 (45%)
Fish intake at least twice per week	1183	316/587 (54%)	304/596 (51%)
Daily intake of vegetables	1187	360/589 (61%)	374/598 (63%)
Self-reported medical disorders			
Hypertension	1177	392/585 (67%)	387/592 (65%)
Hypercholesterolaemia	1180	389/587 (66%)	414/593 (70%)
Diabetes	1186	76/586 (13%)	74/594 (12%)
History of myocardial infarction	1184	29/589 (5%)	31/595 (5%)
History of stroke	1181	32/587 (5%)	34/594 (6%)
Cognition*			
NTB total score	1190	-0·03 (0·55)	0·03 (0·59)
Executive functioning	1189	-0·03 (0·66)	0·03 (0·69)
Processing speed	1190	-0·02 (0·78)	0·05 (0·84)
Memory	1190	-0·03 (0·68)	0·03 (0·66)
Mini mental state examination	1187	28·7 (2·0)	28·8 (2·0)

Data are n, n/N (%), or mean (SD). Analysis was done in the modified intention-to-treat population (participants who underwent at least one post-baseline evaluation of the primary efficacy endpoint). NTB=neuropsychological test battery. *Scores on the NTB total score, and on executive functioning, processing speed, and memory are mean values of Z scores of the cognitive tests included in each cognitive outcome, with higher scores suggesting better performance.

Table 1: Baseline characteristics of participants

Risk factor		Points	Total score	Dementia risk
Age	< 47 years	0		
	47-53 years	3		
	> 53 years	4		
Education	> 10 years	0		
	7-9 years	2		
	< 9 years	3		
Sex	Female	0		
	Male	1		
Blood pressure	< 140 mmHg	0		
	> 140 mmHg	2		
Body mass index	< 30 kg/m²	0		
	> 30 kg/m²	2		
Total cholesterol	< 6.5 mmol/L	0		
	> 6.5 mmol/L	2		
Physical activity	Yes	0		
	No	1		
			0-5	1.8%
			6-7	1.9%
			8-9	4.2%
			10-11	7.4%
			12-15	16.4%

Figure 1. CAIDE Risk Scores: Probability of developing dementia based on midlife risk score categories [4]

I will now talk about the landmark study the FINGER Trial

I. Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

-Aim of this study was to determine if a multidomain, non-pharmacological approach of diet, exercise, cognitive training, and vascular risk monitoring could prevent cognitive decline in at-risk elderly people from the general population.

- It was a double-blind, randomized controlled trial that enrolled participants aged 60–77 years-old who had risk factors associated with dementia, which was defined by an accepted CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Risk Score, and had scored within the normal to mild cognitive impairment range. The participants had CAIDE Risk Scores of at least six points, which is calculated by the following risk factors associated with developing dementia: age, sex, education, systolic blood pressure, body-mass index [BMI], total cholesterol, and physical

activity; Please see Table 1.

- Study Design: Double-blind, RCT control trial:
  - Multidomain intervention: Diet, exercise, cognitive training, and vascular risk monitoring
  - Control Group: Health advice
- Primary outcome: Change in cognition as measured through comprehensive neuropsychological test battery (NTB) Z score
- Secondary outcomes:
  - Change in cognition, or Z scores, in executive functioning, processing speed, and memory tests
  - Vascular and lifestyle factors
  - Depressive symptoms: Zung scale
  - Disability: short physical performance battery
- Outcome measures collected at 12 months and 24 months

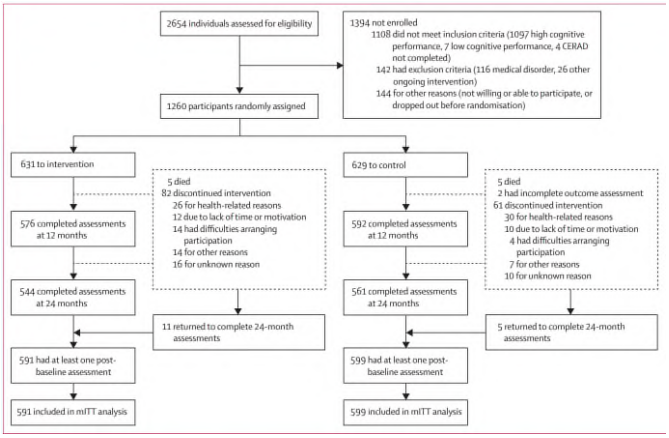
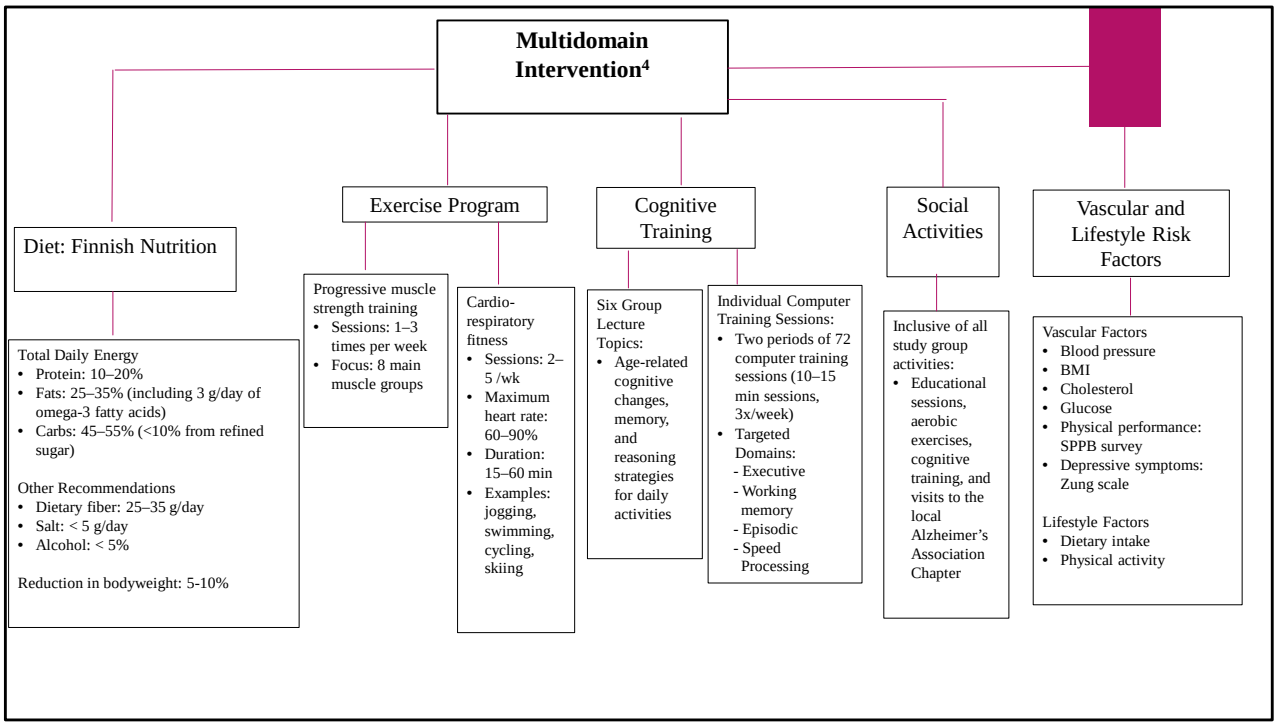


Figure 2. Trial Profile[4]



I. Diet was achieved by consumption of fruit and vegetables, wholegrain cereal products, low-fat milk and meat products; limiting of sucrose intake to less than 50 g/day; use of vegetable margarine and rapeseed oil instead of butter; and, fish consumption at least two portions per week.

II. Exercise program followed the "Modified version of the Exercise Training Study Protocol from *Diet, fitness and metabolic syndrome--the DR's EXTRA study*[5]

-Participants received individually tailored:

a) Progressive muscle strength training, which occurred 1-3 times per week, and it was standardized to focus on the eight main muscle groups.

b) Cardiorespiratory fitness, which included postural stability exercises, was offered individually and in group settings 2–5 times per week. Cardiorespiratory fitness is physical activity of moderate-intensity and corresponds to a maximal heart rate of 60–90 percent, a duration of 15–60 minutes per training session, and the aerobic use of large muscle groups. Examples include: running or jogging, walking or hiking, swimming, skating, bicycling, rowing, cross-country skiing, rope skipping, and various endurance games or sport[6]

-Measurements were collected at baseline and at 1, 3, 6, 9, 12, 18, and 24 months after the start of the exercise intervention

III. Cognitive training consisted of:

-Ten group sessions: Six lectures were on age-related cognitive changes, memory, and reasoning strategies for everyday activities. Four sessions checked the participants' progress from their computer training sessions and included a visit to the local Alzheimer's Association

Chapter.

-Two-periods of 72-individualized computer training sessions. Each period consisted of 72 sessions, with each session lasting 10-15 minutes and occurring 3 times per week either at home or at the study site. The training program included: Executive processes, consisting of updating spatial, letter, and numbers tasks and mental set shifting tasks; Working memory: maintenance tasks; Episodic memory: relational and spatial tasks; and, Mental speed: shape match tasks.

IV. Vascular risk monitoring is management of metabolic and vascular risk factors, and participants vascular and lifestyle risk factors were monitored. Vascular risk factors monitored for inflammatory effects caused by: BP, BMI, cholesterol, glucose, physical performance, and depressive symptoms. Lifestyle factors monitored for fish and vegetable intake, and level of physical activity.

V. Social component included all the group activities in the study, such as the educational sessions, aerobic exercises, cognitive training, and trips to the Alzheimer's Association Chapter.

RESULTS

Primary outcome: Change in cognition as measured through comprehensive neuropsychological test battery (NTB) Z score

Significant beneficial effect of the intervention on primary outcome:

- Estimated mean change in NTB total Z score at 2 years was 0.20 (SE 0.01, SD 0.51) in the intervention group and 0.16 (0.01, 0.51) in the control group
- Mean difference between groups (group × time interaction) in change of NTB total score per year was 0.022 (95%CI 0.002–0.042, p=0.030)
- Improvement in NTB total score after 24 months was 25% higher in the intervention group than in the control group.

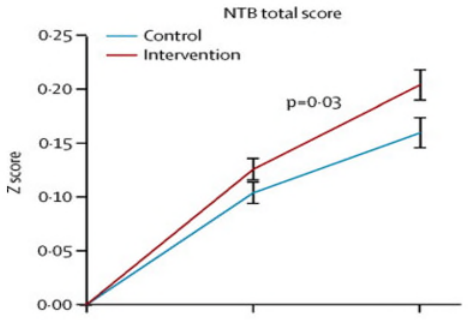


Figure 3. Estimated mean change in cognitive performances during the 2-year, multi-domain study. Significant intervention effect was found on primary outcome of estimated mean change in total NTB Z-score, as improvement in NTB total score was 25% higher in the intervention group compared to the control group after 24 months.[4]

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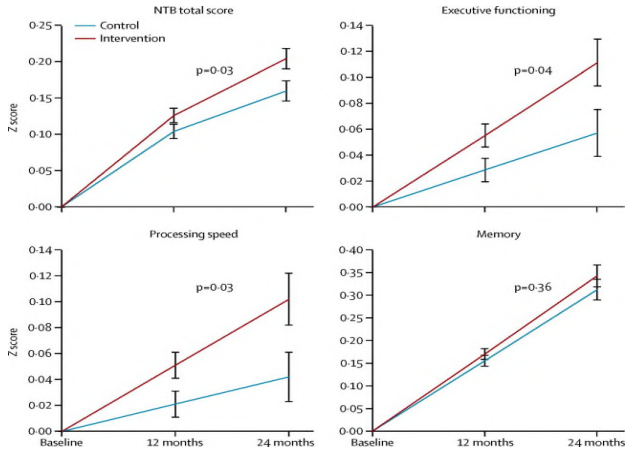
Secondary Outcomes Results[4]



	Odds ratio (95% CI)		p value
	Intervention (n=554)	Control (n=565)	
Overall cognitive decline			
NTB total score	1 (reference)	1·31 (1·01–1·71)	0·04
Cognitive decline per domain			
NTB memory score	1 (reference)	1·23 (0·95–1·60)	0·12
NTB executive functioning score	1 (reference)	1·29 (1·02–1·64)	0·04
NTB processing speed score	1 (reference)	1·35 (1·06–1·71)	0·01

In post-hoc analyses, we defined cognitive decline as decrease in NTB total score (overall decline) and NTB domain scores (decline per domain) between the assessments at baseline and at 24 months. Logistic regression analyses were used to assess risk of cognitive decline in the control group compared with the intervention group. Analyses are based on all participants with data available at both baseline and 24 months. NTB=neuropsychological test battery.

Table 2: **Risk of cognitive decline from baseline to 24 months**

Figure 4. Estimated mean change in cognitive performances during the 2-year, multi-domain study. Significant intervention effect for secondary outcomes of executive functioning (p=0.039) and processing speed (p=0.029) were found, as improvement in executive functioning was 83% higher and processing speed was 150% higher in the intervention group compared to the control group. No significant changes were found in the memory domain. Mixed-model repeated-measures analyses were used to assess between-group differences (group × time interaction) in changes from baseline to the end of the 2-year study in the modified intention-to-treat population.[4]

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Table S4. Other secondary end points from baseline to 24 months, modified intention-to-treat population

	Control	Intervention	Difference between intervention and control groups per year	
	Mean change (SE)	Mean change (SE)	Estimate (95% CI)	P value
Vascular factors				
Body mass index (kg/m2)	-0·33 (0·05)	-0·49 (0·05)	-0·077 (-0·149 - -0·006)	0·02
Systolic blood pressure (mmHg)	-3·37 (0·60)	-3·84 (0·60)	-0·233 (-1·064-0·599)	0·63
Diastolic blood pressure (mmHg)	-1·31 (0·34)	-1·93 (0·35)	-0·306 (-0·785-0·174)	0·22
Serum total cholesterol (mmol/l)	0·00 (0·03)	-0·03 (0·03)	-0·015 (-0·06-0·031)	0·60
Serum HDL cholesterol (mmol/l)	0·02 (0·01)	0·02 (0·01)	0·001 (-0·011-0·012)	0·83
Serum LDL cholesterol (mmol/l)	0·01 (0·03)	-0·02 (0·03)	-0·016 (-0·056-0·025)	0·61
Fasting plasma glucose (mmol/l)	0·12 (0·03)	0·07 (0·03)	-0·024 (-0·065-0·017)	0·11
2 h oral glucose tolerance test (mmol/l)	0·22 (0·08)	0·10 (0·08)	-0·062 (-0·176-0·051)	0·30
Depressive symptoms (Zung scale)	-0·28 (0·25)	-0·68 (0·26)	-0·201 (-0·559-0·157)	0·39
Physical performance (SPPB)*	-0·22 (0·05)	-0·16 (0·05)	0·033 (-0·035-0·101)	0·34
Lifestyle factors				
Fish intake at least twice/week (%)**	+0·8	+11·0	10·2	<0·001
Daily intake of vegetables (%)**	-1·0	+2·9	3·9	0·023
Physical activity 2 or more times/week (%)**	-2·1	+7·0	9·1	<0·001

Figure 5. Other secondary end points from baseline to 24 months, modified intention to treat population. A negative value of the estimate of the between-group differences indicates that the effect is in favor of the intervention group (i.e. a greater decrease in BMI, blood pressure, total cholesterol, LDL, glucose, and depressive symptoms). A positive value of the estimate of the between-group differences indicates the effect is in favor of the intervention group. Mixed-model repeated-measures analyses were used to assess between-group differences (group×time interaction) in the modeled changes from baseline to 24 months based on data from all participants with at least one post-baseline measurement; this was done for all end-points with three available measurements (baseline, 12 months, 24 months). *For SPPB only two measurements were available (baseline and 24 months), and the mean change is adjusted for baseline level; linear regression model was used. **For categorical variables (fish and vegetable intake and physical activity) change in % units between baseline and 24 months is reported, and multi-nominal logistic model was used.[4]

We also noted significant intervention effects after 2 years on BMI, dietary habits, and physical activity.

Conclusion of this study demonstrated that when at-risk participants for dementia were subjected to an intensive multimodal lifestyle intervention for 2 years, there was a significant beneficial intervention effect on global cognition score, as supported by the intervention group scoring 25% higher than that in the control group. This is the first demonstration that cognitive functions can be maintained or improved among older adults. Moreover, the risk for cognitive impairment was 31% higher in the

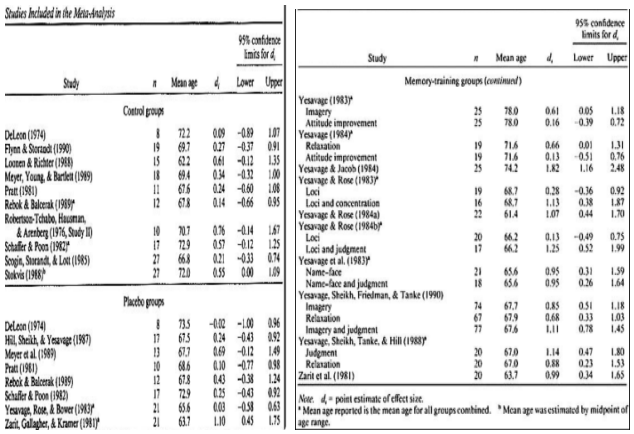
control group compared with the intervention group. These findings indicate that the CAIDE Dementia Risk Score is an extremely valuable tool for detecting individuals at high risk for dementia, who are also likely to benefit from lifestyle interventions and proper management of vascular risk factors.

COGNITIVE TRAINING

"Improving Memory Performance in the Aged Through Mnemonic Training: A Meta-Analytic Study."[7]

- Study Aim: Determine the effectiveness of memory training in participants who are healthy and aged 60 and above
- Study Participant Characteristics:

Table 3. Study participant characteristics.[7]



Studies Included in the Meta-Analysis

Study	*n*	Mean age	d_i	95% confidence limits for d_i Lower	Upper
Control groups					
DeLeon (1974)	8	72.2	0.09	−0.89	1.07
Flynn & Storandt (1990)	19	69.7	0.27	−0.37	0.91
Loosen & Richter (1988)	15	62.2	0.61	−0.12	1.35
Meyer, Young, & Bartlett (1989)	18	69.4	0.34	−0.32	1.00
Pratt (1981)	11	67.6	0.24	−0.60	1.08
Rebok & Balcerak (1989)[a]	12	67.8	0.14	−0.66	0.95
Robertson-Tchabo, Hausman, & Arenberg (1976, Study II)	10	70.7	0.76	−0.14	1.67
Schaffer & Poon (1982)[a]	17	72.9	0.57	−0.12	1.25
Scogin, Storandt, & Lott (1985)	27	66.8	0.21	−0.33	0.74
Stoltzfus (1988)[b]	27	72.0	0.55	0.00	1.09
Placebo groups					
DeLeon (1974)	8	73.5	−0.02	−1.00	0.96
Hill, Sheikh, & Yesavage (1987)	17	67.5	0.24	−0.43	0.92
Meyer et al. (1989)	13	67.7	0.69	−0.12	1.49
Pratt (1981)	10	68.6	0.10	−0.77	0.98
Rebok & Balcerak (1989)	12	67.8	0.43	−0.38	1.24
Schaffer & Poon (1982)	17	72.9	0.25	−0.43	0.92
Yesavage, Rose, & Bower (1983)[a]	21	65.6	0.03	−0.58	0.63
Zarit, Gallagher, & Kramer (1981)[a]	21	63.7	1.10	0.45	1.75

Study	*n*	Mean age	d_i	95% confidence limits for d_i Lower	Upper
Memory-training groups (*continued*)					
Yesavage (1983)[a]					
Imagery	25	78.0	0.61	0.05	1.18
Attitude improvement	25	78.0	0.16	−0.39	0.72
Yesavage (1984)[a]					
Relaxation	19	71.6	0.66	0.01	1.31
Attitude improvement	19	71.6	0.13	−0.51	0.76
Yesavage & Jacob (1984)	25	74.2	1.82	1.16	2.48
Yesavage & Rose (1983)[a]					
Loci	19	68.7	0.28	−0.36	0.92
Loci and concentration	16	68.7	1.13	0.38	1.87
Yesavage & Rose (1984a)	22	61.4	1.07	0.44	1.70
Yesavage & Rose (1984b)[a]					
Loci	20	66.2	0.13	−0.49	0.75
Loci and judgment	17	66.2	1.25	0.52	1.99
Yesavage et al. (1983)[a]					
Name-face	21	65.6	0.95	0.31	1.59
Name-face and judgment	18	65.6	0.95	0.26	1.64
Yesavage, Sheikh, Friedman, & Tanke (1990)					
Imagery	74	67.7	0.85	0.51	1.18
Relaxation	67	67.9	0.68	0.33	1.03
Imagery and judgment	77	67.6	1.11	0.78	1.45
Yesavage, Sheikh, Tanke, & Hill (1988)[a]					
Judgment	20	67.0	1.14	0.47	1.80
Relaxation	20	67.0	0.88	0.23	1.53
Zarit et al. (1981)	20	63.7	0.99	0.34	1.65

Note. d_i = point estimate of effect size.
[a] Mean age reported is the mean age for all groups combined. [b] Mean age was estimated by midpoint of age range.

In this meta-analytic study, its primary aim was to determine the effectiveness of memory training in healthy participants aged 60 and above, along with determining variables that may affect treatment gains. The data comes from 33 studies with a total sample size of 1,539 healthy persons with a mean age of 69.1 who received mnemonic techniques. Each group included in these studies was coded as being either (a) a control group; (b) a placebo group; or (c) a mnemonic-training group, when at least one mnemonic was taught. There were ten control groups, eight placebo groups, and 49 groups for mnemonic training. The placebo treatment received exercises that enhance attention and concentration, relaxation techniques, discussions on personal and memory problems, and information about memory and aging. The sample groups with their characteristics are listed in the above table.

Potential Variables that Can Posttreatment Gains

Table 4. Descriptive Statistics for Continuous Variables Coded for Memory- Training Groups (k=49)[7]

Continuous variable	*M*	*SD*	Min.	Max.
Age (years)	68.99	3.57	61.35	78.00
Pre-to-posttest interval (days)	22.64	23.65	0.08	91.00
Training-to-posttest interval (days)	2.33	2.73	0.00	14.00
No. of sessions	5.76	5.12	1.00	20.00
Duration of sessions (hr)	1.49	0.56	0.33	2.50

Note. Min. = minimum; Max. = maximum.

Table 5. Descriptive Statistics for Variables Coded for Memory Training Groups (k=49)[7]

Dummy variable	Coding	% of 0s	% of 1s
Single vs. multiple mnemonics	Single/multiple	65	35
Pretraining	No/yes	75	25
Memory-related interventions	No/yes	65	35
Real-life tutor vs. manual/tape	Tutor/no tutor	86	14
Group sessions	No/yes	17	83
Publication status	Published/unpublished	22	78
Inclusion of control group	No/yes	70	30
Recruitment for memory training	No/yes	53	47

Table 4 and 5 illustrate variables that might affect pre-to-posttreatment gains, which include age of participants; number of days between pre-and-post testing; number of days between training and post-testing; number of sessions; type of mnemonics; receival of pre-training; receival of memory-related interventions besides mnemonic; receival of instruction either via a real-life tutor or through manuals or tapes; and, whether the sessions occurred in individual or group settings.

Now, pre-training is defined as a non-mnemonic intervention that was provided one or more times before mnemonic training began. These non-mnemonic interventions consisted of relaxation training and visual imagery formation and elaboration training. These pre-trainings were intended to enhance attitudes toward aging.

-Memory-related interventions besides mnemonic trainings consisted of concentration and attention training; external memory techniques; information about memory and aging; group discussions; relaxation training; personal insight techniques; self-monitoring; motivation enhancement; and problem-solving skills.

RESULTS

Primary outcome:

- Change in pre-to-posttest gains on episodic memory tasks were significantly larger in training groups (0.73 SD, k = 49) than in both control (0.38 SD, k = 10) and placebo (0.37 SD, k = 8) groups. [7]

Measure	k	d_+	95% confidence limits for d_+ Lower	Upper	Q_w
Total sample					
Control	10	.38	.16	.60	3.02
Placebo	8	.37	.12	.63	7.91
Memory training	49	.73	.65	.82	86.03
Studies including a control condition[a]					
Control	10	.38	.16	.60	3.02
Memory training	14	.68	.48	.88	10.81
Target versus nontarget measures[b]					
Target	10	.64	.43	.84	7.56
Nontarget	10	.24	.03	.44	5.75

Note. Q_b = 14.03 and 3.99, respectively, for total sample and studies including a control condition, with significant nonhomogeneity at $p < .05$, according to chi-square tests, for both. k = number of effect sizes;

Figure 6. Significance found on primary outcome for increase in scores on episodic memory tasks in training groups.[7]

Figure 6 illustrates primary outcome results showing that change in pre-to-posttest gains on episodic memory tasks were significantly larger in training groups (0.73 SD, k = 49) than in both control (0.38 SD, k = 10) and placebo (0.37 SD, k = 8) groups.

Secondary Outcomes Results:[7]

- Treatment gains/effect sizes in Memory-Training Groups were negatively affected by age of participants and duration of training sessions
- Treatment gains/effect sizes in Memory-Training Groups were positively affected by receival of pre-trainings and additional memory-related interventions that were non-mnemonic and if trainings delivered in group settings
- No differences in treatment gains were obtained as a function of type of mnemonic taught nor the kind of pretraining used

Table 6. Regression of Selected Moderator Variables on Effect Size in Memory-Training Groups [7]

Predictor	B	β	p	R^2 with other predictors
Full model (Q_E = 27.46, df = 35)				
Age	−0.0600	−0.5922	.000	.42
Pre-to-posttest interval	−0.0048	−0.2570	.280	.78
Training-to-posttest interval	−0.0300	−0.1609	.373	.62
No. of sessions	−0.0025	−0.0286	.928	.87
Duration of sessions	−0.4700	−0.5920	.000	.55
Single vs. multiple mnemonics	−0.0395	−0.0529	.787	.66
Pretraining	0.3643	0.4847	.004	.55
Memory-related interventions	0.6609	0.7630	.007	.84
Real-life tutor vs. manual/tape	−0.3207	−0.2760	.412	.89
Group sessions	0.6092	0.4729	.012	.64
Publication status	0.1482	0.1458	.447	.65
Inclusion of control group	−0.1760	−0.1799	.250	.48
Recruitment for memory training	−0.1126	−0.1483	.424	.63
Constant	5.0041		.000	
Restricted model (Q_E = 36.80, df = 43)				
Age	−0.0530	−0.5236	.000	.08
Duration of sessions	−0.4522	−0.5696	.000	.41
Pretraining	0.3187	0.4241	.002	.30
Memory-related interventions	0.1106	0.1277	.373	.39
Group sessions	0.6164	0.4785	.001	.36
Constant	4.4476		.000	

Note. Q_E = statistic for error sum of squares.

Table 7. Effect Sizes as a Function of Type of Mnemonic Taught[7]

Mnemonic	k	d_+	95% confidence limits for d_+ Lower	Upper	Q_W
Method of loci	12	0.80	0.58	1.02	12.78
Name–face	14	0.83	0.69	0.97	23.16*
Pegword	2	0.62	−0.00	1.24	0.01
Imagery (paired associates)	1	0.14	−0.84	1.12	—
Organization	2	0.85	0.38	1.32	0.85
Total (single)	31	0.81	0.70	0.92	39.05

Note. Dashes indicate that homogeneity cannot be computed because there is only one study in the group. For total single mnemonic, Q_B = 2.25, *ns*. k = number of effect sizes; d_+ = mean weighted effect size; Q_W = chi-square statistic for homogeneity within groups; Q_B = chi-square statistic for homogeneity between groups.
* Significant nonhomogeneity at $p < .05$.

Tables 6-7 illustrate secondary outcomes which show that:

- Treatment gains/effect sizes in Memory-Training Groups were negatively affected by age of participants and duration of training sessions

- Treatment gains/effect sizes in Memory-Training Groups were positively affected by receival of pre-trainings and additional memory-related interventions that were non-mnemonic; and, conducting the trainings in group settings

- No differences in treatment gain were obtained as a function of type of mnemonic taught nor the kind of pretraining used. Now, the types of mnemonics taught included: method of loci, nae-face, pegword, imagery, and organization.

Secondary Outcome Results Continued:

- Significant attitude improvement about aging was observed at the end of the study in the Memory-Training Group who received pre-training's.
- No specific type of pre-training was found to be superior

Table 8. Relative Effectiveness of Pre-training as Compared with Attitude Improvement Groups and Effect Size as a Function of Type of PreTraining[7]

Class	k	After pretraining d_+	After pretraining L/U	After pretraining Q_w	After mnemonic training d_+	After mnemonic training L/U	After mnemonic training Q_w
Relative effectiveness							
Pretraining	7	0.33	0.15/0.51	1.79	0.86	0.67/1.05	3.63
Attitude-improvement	2	0.05	−0.37/0.47	0.01	0.19	−0.23/0.60	0.00
Type of pretraining							
Imagery	2	0.34	0.03/0.65	0.00	0.92	0.59/1.24	1.62
Judgment	1	0.49	−0.14/1.12	—	1.14	0.47/1.80	—
Imagery and judgment	1	0.43	0.03/0.83	—	0.75	0.35/1.16	—
Relaxation	3	0.24	−0.06/0.53	0.91	0.71	0.25/1.17	0.54

Note. Dashes indicate that homogeneity cannot be computed because there is only one study in the group. Within-group homogeneity statistics (Q_w) are all nonsignificant at $p < .05$. k = number of effect sizes; d_+ = mean weighted effect size; L/U = lower/upper bound of the 95% confidence interval for d_+; Q_w = chi-square statistic for homogeneity within groups.

Table 8 shows that significant attitude improvement about aging was observed at the end of the study in the Memory-Training Group who received pre-training's. No specific type of pre-training was found to be superior.

Design Your Own Effective Cognitive Training

1) Duration
- Less than 1.5 hours to prevent against fatigue
- Number of Sessions: 6
- Setting: Group Sessions

2) Types of Effective Memory-Related Interventions
- Concentration and attention training
- External memory techniques
- Group discussion
- Relaxation training
- Personal insight techniques
- Self-monitoring
- Motivation enhancement
-Problem-solving skills

3) Techniques to Improve Both Attitude and Episodic Memory Scores
- Relaxation training
- Visual imagery formation and elaboration training

The purpose of reviewing this study was to provide you with ideas on how to create and implement an effective memory-related cognitive intervention based off this studies' findings.

Mnemonic Learning: LOCI Method

- Principle: Strategy of memory enhancement that uses visualizations of familiar spatial environments to enhance the recall of information.

-Synonyms: Memory journey, memory palace, or mind palace technique.

- Method:

- Develop a valid set-list of loci: 18 common nouns

- Memorize this list in four minutes by associating an image with the items to be remembered

- Three minutes are allotted during both immediate and delayed-recall sessions

-Immediate-recall occurs four minutes after participants receive the list

- Delayed-recall occurs five minutes after immediate-recall

- Have participants evaluate their sources of error that include: skipping a locus or failure to develop an image of the item to be remembered

Figure 7. LOCI Method[7]

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Pharmacological Treatments

Symptomatic Medications

- Donepezil
- Memantine

Disease-Modifying Medications

- Aducanumab
- Lecanemab

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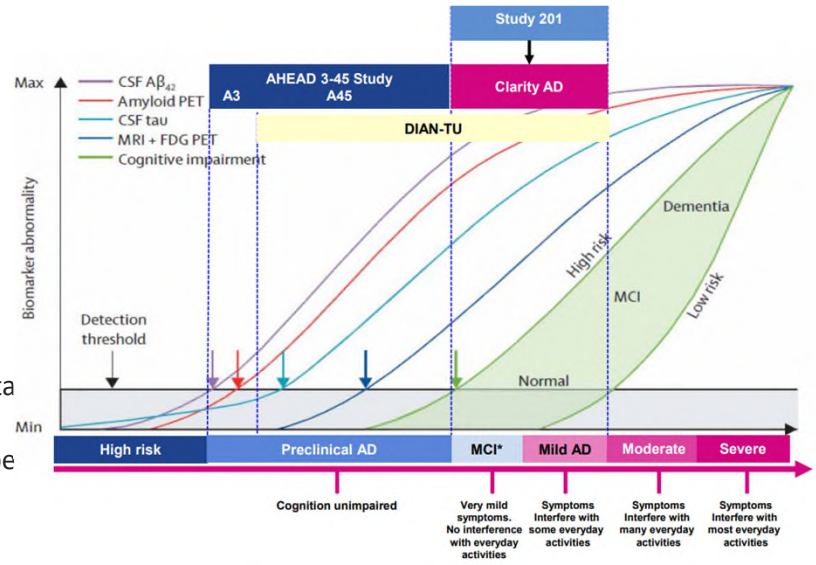
Lecanemab

18

What is Alzheimer's disease?

- Alzheimer's disease (AD) is characterized by the accumulation of misfolded proteins (beta-amyloid and hyperphosphorylated tau) in the brain, causing brain cell loss and inflammation.
- Beta-amyloid accumulates in the brain prior to other changes, including changes in cognition.
- Once AD becomes symptomatic, beta-amyloid is not the only factor contributing to disease progression but continues to be important, especially in early AD.



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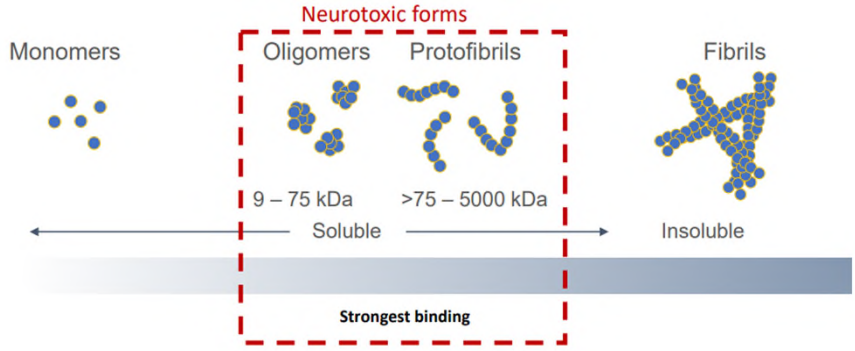
What is lecanemab?

- Lecanemab is a monoclonal antibody raised against a beta-amyloid target that binds both soluble (oligomeric) amyloid as well as amyloid plaques.
- In the earlier studies, the medication was referred to as BAN2401.



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Who qualifies to enroll in the lecanemab treatment program?

- Our criteria will follow the characteristics of patients recruited to the lecanemab clinical trials:
  - 50-90 yo
  - Reasonably healthy and medically stable
  - Evidence for early AD (MMSE > 21, amyloid positive on PET or CSF)
  - No better explanation for cognitive decline (e.g., strokes, etc.)

Inclusion Criteria
Patient has a signed informed consent on file
Patient meets criteria for mild cognitive impairment (MCI) or mild AD dementia
Patient has had MRI scans in the previous 12 months.
Amyloid PET imaging and/or CSF analysis is consistent with Alzheimer's disease.
Mini-Mental State Examination (MMSE) score > 21

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Who should be ruled out for lecanemab treatment program?

Patients with an increased risk of complications are ruled out.

- Patients with unstable medical, neurological, or psychiatric diseases (CTCAE grade > 1 or attending discretion)
- Severe white matter disease: Fazekas 3 or CHS WMH > 7.
- Patients with seizures or strokes in the previous year
- Patients with immunological or active oncological disease (except SCC in situ, BCC and localized prostate cancer).
- Patients with bleeding disorders or on blood thinners
- BMI > 35 or BMI < 17

Exclusion Criteria
Physical, Mental, or Neurological Issue Contribution to Cognitive Impairment
Age Criteria - < 50 y or > 90
MRI Contraindication or MRI Evidence of Neurological Abnormalities
Bleeding Risks and Anticoagulation (Plt < 50k or INR > 1.5)
Unstable medical, oncological or mental health conditions including substance use.
Pregnant or lactating
Body Mass Index (BMI) Range
Immunological Disease or HIV Diagnosis
Seizures or strokes in the last year
Current Use of Specific Immune medications

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What does lecanemab do?

- It binds amyloid, implicated in AD pathology, and facilitates its removal.
- Amyloid is more important to the pathophysiology of AD in the earlier stages of AD.
- The early stages of AD are defined as:
  - Mild cognitive impairment: defined as a decline in cognition without any loss to the patient's abilities to perform their daily tasks.
  - Mild dementia: defined as a stage of dementia when the patient may have difficulty with 'instrumental activities of daily living'.
- Lecanemab showed efficacy in a phase 2 and a phase 3 trial (more on this later).

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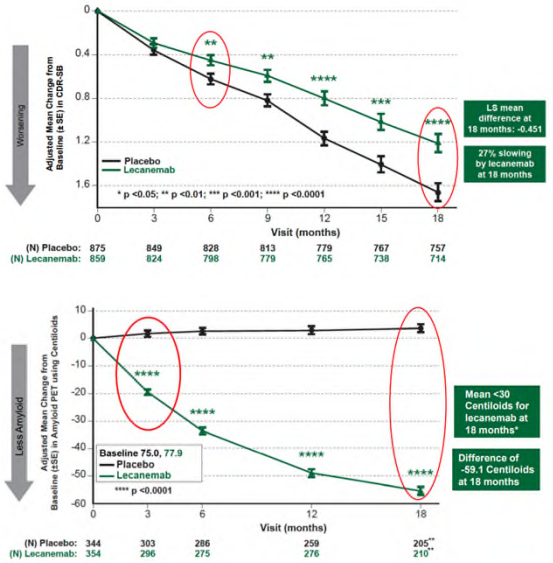
How efficacious is lecanemab therapy?

- Phases 2 and 3 trials showed a modest but significant slowing of the progression of Alzheimer's disease.
- The primary outcome was CDR_SB, which combines subjective cognitive and functional measures and is considered among the best markers of the AD stage.
- All secondary outcomes, including various cognitive and functional scales, were achieved. There was a reduction in tau deposition and a net removal of amyloid during this period.
- The only outcome that moved in the opposite direction was brain volume. We do not yet know how to interpret this.



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What are the drawbacks of lecanemab?

- Lecanemab is costly and requires costly scans for gauging eligibility and for safety surveillance.
  - Medicare will cover one amyloid-PET scan, the costs of the drug, the MRIs, and the administration costs.
  - There may still be up to $10,000 per year in out-of-pocket costs.
  - The manufacturer has some patient assistance programs that may cover some of the medication costs.
- It has to be administered at an infusion center.
  - The present infrastructure may be inadequate for this, given the estimates that 15-20% of all patients with AD may be eligible for the treatment.
  - It reduces the mobility of often otherwise fairly functional elderly people who may want to travel.
- It has a number of significant side effects (more on this later).

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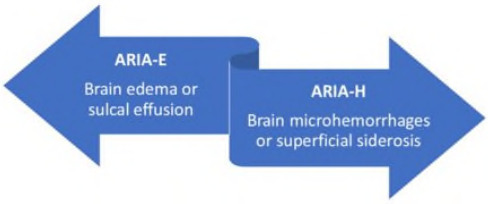
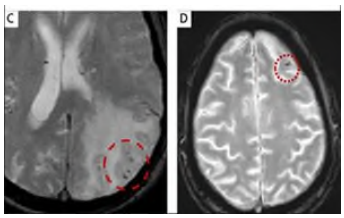
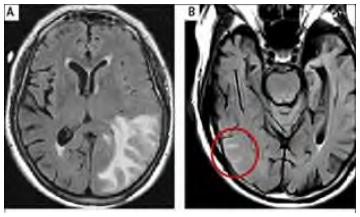
What are the adverse effects of lecanemab?
1- ARIAs







- *Amyloid-related imaging abnormalities* (ARIA) are divided into ARIA-H and ARIA-E:
- 20% of all patients will have ARIA.
- 4% will have symptoms (headaches, visual changes, or confusion).
- Radiologically severe ARIAs occur in 2% of individuals.
- Severe symptoms occur in 0.2% of the population.
- 70–80% will resolve in 3–4 months.
- The risk is increased if the patient is homozygous for APOE4 or on anticoagulants.

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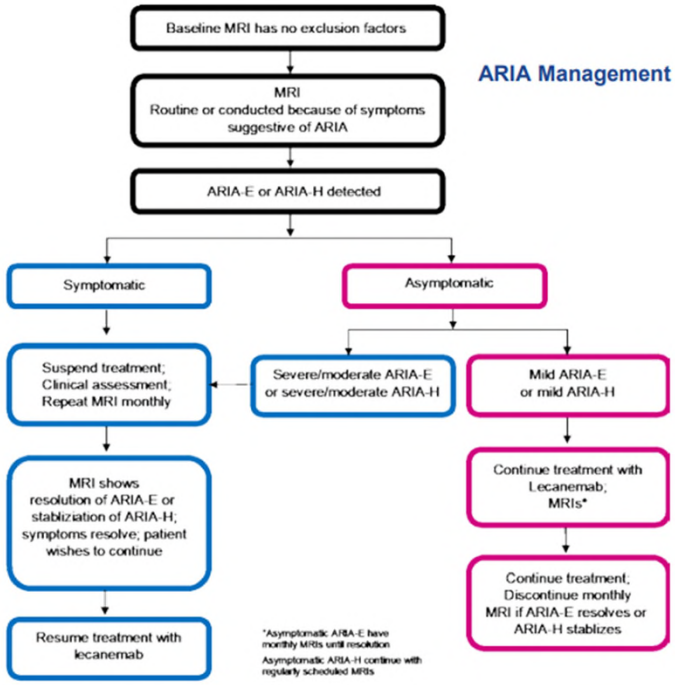
Management of ARIAs



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What are the adverse effects of lecanemab?
2- Infusion reactions

-Infusion reactions fall into two broad categories: anaphylactic and anaphylactoid.
-The former is an acute immune reaction, mostly hypersensitivity types 1 and 2.
-Anaphylactoid reactions are due to the release of cytokines. The symptoms include fever, flu-like symptoms, gastrointestinal upset, blood pressure changes, and oxygen desaturation.

There are additional adverse effects of lecanemab related to infusion reactions.

What are the adverse effects of lecanemab?

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)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
Urinary tract infection	78 (8.7)	82 (9.1)
Covid-19	64 (7.1)	60 (6.7)
Back pain	60 (6.7)	52 (5.8)
Arthralgia	53 (5.9)	62 (6.9)
Superficial siderosis of central nervous system	50 (5.6)	22 (2.5)
Dizziness	49 (5.5)	46 (5.1)
Diarrhea	48 (5.3)	58 (6.5)
Anxiety	45 (5.0)	38 (4.2)

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Safety surveillance

- MRIs to monitor for ARIAs. An additional one before visit 9 for individuals with APOE4 positivity.
- Check for lymphopenia after the first visit.

Ongoing Testing	
Tests	Details
MRI	Baseline and before V5, V7, V9 (for APOE4), V14, V26 and then yearly
Labs	CBC, CMP, INR, PT, Folate, B12, TSH Q6 months
APOE	At baseline
CBC	After the first visit

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Many unknowns

- Length of treatment
- The long-term effects of therapy
- The dose of lecanemab once the PET scan becomes negative
- What potential combination therapies may be helpful?
- What is the significance of the brain shrinkage?

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Questions?

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