

May 4 and 5, 2022

Pharmacologic Treatments

FDA-approved and dietary supplements

Tom Ala, MD

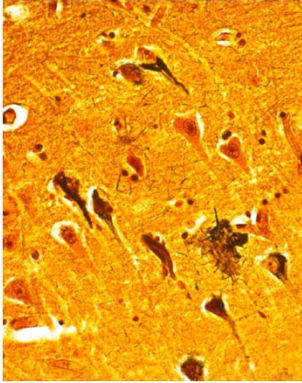


OBJECTIVES TODAY

- What is Alzheimer's disease?
- Explain its disease trajectory.
- Explain how the FDA-approved drugs affect its trajectory.
- Review donepezil, rivastigmine, galantamine, and memantine.
- Review aducanumab and three similar drugs.
 - lecanemab, donanemab, gantenerumab
- Explain what dietary supplements are.

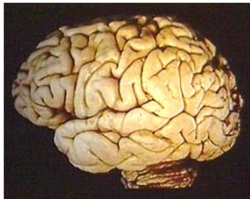
ALZHEIMER'S IS A DEGENERATIVE DISEASE

- The brain cells are dying off.
- The patient's thinking ability fades away.
- The exact cause is uncertain.
- There are no treatments proven to stop or slow the degeneration.



Neurofibrillary tangles
Amyloid plaques
Loss of brain cells
Neurotransmitter imbalances

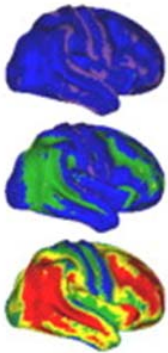
BRAIN ATROPHY



Normal brain



Alzheimer's brain

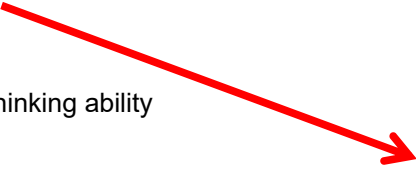


The protein amyloid accumulates in the brain.



PMID: 22108203
Vlassenko. *Biochimica Biophysica Acta* 2012;1822:370


THE TRAJECTORY OF ALZHEIMER'S DISEASE



Thinking ability

Without treatment

MEDICATIONS TO TREAT ALZHEIMER'S



MEDICATIONS TO TREAT ALZHEIMER'S

- Symptomatic drugs
- Disease-modifying drugs

SYMPTOMATIC DRUGS

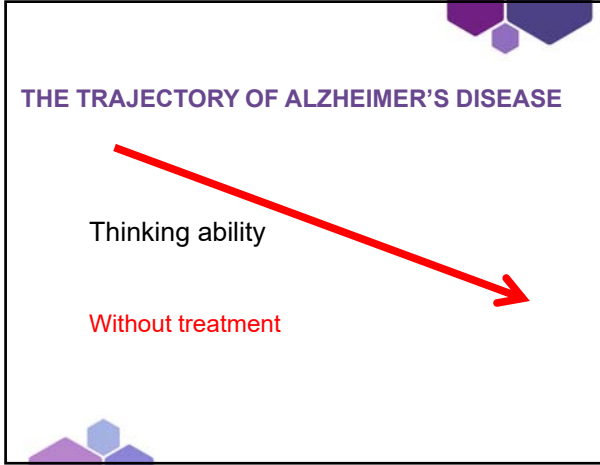
- treat the **symptoms**

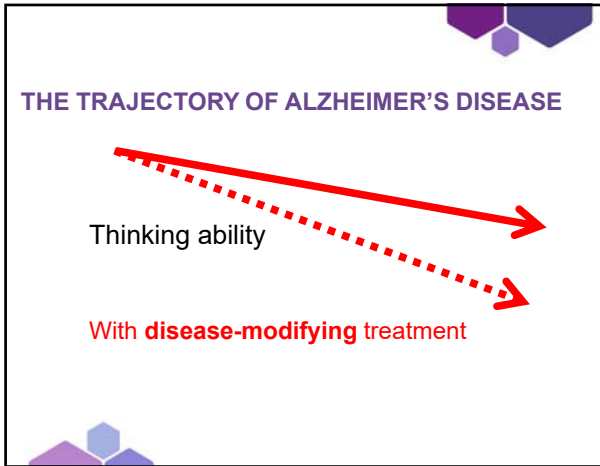
SYMPTOMS OF ALZHEIMER'S

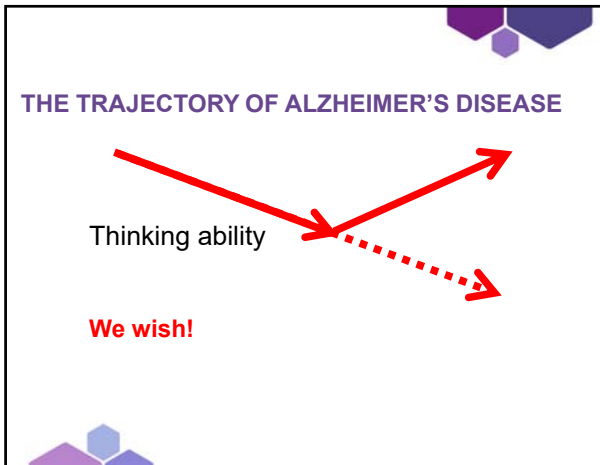
- Memory loss
- Behavioral problems
 - Delusions
 - Hallucinations
 - Anxiety
 - Depression
 - Agitation
 - Apathy
- Disordered sleep
- Etc.

DISEASE-MODIFYING DRUGS

- treat the disease itself







TREATMENT OF ALZHEIMER'S

- Up until 2021, there had been no new FDA-approved drugs to treat AD in the past 18 years.

FDA-APPROVED DRUGS FOR ALZHEIMER'S DISEASE

- | | |
|-----------------------|---|
| donepezil |  |
| rivastigmine |  |
| galantamine |  |
| memantine |  |
| donepezil + memantine |  |

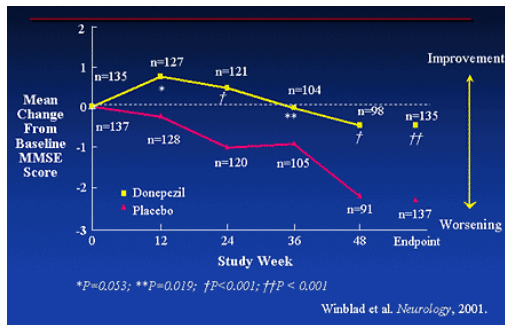
FDA-APPROVED DRUGS FOR ALZHEIMER'S DISEASE

- | | |
|--|---|
| <ul style="list-style-type: none">• donepezil• rivastigmine• galantamine | } increase acetylcholine acetylcholine esterase inhibitors (AChEIs) |
| <ul style="list-style-type: none">• memantine | interferes with glutamate |

FDA-APPROVED DRUGS FOR ALZHEIMER'S

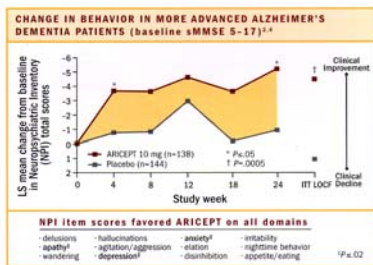
- Alter the balance of neurotransmitters in the brain
 - donepezil (Aricept®)
 - galantamine (Razadyne®)
 - rivastigmine (Exelon®)
 - memantine (Namenda®)

THESE DRUGS CAN IMPROVE COGNITION IN ALZHEIMER'S



PMID: 11502918
Winblad. *Neurology* 2001;14:489

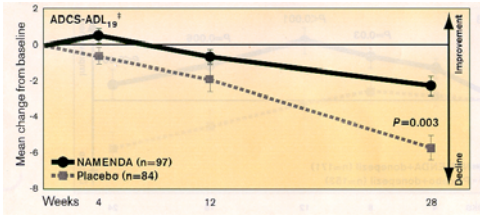
THESE DRUGS CAN IMPROVE BEHAVIOR IN ALZHEIMER'S



Neuropsychiatric Inventory Scale

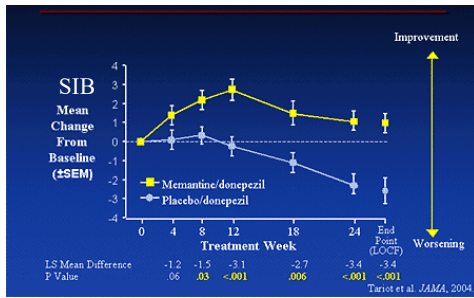
PMID: 11524468
Feldman. *Neurology* 2001;57:613

THESE DRUGS CAN IMPROVE ACTIVITIES OF DAILY LIVING IN ALZHEIMER'S



PMID: 12672860
Reisberg. *NEJM* 2003;348:1333

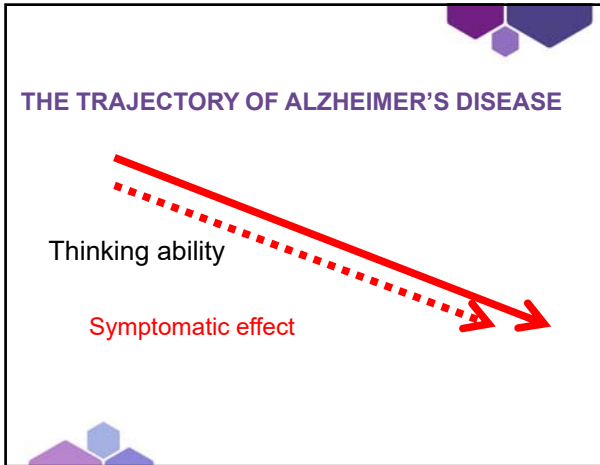
COMBINATION THERAPY

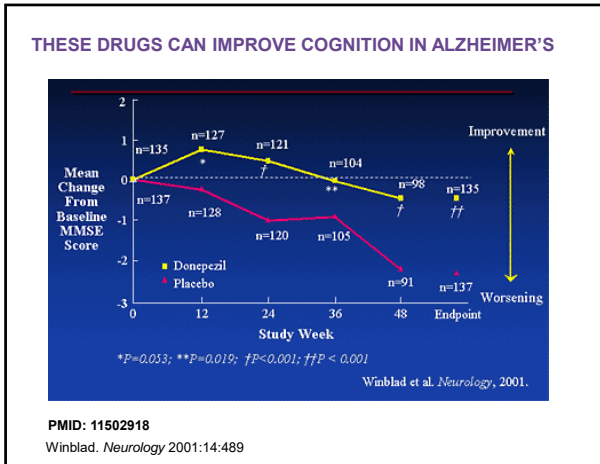


PMID: 14734594
Tariot. *JAMA* 2004;291:317

TREATMENT OF ALZHEIMER'S

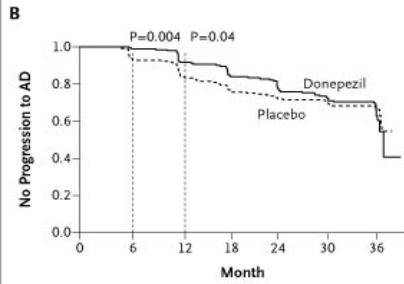
- Up until 2021, there had been no new FDA-approved drugs to treat AD in the past 18 years.
- The drugs that had been approved offer modest *symptomatic* benefit.
- They do not slow or stop the progression of Alzheimer's.





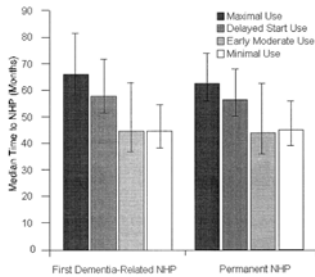
- ### THE BENEFIT OF THESE DRUGS
- The average patient functions a little better.
 - A few patients do significantly better.
 - They delay the conversion to Alzheimer's disease.
 - They help keep the patient out of the nursing home.

DELAYING CONVERSION TO ALZHEIMER'S



PMID: 15829527
Petersen. *NEJM* 2005;352:2379

DELAYING NURSING HOME PLACEMENT



When donepezil was taken at an effective dose for at least 9 to 12 months, conservative estimates of the time gained before NHP were 21.4 months for first dementia-related NHP and 17.5 months for permanent NHP.

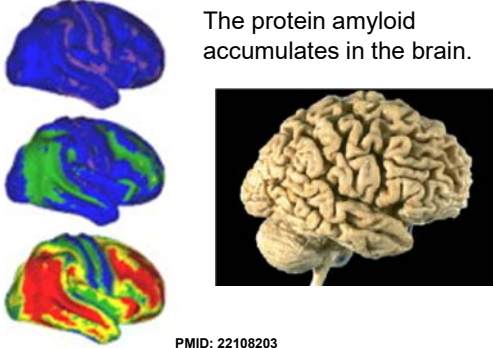
PMID: 12834513
Geldmacher. *JAGS* 2003;51:937

THE BENEFIT OF THESE DRUGS

Like using a crutch if we have severe leg pain...



The protein amyloid accumulates in the brain.

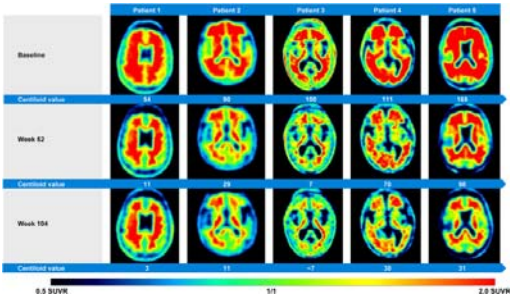


PMID: 22108203
 Viassenko. *Biochimica Biophysica Acta* 2012;1822:370.

DISEASE-MODIFYING DRUGS?

- aducanumab (Aduhelm)
- donanemab
- lecanemab
- gantenerumab

Gantenerumab reduces amyloid- β plaques in patients with prodromal to moderate Alzheimer's disease



PMID: 31831056
 Klein. *Alz Res Ther* 2019;11:101

BUT DOES REMOVAL OF THE AMYLOID PROTEIN AFFECT THE THINKING ABILITY OF THE PATIENT?

Does removal of the amyloid slow the degeneration of the brain cells?



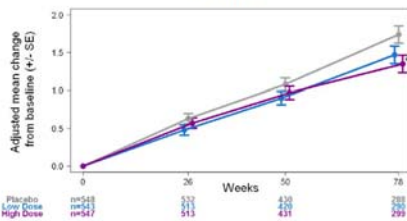
Aducanumab for the Treatment of Alzheimer's Disease: Clinical Overview of Efficacy

Kevin M. Krudys, PhD
Clinical Efficacy Reviewer
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

<https://www.fda.gov/media/143504/download>

ADUCANUMAB


Study 302: Longitudinal Change from Baseline in CDR-SB



www.fda.gov

13

<https://www.fda.gov/media/143504/download>

Evidence of Effectiveness 

- Study 302 provides primary evidence of effectiveness
- Results of Study 103 are appropriately viewed as supportive evidence of the effectiveness of aducanumab
- Study 301 does not contribute to the evidence of effectiveness
 - Analyses allow for independent consideration of Study 302 and do not represent evidence that aducanumab is ineffective

www.fda.gov 35

<https://www.fda.gov/media/143504/download>

ADUCANUMAB

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761178Orig1s000

CLINICAL REVIEW(S)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000MedR_Redacted.pdf

Clinical Review
Kevin Krudys, PhD
BLA 761178
Aduhelm (aducanumab)

FDA CLINICAL REVIEW

| | |
|--|--|
| Application Type | BLA |
| Application Number(s) | 761178 |
| Priority or Standard | Priority |
| Submit Date(s) | 02/20/2020, 05/15/2020, 07/07/2020 |
| Received Date(s) | 07/07/2020 |
| PDUFA Goal Date | 06/07/2021 |
| Division/Office | Division of Neurology 1/Office of Neuroscience |
| Reviewer Name(s) | Kevin Krudys, PhD |
| Review Completion Date | 06/06/2021 |
| Established/Proper Name | aducanumab-avwa |
| (Proposed) Trade Name | Aduhelm |
| Applicant | Biogen Inc. |
| Dosage Form(s) | Solution for injection |
| Applicant Proposed Dosing Regimen(s) | 10 mg/kg as an intravenous infusion every four weeks |
| Applicant Proposed Indication(s)/Population(s) | To delay clinical decline in patients with Alzheimer's disease |
| Recommendation on Regulatory Action | Approval |
| Recommended Indication(s)/Population(s) | Treatment of Alzheimer's disease |

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000MedR_Redacted.pdf

ADUCANUMAB

- Aduhelm™ (brand name).
- Very controversial: many experts disagree about its benefit and whether it should be prescribed.
- Administered by monthly intravenous infusions.
- Very expensive, \$28,000 per year for the drug itself, not including the cost of the infusions.
- At present Medicare will only cover the cost if the patient is in an approved study.
- Patient must have a test that shows that amyloid is accumulating in the brain, either by a spinal tap or an amyloid PET scan.
- Patient must have relatively mild Alzheimer's or only significant memory impairment.
- 20-43% of patients may experience some degree of brain swelling or microhemorrhages.
- Unknown at this time how long the drug should be administered

DISEASE-MODIFYING DRUGS?

- aducanumab (Aduhelm)
- donanemab
- lecanemab
- gantenerumab



HAVE YOU SEEN ANY ADVERTISEMENTS FOR MEMORY PILLS LATELY?

ADS I HAVE SEEN IN THE PAST FEW MONTHS

- Prevagen
- Neuriva
- Focus factor
- Cognimax
- Cognium
- Ceremin
- Neuronol
- Neuro enhancer
- Brain Awake

THERE ARE MANY MORE...

- | | |
|---|--|
| • Procera AVH | • Healthycell Pro |
| • Alpha Brain | • Lumonol |
| • NAD*OVIM | • Brain Awake |
| • Brainjuice | • Brain Armor |
| • Cebria | • brainMD (Brain & Memory Power Boost, Neurovite Plus) |
| • Excelerol | • Clarity Brain Health Formula |
| • NooCube | • Percepta |
| • US Doctor's Clinical Brain Power Advances | • Qualia Mind |
| • Genius Consciousness | • Luein |
| | • Etc, etc, etc |

INGREDIENTS OF THE DIETARY SUPPLEMENTS

- | | |
|---|-------------------------|
| • Apoaquorin | • St. John's Wort |
| • Huperzine A | • L-Glutamine, |
| • Vitamin B Complex | • DMAE Bitartrate |
| • L-Tyrosine | • Green Tea Extract |
| • L-Theanine | • Oolong Tea Extract |
| • Alpha Lipoic Acid | • Caffeine |
| • Guarana | • Vitamin B12 |
| • Ginkgo Biloba | • Acetyl-L-Carnitine |
| • Brahmi (Bacopa monnieri) | • Phosphatidylserine |
| • Bacopa Extract (Bacopa monnieri) | • Creatine |
| • Rhodiola Rosea | • Resveratrol |
| • S-Adenosyl Methionine | • Coffee Cherry Extract |
| • Cat's claw | • Choline |
| • CoQ-10 | • Etc, Etc, Etc |
| • Omega-3 fatty acids (e.g., DHA and EPA) | |

ONE FOR YOU ONE FOR A FRIEND

apoeaquorin
Improves Memory
CHEWABLES
Orange Flavor

apoeaquorin
Improves Memory
CHWABLES
Orange Flavor

**The apoeaquorin
Chewables
Year Supply
Sweepstakes
x2**

Enter for a chance to win a year supply of **apoeaquorin** Chewables for you and a friend!

ENTER NOW

<https://prevagen.com/>

What is apoeaquorin?

apoeaquorin was originally discovered in jellyfish. Apoeaquorin is safe and uniquely supports brain function.*

* Selected as the **#1 Pharmacist Recommended Memory Support Brand in 2021** Pharmacy Times annual survey for third year in a row.

<https://prevagen.com/>

Apoeaquorin is an over-the-counter supplement for healthy brain function and memory improvement.

Based on a clinical study of subgroups of individuals who were cognitively normal or mildly impaired.

<https://prevagen.com/>

Apoaequorin

Madison Memory Study

In a double-blinded, placebo-controlled trial, **apoeq.** demonstrated the ability to improve aspects of cognitive function in subgroups of participants with either normal cognitive aging or very mild impairment, as determined by pre-trial screening. The group of participants taking **apoeq.** improved certain aspects of cognitive function according to computer-based testing. The adults were over 40 years old and took one capsule daily (10 mg) for 90 days.

PMID: 26878676
 Moran. *Adv Mind Body Med* 2016;30:4

<https://prevagen.com/>

Apoaequorin

Study details

A total of 218 participants, ages 40 to 91, with self-reported memory concerns were enrolled in the study. Two hundred and eleven (211) participants completed the study.

Adverse Events
 The Experimental and Control substances were very well tolerated. Two participants experienced adverse events during the study. Each group had a single adverse event, and there were no serious adverse events (SAEs) in the study.

<https://prevagen.com/>

| AD8 test | | Person 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 | NA Don't know |
| 1. Problems with judgment or g. problems making decisions, bad financial decisions, problems with thinking | | | | |
| 2. Less interest in hobbies or duties | | | | |
| 3. Requires the same things over and over (recipes, notes, or statements) | | | | |
| 4. Trouble learning how to use a bank, appliance, or pager (e.g., VCR, computer, microwave, alarm clock) | | | | |
| 5. Forgets current 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 Scahill et al. The AD8, a short informant measure to detect dementia. *Neurology* 2009;68:970-976. Copyright © 2009. The AD8 is a copyrighted trademark of the Alzheimer's Disease Research Center, Washington University, St. Louis, Missouri. All rights reserved.

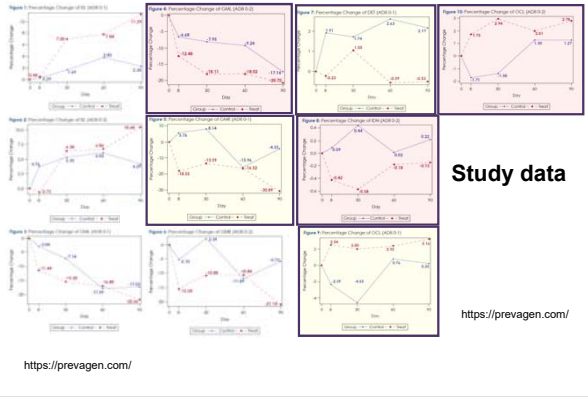
Apoaequorin

Table 1 Cognitive Measurement Tests

| Task | Cognitive Domain Measured |
|---|---------------------------|
| International Shopping List (ISL) | Verbal Learning |
| International Shopping List - Delayed Recall (ISRL) | Memory |
| Orison Maze Learning (OML) | Executive Function |
| Orison Maze Learning - Delayed Recall (OMRL) | Memory |
| Deflection (DET) | Psychomotor Function |
| Identification (IDN) | Attention |
| One Card Learning (OCL) | Visual Learning |
| One Back (ONB) | Working Memory |
| Two Back (TWOB) | Working Memory |

<https://prevagen.com/>

Apoaequorin



Apoaequorin

Study results

Table 3 The Score Differences in the Two Groups Before and After Treatment (AD6 0-1)

| Tasks | Placebo | | Within p value | Apoaequorin | | Within p value | Between Group P value | | | |
|-------|---------------|---------------|----------------|---------------|---------------|----------------|-----------------------|---------|--------------|---------|
| | Day 0 | Day 190 | | Day 0 | Day 190 | | Group | Time | Group x Time | Base |
| IRL | 24.62 ± 3.499 | 25.19 ± 5.163 | 0.373 | 24.49 ± 6.162 | 27.25 ± 5.106 | 0.002* | 0.125 | 0.040* | 0.279 | <0.001* |
| SRL | 8.208 ± 2.449 | 8.904 ± 2.947 | 0.030* | 8.702 ± 2.654 | 9.277 ± 2.614 | 0.091 | 0.704 | 0.134 | 0.897 | <0.001* |
| GML | 61.83 ± 21.54 | 51.00 ± 21.54 | 0.003* | 57.64 ± 18.97 | 44.58 ± 13.69 | <0.0001* | 0.103 | <0.001* | 0.491 | <0.001* |
| GMF | 9.208 ± 4.211 | 8.809 ± 5.182 | 0.296 | 9.324 ± 4.870 | 6.444 ± 3.891 | 0.000* | 0.011* | 0.065 | 0.076 | <0.001* |
| DET | 2.503 ± 0.064 | 2.557 ± 0.096 | 0.009* | 2.543 ± 0.095 | 2.530 ± 0.082 | 0.561 | 0.015* | 0.146 | 0.021* | <0.001* |
| IDN | 2.733 ± 0.066 | 2.727 ± 0.039 | 0.945 | 2.720 ± 0.068 | 2.723 ± 0.039 | 0.854 | 0.246 | 0.979 | 0.460 | <0.001* |
| OCL | 1.014 ± 0.103 | 1.018 ± 0.119 | 0.836 | 1.017 ± 0.103 | 1.049 ± 0.093 | 0.057 | 0.010* | 0.330 | 0.193 | <0.001* |
| ONB | 1.313 ± 0.145 | 1.404 ± 0.160 | 0.019* | 1.356 ± 0.156 | 1.397 ± 0.145 | 0.214 | 0.220 | 0.013* | 0.388 | <0.001* |
| TWOB | 1.220 ± 0.168 | 1.321 ± 0.157 | 0.021 | 1.244 ± 0.148 | 1.312 ± 0.134 | 0.019* | 0.747 | 0.004* | 0.474 | <0.001* |

Notes on Table 3
* Time is the number of visits since the initial Baseline visit and was coded as a categorical variable.

<https://prevagen.com/>

Apoaequorin

Study results

Table 4 The Score Differences in the Two Groups Before and After Treatment (AD6 0-2)

| Tasks | Placebo | | Within p value | Apoaequorin | | Within p value | Between Group P value | | | |
|-------|---------------|---------------|----------------|---------------|---------------|----------------|-----------------------|---------|--------------|---------|
| | Day 0 | Day 190 | | Day 0 | Day 190 | | Group | Time | Group x Time | Base |
| IRL | 24.45 ± 4.075 | 25.30 ± 5.474 | 0.090 | 25.01 ± 5.454 | 27.48 ± 4.634 | <0.0001* | 0.254 | 0.000* | 0.039* | <0.001* |
| SRL | 8.275 ± 2.385 | 9.090 ± 2.998 | 0.012* | 8.762 ± 2.334 | 9.462 ± 2.400 | 0.002* | 0.465 | 0.012* | 0.703 | <0.001* |
| GML | 40.37 ± 21.08 | 50.02 ± 22.43 | 0.000* | 38.39 ± 23.45 | 46.46 ± 18.78 | <0.0001* | 0.040* | <0.001* | 0.463 | <0.001* |
| GMF | 9.400 ± 5.424 | 8.861 ± 5.938 | 0.229 | 8.898 ± 4.470 | 7.017 ± 4.722 | 0.001* | 0.107 | 0.092 | 0.347 | <0.001* |
| DET | 2.500 ± 0.081 | 2.537 ± 0.099 | 0.045* | 2.534 ± 0.104 | 2.533 ± 0.100 | 0.675 | 0.250 | 0.165 | 0.345 | <0.001* |
| IDN | 2.726 ± 0.068 | 2.732 ± 0.064 | 0.367 | 2.729 ± 0.072 | 2.725 ± 0.081 | 0.815 | 0.039* | 0.780 | 0.108 | <0.001* |
| OCL | 1.005 ± 0.113 | 1.018 ± 0.121 | 0.292 | 1.013 ± 0.107 | 1.041 ± 0.100 | 0.046* | 0.020* | 0.437 | 0.357 | <0.001* |
| ONB | 1.298 ± 0.185 | 1.421 ± 0.156 | <0.001* | 1.356 ± 0.163 | 1.397 ± 0.140 | 0.061 | 0.944 | 0.000* | 0.223 | <0.001* |
| TWOB | 1.223 ± 0.164 | 1.317 ± 0.175 | 0.002* | 1.251 ± 0.114 | 1.302 ± 0.127 | 0.028* | 0.934 | 0.000* | 0.290 | <0.001* |

Notes on Table 4
* Time is the number of visits since the initial Baseline visit and was coded as a categorical variable.

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CONCLUSION

apoequorin demonstrated the ability to improve aspects of cognitive function in older participants with either normal cognitive aging or very mild impairment, as determined by AD8 screening.

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HMMMM....

This looks half-way decent!

LEGAL ACTIONS – In the 2019 FDA letter, the agency warned the manufacturer of **apoequorin** about making false therapeutic claims. In November 2020, a nationwide class-action settlement required the company to refund consumers who had purchased the product and change misleading marketing claims. A lawsuit has been filed against Quincy Bioscience by the Federal Trade Commission and the New York State Attorney General that alleges the company made false claims that their product improves memory and brain functioning.

CONCLUSION – There is no acceptable evidence that apoequorin is effective for memory improvement. Patients should be advised not to take it.

PMID: 35085208
Med Lett Drugs Ther 2021;63:175

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- There is no acceptable evidence that apoaequorin is effective for memory improvement. Patients should be advised not to take it.

PMID: 35085208
 Med Lett Drugs Ther 2021;63:175

DIFFERENCE BETWEEN FDA-APPROVED DRUGS AND DIETARY SUPPLEMENTS.

- In order for a drug to be approved by the FDA, it must be proven to be safe and effective.
 - data on the drug's effects have been reviewed by the Center for Drug Evaluation and Research, and the drug is determined to provide benefits that outweigh its known and potential risks for the intended population.
- Unlike new drugs, dietary supplements are not reviewed and approved by the FDA based on their safety and effectiveness.
- When public health concerns arise about a dietary supplement after the product is on the market, the FDA evaluates the product's safety through research and adverse event monitoring.
- Promotional information about the supplement must include the phrase, "These statements have not been evaluated by the FDA and are not intended to diagnose, treat, cure or prevent any disease or health condition."

<https://www.fda.gov/consumers/consumer-updates/it-really-fda-approved>

What is apoaequorin?

apoequorin was originally discovered in jellyfish. Apoaequorin is safe and uniquely supports brain function.*

* Selected as the #1 Pharmacist Recommended Memory Support Brand in 2021 Pharmacy Times annual survey for third year in a row.

These statements have not been evaluated by the FDA and are not intended to diagnose, treat, cure or prevent any disease or health condition

<https://prevagen.com/>



RISK FREE - 90 DAYS - 100% MONEY BACK GUARANTEE
 Money Back Plan: 90 Day, 100% Money Back Guarantee
 "We don't see anything wrong with this product." - FDA



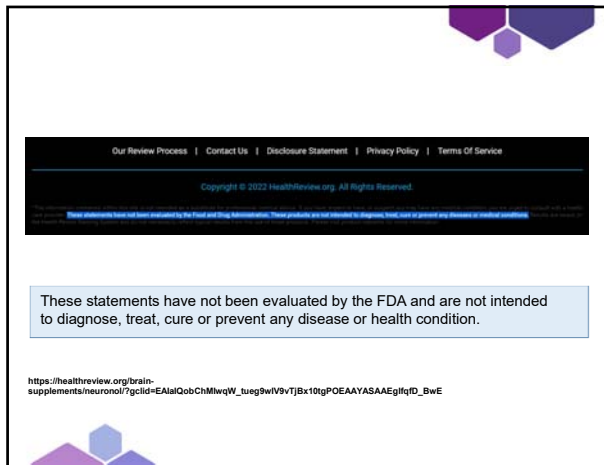

Citations

1. <https://www.fda.gov/oc/opoia/foia/2015/2015-0101>
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https://healthreview.org/brain-supplements/neuronol7gclid=EAlaQobChMwqW_tueg9wIV9VTjBx10tGPOEAYASAAEgIfqD_BwE



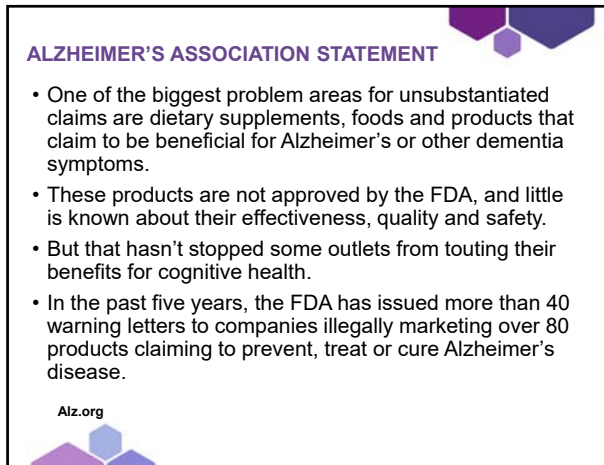
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These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease or health condition.

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ALZHEIMER'S ASSOCIATION STATEMENT

- One of the biggest problem areas for unsubstantiated claims are dietary supplements, foods and products that claim to be beneficial for Alzheimer's or other dementia symptoms.
- These products are not approved by the FDA, and little is known about their effectiveness, quality and safety.
- But that hasn't stopped some outlets from touting their benefits for cognitive health.
- In the past five years, the FDA has issued more than 40 warning letters to companies illegally marketing over 80 products claiming to prevent, treat or cure Alzheimer's disease.

Alz.org

DON'T FALL FOR FALSE HEALTH CLAIMS
YOU DON'T NEED TO BE A SCIENTIST TO THINK
LIKE ONE — USE THESE TIPS TO NAVIGATE THE
CONFUSING WORLD OF RESEARCH

- Be savvy
 - review research news with a critical eye.
- Supplement your awareness
 - Talk to your doctor.
 - Look for FDA-approved treatments.
- Be your own advocate
 - "The most important thing you can do is to demand evidence rigorously backed in science"
- Think like a scientist
 - Is there sufficient evidence?
 - Who conducted the research?
 - How was the research conducted?
 - Does it sound too good to be true?
 - Where was the research announced?

Alz.org

BOTTOM LINE...

- Not recommended.
- But use your judgment; it's up to you.
 - Can you afford it?
 - Is it OK with your primary MD?
 - No side effects?
