Is Prevagen the ‘silver bullet’ supplement to treat Alzheimer’s disease? Distinguishing hope from hype in the battle against cognitive decline

The avalanche of TV ads for Prevagen that coincided with my reaching Medicare age has inspired me to investigate what’s coming for Alzheimer’s disease (AD) – real treatments. Prevagen is not that.

Deceptive advertising

The scenes, unending lest they immediately vanish from the viewer’s disintegrating memory, show gorgeous older folks, especially couples, enjoying life and claiming that Prevagen keeps them thinking clearly, implying that they wouldn’t have otherwise. A banner on the lower right proclaims “Prevagen improves memory.” Yet there’s no evidence that this is in fact true.

Credit: Prevagen

Prevagen pitches don’t mention the class action lawsuit against Quincy Bioscience that was settled in 2020. Customers who had their receipt could get $70 back, and those who didn’t, a generous $12. The red flag? Those claims to improve memory.

Prevagen, a “brain health supplement” and not a drug, falls into that regulatory backwater for products

skirting rigorous clinical trials. The settlement demanded the company stop the claims, but “Buy Prevagen® Brain Health & Memory Improvement Supplements” appears instantly on Google. The asterisk above “Supplements” is the standard disclaimer: “These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.”

Since the label doesn’t explicitly say “dementia,” claiming to quell normal decline is apparently kosher. So what, exactly, is in Prevagen?

The main ingredient, apoaequorin, is a protein that a jellyfish, Aequorea victoria, makes and that emits blue light when it binds calcium. And age-related mental decline can involve a glitch in calcium regulation! Vitamin D and calcium are included in the recipe for Prevagen.

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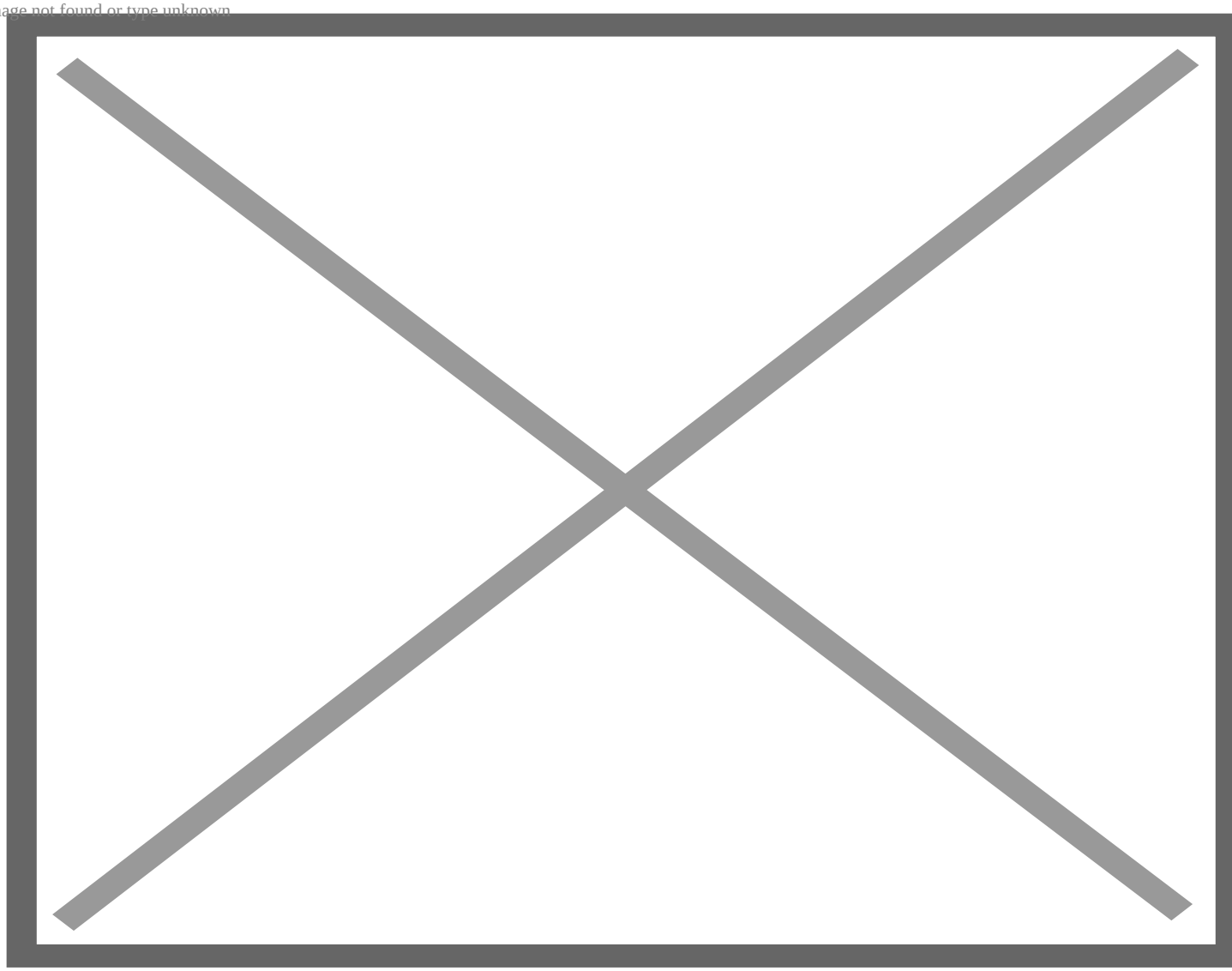


Credit: Virunja/Shutterstock

What's more, jellyfish apoaequorin resembles a human calcium-binding protein. So, wouldn't it counter the inevitable mental decline that is part of my encroaching decrepitude? Of course that can't be known without a randomized, controlled clinical trial, the gold standard for evaluating safety and efficacy.

So I searched Clinicaltrials.gov for apoaequorin and dementia and got zero. Ditto for Alzheimer's. But where's the incentive to do a clinical trial if a company can market it as a supplement and get services like Spectrum to blast ads out to seniors worrying about their forgetfulness? The ads are not only deceiving but, for a disease like Alzheimer's, cruel.

Here's a look at a few possible future treatments. Real ones. It's always important to look at primary sources – the medical journals that publish clinical trial findings. They tell the truth.

Monoclonal antibody drugs

Prevagen was on my mind when I saw "Alzheimer's Drugs Show Promise" in the latest AARP Bulletin, mostly about Eli Lilly's drug candidate donanemab.

"The 18-month study, which followed 272 people whose brain scans showed Alzheimer's, found that patients who took donanemab had a 32% slower rate of decline than those who received a placebo," read the news item, followed by the requisite quote from an expert: "It's very encouraging because this is the first time a drug of its kind has had positive results in early-stage trials." The drug cleared away some amyloid (one of two proteins that build up in the brain in excess) and "slowed the symptoms of the disease in those patients."

Sounds great! But looking at the report evaluating the drug in The New England Journal of Medicine reveals AARP's take to be a tad overoptimistic.

The drug slowed a measurement of disease progression called the iADRS scale. Scores range from 0 to 144, and those among people taking the drug were on average 3.2 points lower than those given placebo – that is, progression at this early point is very slightly slower. But how much of a difference is important clinically? In terms of day-to-day functioning and symptoms? That hasn't been established, the report claims.

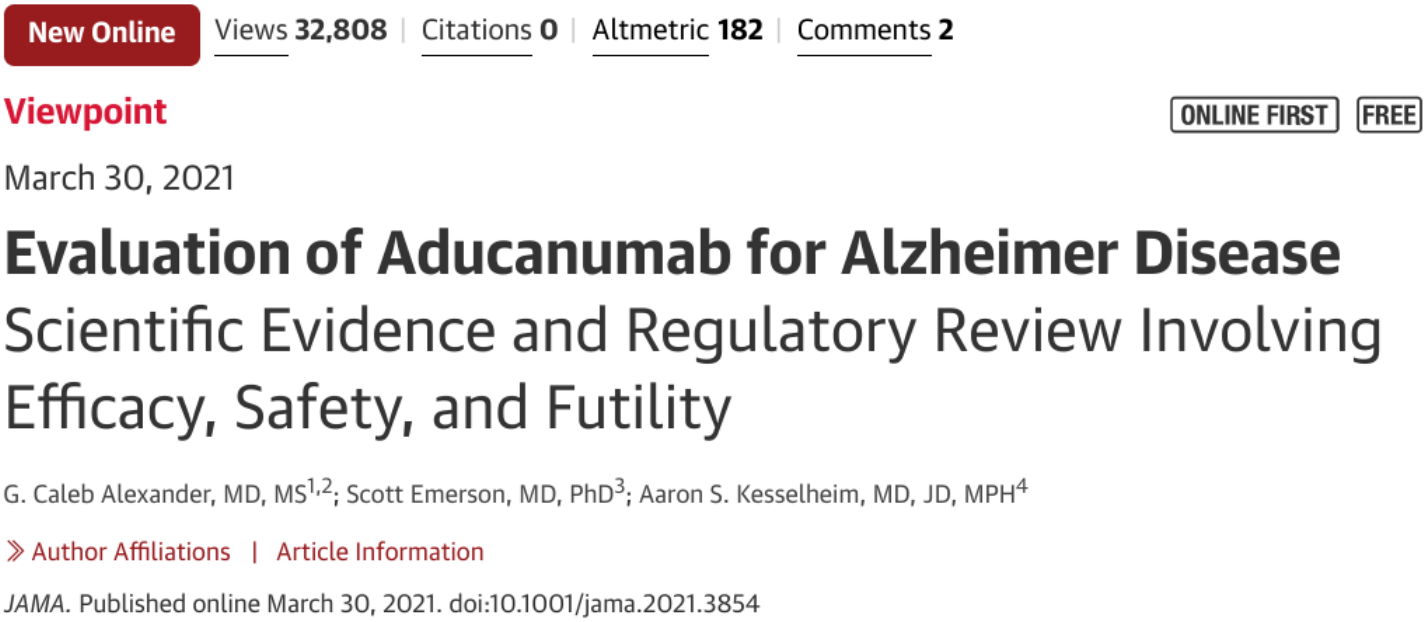
Even though amyloid plaque level decreased compared to placebo, again the findings didn't support a change in clinical status. Nor did analysis of secondary outcomes show efficacy: rating scales for clinical dementia, cognition, activities of daily living, and mental state, as well as buildup of amyloid and tau proteins on PET scans.

Getting picky, the NEJM paper lists 257 participants, not the 272 AARP cites, and states that few of them were non-White. I'll bet more seniors are reading the AARP Bulletin than the NEJM – and getting a misleadingly rosy view.

Like donanemab, aducanumab, from Biogen, is a monoclonal antibody (hence the "mab" ending). That's a single type of antibody that binds a specific molecule, like amyloid, giving off a detectable signal (if a

diagnostic) or dismantling it (if a therapeutic).

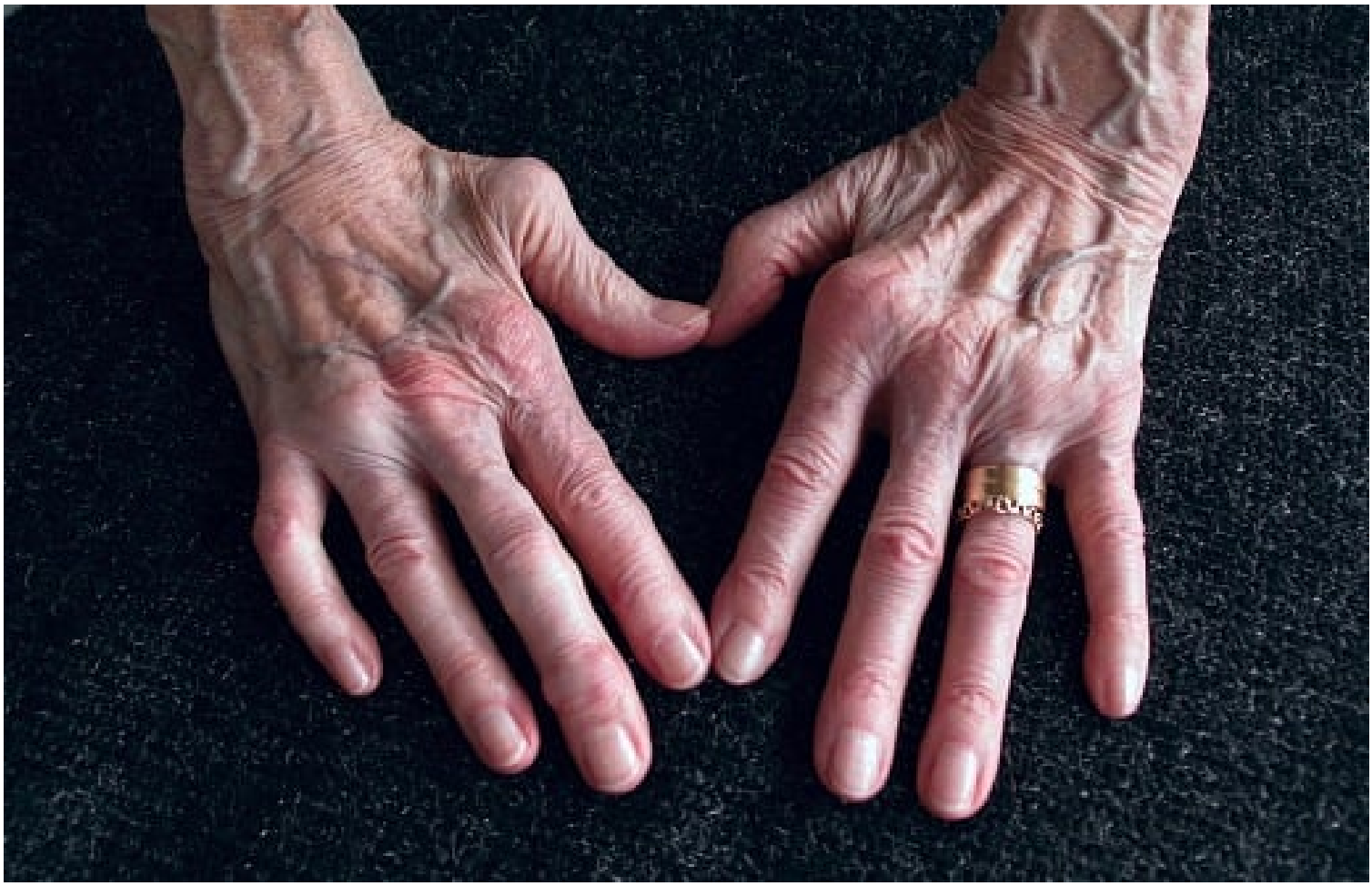
The regulatory history behind aducanumab is complex, with approval recently delayed for FDA reconsideration in June. The headline of this article in JAMA says it all: Evaluation of Aducanumab for Alzheimer Disease: Scientific Evidence and Regulatory Review Involving Efficacy, Safety, and Futility.



The drug had shown safety, but not efficacy, in early trials called ENGAGE and EMERGE that differed by dosage. But phase 3 trials didn't reveal efficacy. However, parsing participants by subtype might reveal that the drug works for some people – hence the delay and not outright rejection of the drug. Only a fraction of AD cases, for example, are inherited, and these people might respond differently.

A repurposed drug

People with rheumatoid arthritis (RA), whose joints are wracked with inflammation, don't get Alzheimer's. Could their excess levels of an immune system protein protect their brains from amyloid accumulation?



The protein is granulocyte-macrophage colony stimulating factor (GM-CSF), used for many years to boost white blood cell counts after cancer therapies. It also mops up debris, including amyloid. In addition, GM-CSF “reduced amyloid deposition in Alzheimer’s mice and returned their poor memory to normal after a few weeks of treatment,” said Huntington Potter, PhD, part of a team at the University of Colorado Alzheimer’s and Cognition Center in Denver that tested the drug sargramostim (aka Leukine), a version of GM-CSF, against AD. Results of their clinical trial appeared recently in Alzheimer’s & Dementia: Translational Research and Clinical Interventions.

The randomized, placebo-controlled clinical trial enrolled 40 patients with mild-to-moderate AD who received the drug subcutaneously 5 days a week for 3 weeks, and were evaluated for 109 days. A scale of 13 tasks assessed cognition, memory, language, and attention, in addition to neuroimaging and biomarkers.

News coverage was, again, inappropriately rosy, taking the lead from the study news release full of quotes claiming demonstration of safety and improvement in memory and biomarkers, including brain amyloid, tangles, and neurodegeneration. But many reporters don’t delve any farther than the news release. So HealthDay wrote: “A drug with a 30-year track record as an effective tool for fighting cancer

may significantly improve memory and thinking in patients with mild-to-moderate Alzheimer's disease, new research suggests."

Well, not exactly. Isn't that a leap from a study done on 40 people for a few weeks? Like the AARP Bulletin, the tone is one of overoptimism.

Wearable technology to catch AD early

The future of AD treatments might depend on early diagnosis made possible by wearable technology, picking up physiological cues 10 to 15 years before the first signs and symptoms. The global Early Detection of Neurodegenerative Diseases (EDoN) initiative "aims to use smartphone apps and wearables like smart watches and headbands to collect digital data on a range of measures including sleep, neural activity, cognition, speech and language, gait, heart rate, fine motor skills and physical activity."

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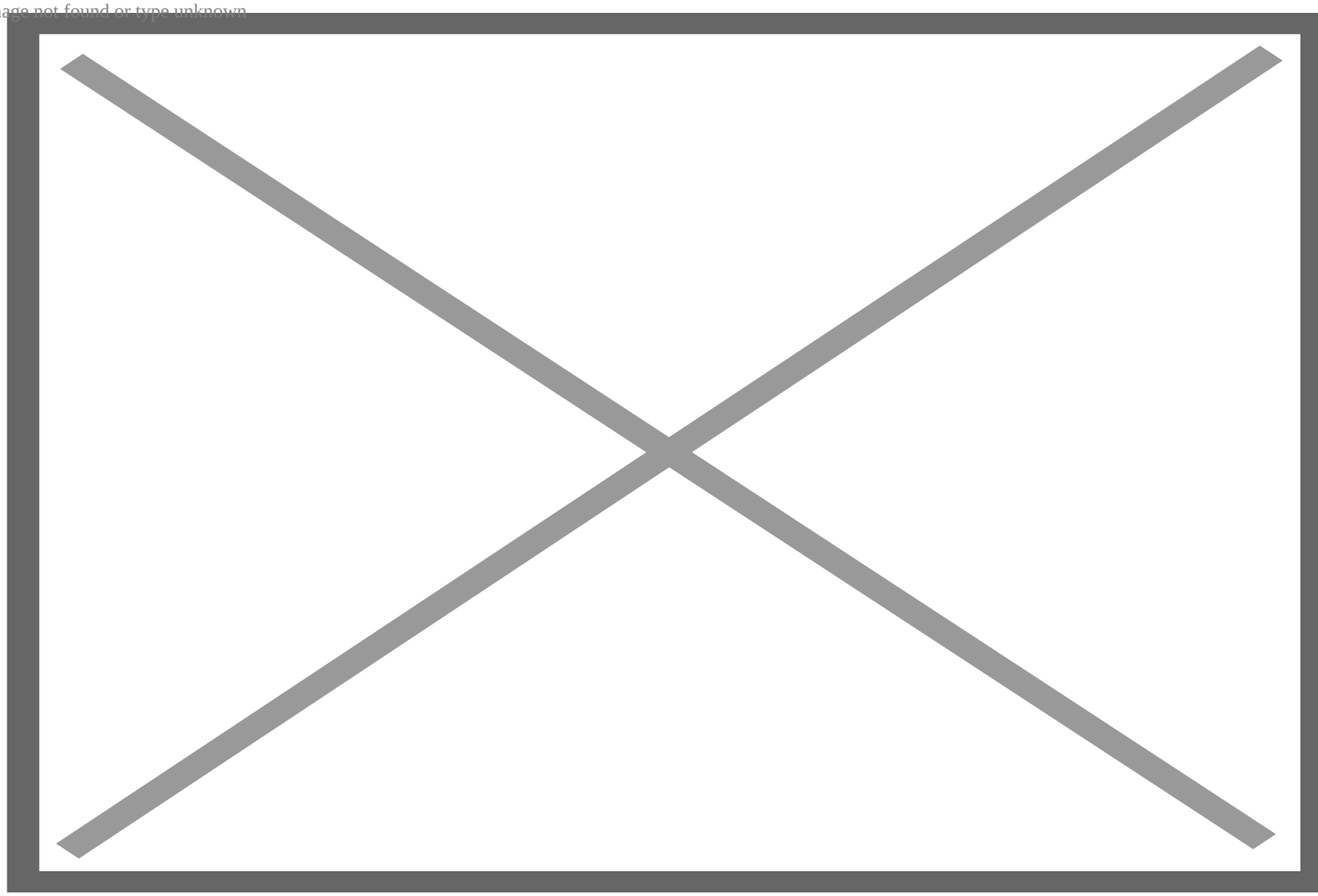

Credit: Counterpoint

The goal: to feed digital and clinical data, collected retrospectively and prospectively, into machine learning models to pick up subtle 'fingerprints' that foretell disease. EDoN will amass data from up to

50,000 people in research studies globally and then test a final digital device in up to one million healthy people.

Imagine getting a decade heads-up for Alzheimer's! Said Jesse Mez, MD, Associate Director of the Alzheimer's Disease Center Clinical Core at Boston University:

> The diseases that cause dementia can start in midlife, but we currently don't have inexpensive and non-invasive methods to detect this early disease. Digital technologies like smartphones and wearables could provide a low cost, easy-to-use way to pick up some of the very subtle early changes in diseases like Alzheimer's. The findings of this study could really transform the way we tackle these diseases in the future.

Good news for old drugs

Another recent study shows drugs already recommended for AD, the cholinesterase inhibitors, slow cognitive decline and lower mortality for up to five years following diagnosis. The work is from the Karolinska Institute and published in Neurology.

Acetylcholine is a neurotransmitter that functions in memory, attention, and concentration. In AD, an enzyme (acetylcholinesterase) breaks the neurotransmitter down too quickly; inhibiting the enzyme keeps more of the needed molecule in brain synapses, facilitating neuron-to-neuron crosstalk. Three such drugs are galantamine, donepezil, and rivastigmine.

Studies so far have followed too few patients for too little time to demonstrate efficacy, but the Swedish investigation compared 11,652 patients treated with the drugs to 5,826 untreated patients, for five years from diagnosis. The drugs were associated with slower cognitive decline and 27% lower mortality.

A tip from a rare disease

Sometimes treatments for common conditions follow from success in treating rare diseases, such as the statins. In hereditary cystatin C amyloid angiopathy (HCCAA), amyloid gloms onto the insides of blood vessels in the brain, somewhat like in AD. HCCAA causes strokes, brain bleeds, and dementia, leading to death in early adulthood.

Researchers from Children's Hospital of Philadelphia suggest in Nature Communications that a widely-used nutritional supplement that lowers risk of fatal stroke in HCCAA by blocking amyloid formation may also block or break up amyloid plaque associated with dementia, possibly including Alzheimer's.

The team looked at a supplement called N-acetyl-cysteine (NAC), which is already used to break up

mucus in the lungs and to protect the liver from acetaminophen overdose. NAC applied to pieces of skin from patients with the rare disease dismantled the amyloid protein deposits.

The supplement may turn out to be a lifesaver for people with HCCAA – and perhaps a new candidate to slow amyloid buildup in AD.

Coda

It's intriguing that this post began by criticizing a supplement, and ends with suggesting that one might in fact hold promise to help counter the amyloid gunk of Alzheimer's. The distinction is science.

The researchers writing in Nature Communications are providing the idea, the hypothesis, to form the basis of a randomized, controlled, clinical trial ("RCT"). And RCT is called the gold standard of biomedical research for a reason. For it isn't jargon, just common sense.

The happy couples traipsing along in the Prevagen ads have nothing to compare their experience to. They can't possibly know how forgetful they would have become had they not shelled out about $40 a month for however many years to partake of the jellyfish glowing protein. But a clinical trial would answer the question of efficacy. Finally.

It's all about science – not faith or belief that a "brain health supplement" is actually a treatment for a devastating disease.

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