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1 Overview

Summary and Quick Facts for Alzheimer's Disease

- Alzheimer’s disease is a neurodegenerative disorder characterized by cognitive decline that eventually leads to death. Estimates suggest that in the United States alone there will be 11 to 16 million individuals aged 65 and older diagnosed with Alzheimer’s disease by 2050.
- A comprehensive approach to Alzheimer’s disease treatment is required that acknowledges and targets the many possible factors underlying the changes in brain structure and function that drive this complex condition. In this protocol, you will learn about theories of Alzheimer’s disease, risk factors, conventional treatment, novel and emerging approaches, and the roles of hormone replacement, dietary and lifestyle management strategies, and targeted nutritional therapies.
- While available treatments may slightly improve symptoms, they do not alter the course of the disease. However, natural interventions such as Huperzine A and lipoic acid may help protect cognitive function and promote brain health.

What is Alzheimer’s Disease?

Alzheimer's disease is a neurodegenerative disorder characterized by cognitive decline that eventually leads to death. The underlying cause of Alzheimer's disease is not fully understood; however, it appears to be the consequence of many converging factors of aging, including accumulation of toxic protein aggregates in the brain, mitochondrial dysfunction, oxidative stress, and inflammation. Chronic infection with bacterial or viral pathogens also seems to play an underappreciated role in progression of the disease.

There is no cure for Alzheimer's. And while available treatments may slightly improve symptoms, they do not alter the course of the disease. However, natural interventions such as **huperzine A** and **lipoic acid** may help protect cognitive function and promote brain health.

What are the Risk Factors for Alzheimer's Disease?

- Advanced age
- Family history/carrying a genetic variant
- Certain infections
- Vascular conditions (eg, high blood pressure, diabetes)
- History of head trauma
- High homocysteine levels
- Nutrient deficiencies
- Silent strokes
- Central obesity (ie, high hip-to-waist ratio)

What are Medical Treatments for Alzheimer's Disease?

- Cholinesterase inhibitors (eg, donepezil [Aricept], rivastigmine [Exelon], and galantamine [Razadyne])
- NMDA receptor blockers (eg, memantine [Namenda])

What are Emerging Therapies for Alzheimer's Disease?

Note: Many of the therapies listed below are debated, with some studies that show benefit and others that do not. Alzheimer's research to determine the efficacy of various treatments is always ongoing.

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Blood pressure lowering drugs
- Lithium
- Etanercept (Enbrel), a drug used for certain inflammatory conditions, may have benefits for Alzheimer's disease.
- Granulocyte colony-stimulating factor (G-CSF), a growth factor that promotes creation of new neurons, has shown benefit in animal models.
- Brain-derived neurotrophic factor (BDNF), a signaling protein that declines with age and Alzheimer's, is a potential therapy.
- Selective estrogen receptor modulators (SERMs)
- Vaccines to clear plaque from the brain
- Antibiotics
- Hormone replacement therapy, and others

What Dietary and Lifestyle Changes Can Be Beneficial for Alzheimer's Disease?

- The Mediterranean diet has been linked to a reduced risk of Alzheimer's and other neurodegenerative diseases.
- Low-calorie diets have been linked to a reduced risk of cognitive decline.
- Regular exercise can improve brain health.

What Natural Interventions May Be Beneficial for Alzheimer's Disease?

- **Huperzine A**. Derived from the plant *Huperzia serrata*, huperzine A has a mechanism of action similar to existing Alzheimer's drugs and has been shown to improve cognition in Alzheimer's patients.
- **Lion's mane**. Lion's mane is a mushroom used traditionally in Asia to improve memory. Preclinical and small preliminary clinical trials show promise for improving cognition in Alzheimer's.

- **Lipoic acid**. This antioxidant reduces inflammation and has been shown to slow disease progression in small clinical studies of Alzheimer's patients.
- **Acetyl-L-carnitine**. Another antioxidant, acetyl-L-carnitine has been shown to benefit patients with mild cognitive impairment and mild Alzheimer's.
- ***Panax ginseng***. The *Panax ginseng* plant produces memory improvements. Alzheimer's patients given a high dose saw improvements in their cognitive abilities.
- **Vitamins C and E**. Vitamins C and E are well known for their antioxidant properties. Supplementation has been shown to reduce the risk of developing Alzheimer's.
- **Omega-3 fatty acids**. Supplementation with omega-3 fatty acids, such as docosahexaenoic acid (DHA), improved cognitive function and memory in people with age-related cognitive decline.
- **Phosphatidylserine**. Supplementation with phosphatidylserine, a natural component of cell membranes, improved cognition in elderly people with cognitive impairment.
- **Coffee**. Coffee consumption is linked with a reduced risk of Alzheimer's and Parkinson's disease. Long-term coffee intake may enhance working memory as well.
- **B vitamins**. B vitamins lower homocysteine levels, a risk factor for Alzheimer's. Multiple studies have shown that low levels of B vitamins (B12, folate, niacin, etc.) are associated with an increased risk of Alzheimer's and impaired cognitive function while higher levels are protective.
- Many additional natural interventions may be beneficial for cognitive health, including **ginkgo biloba**, **curcumin**, **melatonin**, **vinpocetine**, **pyrroloquinoline quinone (PQQ)**, **grape seed extract**, and others.

2 Introduction

Alzheimer's disease is a neurodegenerative disorder characterized by a decline in cognitive function that eventually leads to death (Upadhyaya 2010; Stern 2008; Knopman 2012; Mayo Clinic 2011). Research in Alzheimer's disease has not yet identified a cure for the disease. Advanced age is a risk factor for development of the disease (Alzheimer's Association 2012b; Knopman 2012).

With an increase in the aging population, the worldwide prevalence of Alzheimer's disease has increased remarkably and is expected to continue to do so. Estimates suggest that in the United States alone there will be 11-16 million individuals aged 65 and older diagnosed with Alzheimer's disease by 2050 (Zhao 2012; Tarawneh 2012).

Alzheimer's disease appears to be the consequence of several convergent factors including **oxidative stress**, **inflammation**, **mitochondrial dysfunction**, and accumulation of **toxic protein aggregates** in and around neurons (Luan 2012; Teng 2012; Rosales-Corral 2012; Wang 2007; Fonte 2011; Ittner 2011). Emerging, intriguing research implicates *chronic infection* with several pathogenic organisms in the development and progression of Alzheimer's disease as well (Miklossy 2011). Moreover, age-related changes such as declining hormone levels and vascular dysfunction are thought to contribute to some aspects of Alzheimer's disease (Vest 2012; Barron 2012; Baloyannis 2012).

Conventional pharmacologic interventions target symptoms, but fall short of addressing underlying, contributing factors for Alzheimer's disease. This results in a small reduction of symptoms, but does not halt or reverse disease progression (Sadowsky 2012; Alkadhi 2011).

A comprehensive approach to Alzheimer's disease treatment is required that acknowledges and targets the many possible factors underlying the changes in brain structure and function that drive this complex condition (Sadowsky 2012).

3 Theories of Alzheimer's Disease

Research into the potential causes of Alzheimer's disease has been frustrating. A number of processes are believed to contribute to the cognitive decline observed in Alzheimer's disease. Brain deterioration in Alzheimer's disease is thought to begin decades before symptoms become evident. Outlined below are several factors postulated to contribute to Alzheimer's disease; each also represents a potential therapeutic target (Luan 2012; Teng 2012).

Senile Plaques

A prominent finding in Alzheimer's disease is that senile plaques, which are comprised of "clumps" of the protein fragment ***amyloid beta***, accumulate and cause cellular damage in key areas of the brain, especially the hippocampus, which is involved in memory consolidation and spatial navigation (Biasutti 2012). Aggregates of amyloid beta have been shown to contribute to oxidative damage, excitotoxicity, inflammation, cell death, and formation of ***neurofibrillary tangles*** (NFTs) (see below) (Massoud 2010). However, therapies aimed solely at reducing amyloid beta have proven disappointing, suggesting a more complex process is involved (Marchesi 2012; Schmitz 2004; Holmes 2008).

Neurofibrillary Tangles

Neurons contain a cellular skeleton made up of *microtubules,* secured in place by specialized proteins called *tau*. In Alzheimer's disease, microtubules disintegrate and tau proteins "clump" together to form aggregates called ***neurofibrillary tangles*** or NFTs. NFTs function much the same as amyloid beta aggregates in that they initiate several process that lead to cellular dysfunction and death. Whether amyloid beta or NFTs arise first in Alzheimer's disease is unclear, and this remains a heavily debated topic within the scientific community (Massoud 2010; Crespo-Biel 2012).

Acetylcholine deficit

A theory once widely advocated, but which has proved to be disappointing at addressing underlying disease progression, is the cholinergic hypothesis. This view suggests that Alzheimer's disease is the consequence of insufficient synthesis of the neurotransmitter acetylcholine, which is fundamental in many aspects of cognition (Munoz-torrero 2008; Nieoullon 2010).

Clinical trials have shown medications that support acetylcholine signaling reduce symptoms, but do not reverse or halt the disease. Therefore, inadequate cholinergic neurotransmission is now viewed as a consequence of generalized brain deterioration observed in Alzheimer's disease, rather than a direct cause. Nonetheless, drugs that modulate acetylcholine signaling are still a mainstay of symptomatic management of Alzheimer's disease (Munoz-torrero 2008; Nieoullon 2010).

Oxidative Stress

Oxidative stress is a process in which highly reactive molecules called ***free radicals*** damage cellular structures. Free radicals are byproducts of normal metabolism, but during states of metabolic abnormality such as mitochondrial dysfunction (see below), they are created more rapidly and in greater quantity. In the case of Alzheimer's disease, oxidative stress both facilitates some of the damage caused by amyloid beta *and* spurs its formation (Dong-gyu 2010; Hampel 2011).

Oxidative stress propagates Alzheimer's disease via another route as well. As neurons become damaged, free iron accumulates on their surfaces and within nearby cells called microglia. Free iron causes radical formation and drives oxidative stress (Mandel 2006).

Inflammation

The inflammatory process appears to play an important role in the development of Alzheimer's disease. Glial cells, such as microglia, function to eliminate potential pathogens and harmful particles (eg, amyloid beta). However, this process, though helpful, can contribute to neuroinflammation (Twarowski 2023).

When high levels of amyloid beta accumulate in the brain, it activates the body's immune response, resulting in inflammation that damages neurons (Salminen 2009). Part of the inflammatory response to amyloid beta appears to be facilitated by ***tumor necrosis factor-alpha*** (TNF-α) (Tobinick 2008a). TNF-α is a pro-inflammatory cytokine that is often found in high levels in serum and cerebral spinal fluid (CSF) of Alzheimer's patients; it represents a potential target for novel Alzheimer's disease therapies (Culpan 2011; Ardebili 2011; Tobinick 2008a).

Mitochondrial Dysfunction

Mitochondria are the energy power plants of cells; they generate energy in the form of adenosine triphosphate (ATP), which is necessary for cellular function. Mitochondrial dysfunction has been implicated in many age-related diseases, including Alzheimer's disease (Chen 2011). One line of evidence that supports a link between

Alzheimer's disease and mitochondrial dysfunction is the finding that ApoE4, a genetic variant associated with Alzheimer's disease and amyloid beta deposition within the brain, seems to play a role in disrupting mitochondrial respiratory chain function (Caselli 2012; Chen 2011; Polvikoski 1995).

Dysfunctional mitochondria are important mediators of amyloid beta toxicity (Leuner 2012). Mitochondrial dysfunction contributes to an increased burden of oxidative stress as well, which itself is another mediator of amyloid beta toxicity. Mitochondrial dysfunction and oxidative stress then drive the formation of additional amyloid beta, creating a vicious, self-propagating cycle that ultimately leads to neuron death (Leuner 2012).

Excitotoxicity

Glutamate is the most abundant excitatory neurotransmitter in the brain and is necessary for normal brain function. However, too much glutamatergic neurotransmission can be toxic to neurons, a phenomenon known as "excitotoxicity". Excitotoxicity is thought to contribute to neuronal degeneration in Alzheimer's disease because it is promoted by amyloid beta, neurofibrillary tangles, mitochondrial dysfunction, and oxidative stress among other factors (Danysz 2012).

Glutamate excitotoxicity is the result of over activation of *N*-methyl-D-aspartate (NMDA) receptors. Therefore, modulating this receptor is a way to lessen some of the damaging effects of excess glutamate signaling. The FDA has approved memantine (e.g., Namenda®), an NMDA receptor blocker, for the treatment of moderate to severe Alzheimer's disease (Danysz 2012).

Loss of Sex Hormones

Evidence suggests that age-related loss of sex hormones – estrogen in women and testosterone in men – may contribute to Alzheimer's disease. Although the specific mechanisms are unclear, sex hormones appear to protect the brain against the development of Alzheimer's disease (Vest 2012; Barron 2012). For example, declining estrogen and testosterone levels seem to be associated with increased amyloid beta and tau abnormalities (Overk 2012).

Infections

An intriguing theory that remains largely unappreciated by the medical community is that chronic infection with a variety of pathogenic bacteria and/ or viruses may contribute to the development of Alzheimer's disease. Research indicates that some common pathogens are consistently detected in the brains of Alzheimer's patients. For example, a comprehensive analysis of studies found that *Spirochetes*, a family of bacteria, was detected in about 90% of Alzheimer's patients and was virtually absent in healthy age-matched controls. Further statistical evaluation revealed a high probability of a causal relationship between *Spirochetes* infection and Alzheimer's disease (Miklossy 2011).

Spirochetes and other bacteria can linger in the brain and drive inflammation and the formation of amyloid beta and neurofibrillary tangles, all of which are hallmarks of Alzheimer's disease (Miklossy 2011). Moreover, laboratory studies indicate that amyloid beta is an antimicrobial peptide, suggesting its formation could be an adaptive response to infectious organisms (Soscia 2010). These and other findings have led some researchers to hypothesize that "*…early intervention against infection may delay or even prevent the future development of [Alzheimer's disease]*" (Honjo 2009).

There is some evidence suggesting periodontal disease (gum disease) is associated with an increased risk of developing Alzheimer's disease (Beydoun 2020). In a study of elderly participants, those with evidence of amyloid beta in their brains had significantly higher scores of periodontal dysbiosis (Kamer 2021). Participants with periodontal dysbiosis had overgrowth of harmful bacteria, such as those from genera *Treponema*, *Porphyromonas*, and *Tannerella*, along with decreased levels of healthy bacterial genera such as *Rothia* and *Corynebacterium*.

A recent article published in *Science Advances* provides intriguing evidence that Alzheimer's disease could be caused, in part, by infection with *Porphyromonas gingivalis*,a keystone pathogen of chronic periodontitis and significant risk factor for developing amyloid beta plaques, dementia, and Alzheimer's disease. *P. gingivalis* produces virulence factors called gingipains—proteases essential for its survival and pathogenicity. The authors hypothesized that gingipains promote neuronal damage in Alzheimer's patients and may contribute to the pathogenesis of Alzheimer's disease.

The scientists began by studying and comparing brain tissue samples from Alzheimer's disease patients and neurologically normal controls. They found that the gingipain load was significantly higher in Alzheimer's disease samples than in controls, indicating gingipain load is correlated with Alzheimer's disease diagnosis and disease markers. Interestingly, the scientists found a portion of the "healthy" brains were infected as well indicating that "… brain infection with *P. gingivalis* is not a result of poor dental care following the onset of dementia or a consequence of late-stage disease, but an early event that can explain the pathology found in middle-aged individuals before cognitive decline."

In addition to identifying *P. gingivalis* in the brains and cerebrospinal fluid of Alzheimer's disease patients, they also developed potent small molecule gingipain inhibitors which protected neurons from *P. gingivalis*-induced cell death. Mouse studies also showed the inhibitors could protect against neurodegeneration caused by *P. gingivalis* infection and provided direct evidence that oral infection with *P. gingivalis* can result in brain infiltration, increases in the conventional Alzheimer's disease biomarker Aβ1-42, and neurodegeneration. COR388, an analog of the most potent inhibitor with better oral bioavailability and central nervous system penetration, was shown to treat an existing brain *P. gingivalis* infection and reduce bacterial load, Aβ1-42 levels, and tumor necrosis factor-α levels (Dominy 2019).

These findings offer compelling evidence that *P. gingivalis* infection and gingipains in the brain play an important role in the pathogenesis of Alzheimer's disease. Furthermore, it demonstrates that oral administration of a small molecule gingipain inhibitor is effective for blocking gingipain-induced neurodegeneration and reducing bacterial load in mouse brains.

Exposure to Aluminum

Aluminum's role in the pathogenesis of Alzheimer's disease has been debated for well over a century. Aluminum is neurotoxic even in small amounts, and some scientists suggested accumulation in the brain over a lifetime may contribute to the development of Alzheimer's disease (Tomljenovic 2011; Colomina 2017). Aluminum has been linked to accumulation of amyloid beta and tau proteins (Huat 2019). In a study of brain tissue from patients with familial Alzheimer's disease, aluminum was found near modified tau proteins characteristic of neurodegenerative disease in the temporal cortex. Aluminum has also frequently been found near amyloid beta plaques in the brain's coretex (Mold 2021). The nature of the potential connection between aluminum and Alzheimer's disease requires further study.

Herpesviruses and Alzheimer's/Dementia Risk

Herpes-type viruses, such as herpes simplex virus type 1, Epstein-Barr virus (most common cause of mononucleosis), and the varicella zoster virus (the cause of chickenpox and shingles), may increase the risk of Alzheimer's and dementia (Nath 2019). Preclinical research has shown that herpesviruses could potentially contribute to Alzheimer's by seeding amyloid-beta plaques, which are believed to be partly responsible for the symptoms of Alzheimer's (Eimer 2018).

In a cell culture study, human-induced neural stem cell cultures were infected with the varicella virus and/or herpes simplex virus type 1. The cells infected with only the varicella virus showed detrimental glial cell changes and increased pro-inflammatory cytokines, but there was no accumulation of amyloid-beta or tau proteins. Interestingly, cells that were latently (inactively) infected with herpes simplex-1 had reactivation of the herpes simplex-1 virus upon varicella virus infection, which led to an accumulation of tau and amyloid-beta. More research is needed to understand the potential connection between these two different herpesviruses and their association with Alzheimer's (Cairns 2022).

Some evidence supports the theory that the varicella virus might reside latently in the brain, and that upon reactivation it can cause problems that could contribute to Alzheimer's (Lophatananon 2021). A meta-analysis of epidemiological studies published in 2019 found that past infection does not increase the risk. One cohort study found that reactivation of the virus, as shingles of the eye (Herpes zoster ophthalmicus), was associated with an increased risk (Warren-Gash 2019).

A relatively small observational study in people suffering from disorientation or memory loss, published in 2021, found that vaccination against shingles reduced the risk of dementia (Lehrer 2021). In 2022 observational

findings from a cohort including over 300,000 adults over age 65 years and without dementia showed that herpes zoster vaccination, compared with no vaccination, was associated with a 31–35% lower risk of dementia and a lower risk of Alzheimer's disease (Scherrer 2022).

In 2023 news came out of a large population-based study that deemed the relationship between shingles and Alzheimer's to be causal (Eyting 2023). The study included a total of 282,541 elderly people in Wales that either received the shingles vaccine on or after September 1st, 2013 or were ineligible to receive the vaccine as part of a policy change. Participants were followed until 2020 and the results showed that those who were vaccinated had a nearly 20% relative risk reduction in Alzheimer's disease compared with controls (ie, people who were ineligible for vaccination). This translates to a 3.5% absolute risk reduction. The researchers attempted to ensure no confounding factors were at play for the differences between groups. Although the researchers who conducted this study interpreted their findings as providing causal evidence that shingles vaccination reduced the risk of Alzheimer's disease, their report had not undergone peer review as of the time of this writing. More research should be conducted to confirm these results.

In 2024, a study was published that showed further evidence that the shingles vaccine is associated with lower risk of dementia. The study used a natural experiment opportunity created in the United States when in October 2017, live attenuated shingles vaccines were rapidly abandoned in favor of the more protective recombinant vaccines. Within six years of vaccination, those who received the recombinant vaccine, compared with those who received the attenuated-vaccine, had a 17% increase in time without a diagnosis of dementia, equal to 164 days more than with the attenuated live vaccine (Taquet 2024). Shortly after the publication of this study, results from a prospective study on shingles history and cognitive decline were published. Drawn from data from three large cohorts totaling close to 150,000 people, this study found that people with a history of shingles had a greater risk of significant cognitive decline, ranging from 14–24% greater, than those with no history of shingles (Yeh 2024).

Influenza and pneumonia may activate dormant herpesviruses, and research has shown that vaccination against influenza and pneumonia is associated with a reduced risk of Alzheimer's (Lehrer 2022). In a cohort study that included over 900,000 individuals, the incidence of Alzheimer's in people over age 65 years was 5.1% for people vaccinated against the flu compared with 8.5% in the unvaccinated people over a median follow-up of 46 months (Bukhbinder 2022). In a different cohort study of people between ages 65 and 75 years, those who were vaccinated against pneumonia had 30% lower odds of Alzheimer's compared with unvaccinated controls (Ukraintseva 2020).

Ask the Scientist – Herpesviruses and Alzheimer's Disease

Prof. Ruth Itzhaki is Professor Emeritus of Molecular Neurobiology at University of Manchester and Honorary Research Fellow at the University of Oxford.

1. **Hi, Professor Itzhaki. Thank you for taking time out of your day to share your thoughts with us. Would you tell us a little bit about your background and training?**

I graduated in Physics and then did an MSc and then a PhD in Biophysics (on different research topics), all University of London degrees. Subsequently, I was involved in research on the structure of chromatin, then on carcinogen effects on chromatin and more recently, on Alzheimer's disease, starting work on a possible role of a virus in the disease way back in 1989.

2. **You've been studying the association between herpesviruses and Alzheimer's disease and dementia for quite some time. Why were you drawn to this area of study?**

Little was understood at the time I started and even the name of the disease was almost unknown to the public. Also, it was a challenge which appealed to me—and the possibility that a virus might be involved fascinated me. Another reason was that my father unfortunately had a type of dementia (probably Lewy Body dementia), so I was glad to work on a related topic.

3. **Given that you've clearly been persistent in studying this topic, how has your understanding of the potential link between herpesviruses and Alzheimer's disease changed over the years as you've examined this link more closely?**

It started as a vague though quite reasonable possibility but has now become a probability, particularly about 10 years ago when other labs started working on the topic—so I was no longer alone!

4. **Your work is considered controversial by some in the field of Alzheimer's disease research** . What key items still need to be addressed that make the work you're doing important?

I agree that it is considered controversial but as our opponents, though virulently hostile, never produce any arguments against the HSV1-Alzheimer's disease concept, the results could hardly be called controversial (as controversy by definition needs both pro and con arguments!). As for key items, I think they are to: (a) set up a clinical trial to investigate the effect of anti-herpes antiviral treatment of Alzheimer's disease patients; (b) find if one or more microbes are involved in any one brain; (c) repeat the Taiwan studies; (d) determine the critical pathways by which the virus and *APOE-e4* are involved in the development of the disease; and (e) develop a vaccine specifically against HSV1.

5. **Do you personally believe that herpesviruses are causally linked to Alzheimer's disease?**
    a. **If so, what key pieces of evidence have been most convincing from your perspective?**
    b. **If you are of the opinion that the relationship is probably correlational and not causal, what evidence do you believe is the strongest indicator that the link is probably not causal?**

The population epidemiological studies in Taiwan provide good evidence that HSV1 is a risk factor for Alzheimer's disease and that anti-herpes antivirals would target the virus very effectively. All previous studies, reported in over 150 refereed publications, although important show only associations between virus and the disease, not whether the virus is a cause. The Taiwan studies are the first to provide evidence that the virus is a cause, so I regard them as key work. However, of course they need to be replicated in other countries.

6. **Do you believe that antiviral therapies could have a role in the prevention or treatment of Alzheimer's disease in some cases? If so, what key features would help select patients most likely to benefit?**

Yes, judging by all the research carried out, treatment should have a major effect. Prevention would be even better, but no vaccine is yet available and the apparent prevention shown by antiviral treatment in the Taiwan studies is very hard to explain (though I and Prof R. Lathe suggested a speculative explanation in our article in *J. Alzheimer's Disease*, 2018). For treatment, patients would be selected who have mild disease, who definitely harbour the virus (shown by seropositivity to it) and who, preferably, are carriers of the type 4 allele (form) of the APOE gene.

7. **Do you think any particular dietary, lifestyle, or environmental factors modulate the relationship between herpesvirus and Alzheimer's disease. If so, what factors do you think exert the most influence?**

Unfortunately, there is really no information about these factors in relation to herpesviruses and Alzheimer's disease, but exercise and a good diet seem important in any case.

8. **The immune system does a pretty good job keeping HSV1 at bay in younger, healthy people. Do you think that age-related immune senescence is an important factor that may allow HSV1 to escape immune control and potentially contribute to Alzheimer's disease in aging people?**
    a. **If so, do you think taking steps to maintain healthy immune function with advancing age might help keep HSV1 at bay and maintain brain health?**

Yes, I think it is the decline in the immune system that allows virus entry into the brain, and keeps it latent (ie, dormant) there, at least part of the time. Possibly, virus entry might be prevented by treating seropositive people who have an *APOE-e4* allele in early middle age with anti-herpes antivirals—but this is very speculative—as mentioned in my recent review in *Frontiers in Aging Neuroscience*, 2018.

4 Risk Factors for Alzheimer's Disease

Several factors influence the risk of Alzheimer's disease. Some are modifiable, such as obesity and nutrient deficiencies, but others, such as carrying the ApoE4 gene, are not. Below is a partial list of factors known to be

associated with an increased risk of Alzheimer's disease (Yilmaz 2012; Daviglus 2011; Harrison 2012; Hinterberger 2012; Luchsinger 2012; van Himbergen 2012; Stern 2008; Blum 2012; Miklossy 2011; Fenton 2023; Xiong 2022).

- Advancing age
- Family history of Alzheimer's disease
- Carrying the ApoE4 genetic variant
- Certain bacterial infections
- Vascular risk factors (e.g., diabetes, atherosclerosis, high blood pressure, high cholesterol) appear to encourage the development of phenomena associated with Alzheimer's disease such as accumulation of amyloid beta (Kalaria 2012).
- History of head trauma
- High homocysteine levels
- Nutrient deficiencies
- Silent strokes
- Central obesity (i.e., high waist-to-hip ratio)
- Inadequate sleep

Type 3 Diabetes

People with poorly controlled type 2 diabetes have an increased risk of developing Alzheimer's disease (Xu 2009; Lee 2018). Excess glucose levels reduce the brain's ability to degrade and clear away amyloid beta, while brain insulin resistance increases amyloid beta accumulation. Buildup of amyloid beta forms the plaques characteristic of Alzheimer's disease (Lee 2018; Kellar 2020). In fact, it has been suggested that diabetes- and insulin resistance-related Alzheimer's disease be termed "***type 3 diabetes***" (de la Monte 2018).

Glucose metabolism in the brain appears to be severely disrupted in Alzheimer's disease. In a post-mortem analysis of Alzheimer's patients' brains, researchers found widespread impairment in glycolytic (glucose metabolism) gene expression (Saito 2021). In contrast, ketolytic (ketone metabolism) gene expression only had limited impairment. The altered gene expression pattern indicates that a brain with Alzheimer's cannot properly utilize glucose, but ketones may be a helpful alternative source of energy.

Type 2 diabetes and Alzheimer's disease share another feature—insulin resistance. Insulin signaling is involved in numerous functions in the brain; resistance to insulin is linked to neuroinflammation, mitochondrial dysfunction, and ultimately neurodegeneration (de la Monte 2017).

In preclinical models, irregular insulin signaling in the brain interferes with learning and memory. At least one researcher has suggested that Alzheimer's disease should be considered a degenerative metabolic condition caused by brain insulin defects, including insulin resistance. This theory highlights some of the metabolic abnormalities that seem to occur in Alzheimer's disease and diabetes (de la Monte 2017).

Interestingly, intranasal insulin therapy has shown some promise in treating cognitive dysfunction or symptoms of Alzheimer's disease. Similar findings have been reported for common diabetes medications like metformin and thiazolidinediones (Halmos 2016). Unfortunately, clinical results have been mixed. Further research is needed to determine whether diabetes treatments can help mitigate Alzheimer's and dementia as well (Bendlin 2019).

Research has suggested inhibiting an enzyme called ***glycogen synthase kinase-3 (GSK-3)*** may combat metabolic derangements common to both Alzheimer's disease and diabetes. GSK-3 contributes to the formation of plaques and tangles, which disrupt normal cellular machinery and cause dysfunction in the brain. Blocking GSK-3 has been shown to suppress *tau hyperphosphorylation* and levels of *amyloid beta*, which contribute to plaques and tangles. Moreover, inhibiting GSK-3 appears to promote neurogenesis, or the formation of new neurons, in the hippocampus (Maqbool 2016).

One compound that has gained attention in diabetes and Alzheimer's disease research communities is ***lithium***. GSK-3 inhibition by physiologically relevant concentrations of lithium has been noted in many studies, and lithium treatment has been shown to mitigate cognitive impairment associated with diabetes in animal models

(King 2014). Clinical trials have also shown lithium's ability to effectively decrease cognitive decline compared with placebo (Matsunaga 2015).

Lithium's ability to modulate brain activity is not a new discovery. The metal has been used as a psychiatric drug for more than 70 years, particularly in the treatment of bipolar disorder. More recently, studies have revealed some of the mechanisms that underlie lithium's remarkable effects on the brain. Research has shown lithium increases the proliferation of neuronal progenitor cells and enhances the ability of specialized neuro-protective cells (ie Schwann cells) to divide (Ferensztajn-Rochowiak 2016). Lithium also appears to upregulate brain-derived neurotrophic factor (BDNF) (Won 2017).

These effects are thought to contribute to increased ***synaptic plasticity***. This elegant process allows the brain to adapt to new stimuli and is an important aspect of learning and memory (Ramirez 2016). Lithium also appears to have several neuroprotective properties (Won 2017).

5 Diagnosis

Overview

Thanks to remarkable technological advances in recent years, the Alzheimer's disease research community is currently revisiting not only the approach to the diagnosis of the disease, but even how it is defined and described.

In 2018, the National Institute on Aging (NIA) and the Alzheimer's Association (AA) teamed up to form the NIA-AA Workgroup. The Workgroup was tasked with developing a new, objective, clinically useful, diagnostic and staging approach to Alzheimer's disease based on amyloid and tau biomarker profiles (Jack 2018). Biomarker testing may improve the ability to diagnose Alzheimer's disease in its earliest stages, help predict its course in individual patients, and guide therapy (Leuzy 2025).

The proposed diagnostic system, which was updated in 2024 and is under review as of mid-2025, considers Alzheimer's disease as a progressive condition that occurs on a continuum, grounded in brain tissue changes that result in symptoms. According to the 2024 update, positive results on **amyloid beta** and/or **tau** biomarker tests indicate the presence of Alzheimer's disease–related brain tissue damage and are sufficient for diagnosing Alzheimer's disease. Signs of neurodegeneration, detected on brain magnetic resonance imaging (MRI) or using non-specific biomarkers, may be useful for supporting the diagnosis, helping with staging, or indicating the possibility of a co-occurring condition (Hazan 2024; Jack 2024).

One important goal of the NIA-AA Workgroup is to develop a set of guidelines for physicians indicating appropriate uses and interpretation of biomarker tests. Several tests for amyloid and tau biomarkers in cerebrospinal fluid (CSF) have been approved or cleared for use (a step below approval) by the U.S. Food and Drug Administration (FDA). These tests are already being used to improve the accuracy of clinically based diagnosis in specialized memory clinics (Leuzy 2025).

More recently, a plasma biomarker, which can be measured in a blood sample, was cleared by the FDA. The biomarker is called **p-tau217-to-amyloid beta 42 ratio** and when elevated is a highly accurate indicator of Alzheimer's disease (Ashton 2024). It is available through certain U.S. clinical laboratories, including LabCorp and Quest Diagnostics. This and other blood tests are anticipated to be able to replace invasive CSF tests and expensive brain imaging in the future (Ashton 2024; LabCorp 2025). Lacking FDA approval, however, this and other blood biomarker tests are not yet widely covered by health insurance providers, and costs for patients may vary among treatment centers. As of mid-2025, blood-based biomarker tests should be implemented with the guidance of a care team experienced in the diagnosis and management of Alzheimer's disease.

FAQs About Alzheimer's Disease Diagnosis

1. **How accurate is early testing for Alzheimer's?**
   For people with symptoms characteristic of Alzheimer's disease, biomarker testing can lead to a clear diagnosis with a high degree of accuracy. On the other hand, such testing may not accurately predict the likelihood of developing Alzheimer's disease in people without characteristic cognitive impairment or dementia due to a high rate of false positives (positive test results in people who do not go on to develop the

condition) (Bouteloup 2025). Since these tests are currently evolving, future research may help clarify how to interpret them to maximize their usefulness. As of mid-2025, biomarker testing, particularly blood-based biomarker testing, should only be implemented under the guidance of a medical team experienced in the diagnosis and management of Alzheimer's disease. Moreover, the direct financial costs borne by patients associated with these new tests can vary across care centers and with insurance coverage. Thus, patients interested in biomarker testing for Alzheimer's should discuss these tests with their care team.

2. **How is Alzheimer's diagnosed and how long does it take?**
   Diagnosing Alzheimer's disease takes time because it involves cognitive and functional assessments. Your physician may also order brain imaging and/or CSF tests, both of which need to be performed in a hospital, to confirm the diagnosis. Certain blood tests are being investigated for their ability to more rapidly identify Alzheimer's disease. Once guidelines for how to use these tests are developed for healthcare providers, they may become standard and sufficient for a definitive diagnosis.
3. **What is different about diagnosing younger-onset Alzheimer's?**
   In people under 65 years of age, early Alzheimer's disease is sometimes confused with a psychiatric or other neurological disorder and diagnosis is often delayed. The diagnostic process is the same for people of all ages; thus, a young person suspected of having Alzheimer's disease should be provided a thorough assessment, including neuroimaging and CSF testing, to help them access timely and appropriate care (Kusoro 2025; Loi 2023).
4. **What are the early symptoms?**
   Some early symptoms of Alzheimer's disease are (Johns Hopkins Medicine 2025):
   - forgetting important things, especially things that were just learned
   - asking the same question or saying the same thing over and over
   - new difficulties solving basic problems or following directions
   - losing track of the date or season
   - losing track of your location and how you got there
   - vision problems, such as difficulty with depth perception
   - difficulty finding words for things or following a conversation
   - misplacing things and not being able to figure out how to find them
   - showing poor judgement
   - withdrawing from family, friends, and colleagues
   - mood and personality changes
5. **What doctor do I start with?**
   If you suspect you or someone you know might have Alzheimer's disease, consulting your primary care physician is the first step.
6. **Are blood tests available?**
   Blood tests for Alzheimer's disease biomarkers are becoming increasingly available, but the best ways to interpret these tests are still being investigated.
7. **Do I need a brain scan?**
   Though not always needed, a brain scan can provide important information that may help your doctor confirm whether you have Alzheimer's disease or another condition causing your symptoms.
8. **Is a spinal tap necessary?**
   If your doctor wants to check for biomarkers in CSF to help determine a diagnosis, a spinal tap will be needed. Emerging blood tests for Alzheimer's disease biomarkers are much less invasive.
9. **How do PET, MRI, CSF, and blood tests differ?**
   A brain MRI scan can show if a stroke or a bleed has occurred or if a mass or lesion is present, providing information about other possible causes of cognitive impairment or dementia. It also provides information about changes in brain volume that may occur during the course of a neurological disease. A brain positron emission tomography (PET) scan shows the activity level in different parts of the brain and detects brain regions that are not functioning properly. Cerebrospinal fluid tests show whether proteins and other markers

involved in Alzheimer's disease–related brain damage are present in the fluid that surrounds the brain and spinal cord, and blood tests show if they are present in circulating blood. With the use of specialized tracers, PET scans can also show where amyloid plaque and tau tangles are present (Høilund-Carlsen 2024).

10. **What happens after an Alzheimer's diagnosis?**
    If your doctor determines you are suffering from Alzheimer's disease, they will want to have regular check-ins to monitor your symptoms over time. Depending on your circumstances, they may refer you for social support services and resources to help you and your family or close friends make decisions about your future. You may benefit from memory aids and extra safety measures, especially when it comes to driving. There may also be lifestyle changes you can make to improve your prognosis (Hansson 2023). Your doctor may also prescribe medication to assist with memory and slow disease progression.
11. **What are the typical follow-up steps after the first appointment?**
    If your doctor suspects Alzheimer's disease, they may perform a screening test in the office, which may lead to a follow-up involving more cognitive and functional tests, and possibly a brain scan and/or CSF or blood testing.

Historical Approach to Diagnosis

The current approach to diagnosing Alzheimer's disease begins with:

- obtaining a detailed patient history
- performing standardized cognitive function testing
- running lab tests (mainly to rule out other causes)
- possibly examining the brain through imaging

A history of unexplainable progressive cognitive decline, including declining performance on cognitive tests, has been considered sufficient for a diagnosis of "probable Alzheimer's disease." A definitive diagnosis requires examination of brain tissue, typically as part of an autopsy after death (Wolk 2025).

Alzheimer's disease typically progresses through the following stages (Alzheimer's Association 2025a):

- mild cognitive impairment
- early stage/mild dementia
- middle stage/moderate dementia
- late stage/severe dementia

The use of biomarkers in asymptomatic individuals may someday lead to recognition of an earlier stage, with no cognitive impairment but with markers of the disease in the brain (Jack 2024; Petersen 2021).

Biomarkers of Alzheimer's Disease

Since Alzheimer's disease has a clear biological basis involving a specific type of nerve damage and dysfunction in the brain, researchers have sought diagnostic criteria that uses objective biological test results. **Amyloid beta**, found in characteristic plaques, and **tau proteins**, components of neurofibrillary tangles, are the hallmarks of Alzheimer's disease–related brain tissue damage and have emerged as key biomarkers that may allow for diagnosis during life, possibly even before symptoms begin. These biomarkers are detectable through brain PET scans, CSF tests, and some blood tests (Jack 2024).

Amyloid beta is produced through cleavage of a large protein known as amyloid precursor protein. Normal amounts of amyloid beta support memory function; however, excess amyloid beta, particularly longer units, can accumulate in brain tissue forming aggregates or clumps known as plaques that disrupt brain function. Increased plaque burden has been associated with progressive cognitive dysfunction and eventual dementia that characterize Alzheimer's disease (Pokrzyk 2025).

Tau proteins are normally found in axons—nerve fibers that transmit signals between neurons and other cells. In Alzheimer's disease, tau proteins malfunction and undergo abnormal modifications called phosphorylation (attachment of phosphate groups). Phosphorylated tau proteins tend to aggregate, or stick together, forming fibrillary tangles and causing nerve cell dysfunction (Hong 2025).

Amyloid beta and tau proteins interact with one another: amyloid beta aggregates trigger phosphorylation of tau proteins and abnormal tau proteins contribute to amyloid beta production and aggregation (Hong 2025).

Core Biomarkers in Alzheimer's Disease Diagnosis
The most important Alzheimer's disease biomarkers are classified as Core 1 and Core 2.

Core 1 biomarkers can be detected early in the disease continuum and are highly specific indicators of Alzheimer's disease–related changes in the brain. In the proposed diagnostic system, the presence of a Core 1 biomarker is considered sufficient for diagnosing Alzheimer's disease (Jack 2024).

Core 2 biomarkers typically become abnormal later in the disease, frequently when symptoms are already present, and generally do not provide accurate diagnostic information in early-stage disease. Instead, Core 2 biomarkers can be used to confirm a diagnosis and provide important information about severity and prognosis (Jack 2024).

The specific biomarkers that fall into these classifications are evolving as new biomarkers are identified and validated. In addition, not all tests for Core 1 and Core 2 biomarkers are reliable enough to accurately diagnose Alzheimer's disease (Jack 2024).

It is important to note that, using the proposed diagnostic system, Alzheimer's disease–related brain changes can be identified prior to symptom onset and Alzheimer's disease can be diagnosed in its earliest asymptomatic stage (Jack 2024).

Table 1: Core 1 and Core 2 Biomarkers of Alzheimer's Disease

	Assessed in Serum or CSF	**Assessed Through Imaging**
Core 1 Biomarkers:		
• Amyloid	Amyloid beta 42 Amyloid beta 42-to-40 ratio	Amyloid PET
• Tau	Phosphorylated (p)-tau217 p-tau181 p-tau231	
• Hybrids	p-tau217-to-amyloid beta 42 ratio p-tau181-to-amyloid beta 42 ratio total tau-to-amyloid beta 42 ratio	
Core 2 Biomarkers:		
• Tau	Other p-tau Non-phosphorylated tau MTBR-tau243	Tau PET

Based on Jack CR, Jr., Andrews JS, Beach TG, et al. Alzheimers Dement. Aug 2024;20(8):5143-5169.

Amyloid biomarkers. A brain PET scan can be used to visualize and quantify brain amyloid deposits. Known as amyloid PET, this is a Core 1 biomarker (Jack 2024).

Amyloid beta 42 is a potent plaque-causing fragment of amyloid beta precursor protein that is 42 amino acids in length. Low levels of amyloid beta 42 in CSF or plasma indicate more amyloid beta 42 has been deposited in the

brain. In other words, if there is not much amyloid beta 42 in the blood plasma or CSF, more of it is stuck in the brain, forming clumps that contribute to Alzheimer's disease. **Thus, low levels of amyloid beta 42 in plasma or CSF, not high levels, are associated with Alzheimer's disease** (Leuzy 2025). CSF or plasma amyloid beta 42 is a Core 1 biomarker (Jack 2024).

Levels of amyloid beta 42 are sometimes reported in relation to amyloid beta 40 levels, which do not change in Alzheimer's disease; thus, a **low amyloid beta 42-to-40 ratio reflects amyloid accumulation in the brain** (Leuzy 2025). This ratio, based on CSF or plasma levels, is also a Core 1 biomarker (Jack 2024).

Tau biomarkers. Phosphorylated tau proteins (p-tau) in the brain, CSF, and plasma are indicators of Alzheimer's disease–related brain changes. High levels of plasma or CSF p-tau are hypothesized to reflect nerve damage and are closely related to amyloid plaque burden. Tau proteins that have been phosphorylated at amino acids 217, 181, or 231 are especially problematic. These modified forms of tau protein are called p-tau217, p-tau181, and p-tau231, respectively. They can be measured in plasma or CSF and are Core 1 biomarkers (Jack 2024).

Levels of p-tau217, 181, or 231 are sometimes reported in relation to amyloid beta 42 levels. Thus, high p-tau217-to-amyloid beta 42, p-tau181-to-amyloid beta 42, or total tau-to-amyloid beta 42 ratios in plasma or CSF reflect amyloid accumulation in the brain and are Core 1 biomarkers (Leuzy 2025; Hansson 2023).

Abnormal tau in brain tissue can be visualized with a brain PET scan. This test is called tau PET and is most often positive in symptomatic Alzheimer's disease patients. Tau PET has been correlated with symptom progression, and may therefore be helpful for predicting a patient's likely course (Chen 2021). It is a Core 2 biomarker (Jack 2024).

Other forms of phosphorylated and non-phosphorylated tau can be measured in CSF or plasma and are Core 2 biomarkers (Jack 2024). Another emerging biomarker called **tau microtubule-binding region containing residue 243** (MTBR-tau243) can be measured with a blood test and was shown to be strongly correlated with tau PET (Jack 2024; Horie 2025).

Blood-Based Biomarker Testing

A clinical practice guideline issued in July 2025 by the Alzheimer's Association offered important advice on how to use blood-based biomarker testing in specialized care settings for patients suspected of having Alzheimer's disease. These tests measure specific substances in the blood, such as certain forms of phosphorylated tau (p-tau217, p-tau181, and p-tau231) and an amyloid beta peptide ratio (amyloid beta 42-to-40), which reflect brain tissue changes that underlie Alzheimer's disease (Palmqvist 2025).

Blood-based biomarker tests are less invasive, better tolerated, and more accessible than standard diagnostic tests like CSF analysis and amyloid PET scans. By potentially streamlining the diagnostic process and detecting Alzheimer's disease pathology earlier, blood-based biomarker testing may result in earlier interventions and better care planning (Palmqvist 2025).

The guideline included the following recommendations:

- Blood-based biomarker tests with at least 90% sensitivity (ability to identify the condition and avoid false-negatives) and at least 75% specificity (ability to distinguish the condition and avoid false-positives) can be used as part of a preliminary assessment. Such tests provide information about the likelihood of Alzheimer's disease and help guide appropriate referrals and further testing.
- Blood-based biomarker tests that have both sensitivity and specificity of 90% or higher can be used in place of more invasive or expensive tests, such as amyloid PET imaging or CSF biomarker testing, to confirm a diagnosis of Alzheimer's disease in patients with cognitive impairment.

The guideline also warned that many available tests do not meet these sensitivity and specificity thresholds (Palmqvist 2025).

It is important to note that blood-based biomarker testing should only be done as part of a thorough clinical evaluation by a qualified healthcare professional. Using blood-based biomarker tests outside specialized settings or without proper clinical judgment can lead to inappropriate interpretation and follow-up (Palmqvist 2025).

Non-Specific Biomarkers of Neuropathology

Neurofilament light chain and glial fibrillary acidic protein are emerging biomarkers of brain disease. Because they are not specifically related to Alzheimer's disease, they are not used in diagnosis. Instead, they can be useful markers of underlying biological changes such as neurodegeneration and neuroinflammation and may be helpful in staging, prognosis, and monitoring treatment response (Jack 2024).

Neurofilaments are structural proteins in neurons. When these proteins become dysregulated, mutated, or aggregated, they are secreted into CSF and can reach the bloodstream (Devarakonda 2024). Increased neurofilament light chain levels in CSF or blood reflect degeneration of longer myelinated axons in the brain and spinal cord. As such, elevated neurofilament light chain levels are seen in Alzheimer's disease and other neurological disorders, including amyotrophic lateral sclerosis (ALS), multiple sclerosis, frontotemporal dementia, Huntington's disease, atypical Parkinsonian disorders, and traumatic brain injury. In addition, higher neurofilament light chain levels are correlated with faster disease progression (Hansson 2023; Devarakonda 2024).

Glial fibrillary acidic protein is a type of filament protein found mainly in non-nerve brain cells known as astrocytes. Astrocyte number and activity increase in response to brain injury or dysfunction, leading to increased release of glial fibrillary acidic protein into CSF and the bloodstream. High levels of glial fibrillary acidic protein are considered a marker of neuroinflammation (Leipp 2024). Glial fibrillary acidic protein is mainly measured in plasma and, although not specific to Alzheimer's disease, higher levels have been associated with an increased rate of cognitive decline and increased risk of dementia (Jack 2024; Leipp 2024).

Current and Future Use of Biomarkers

A study involving data from 4,660 participants in the Mayo Clinic Study of Aging and 553 individuals with dementia examined biomarker profiles and compared them to clinical status. The study found that, in every age group studied, more participants tested positive for amyloid and tau on brain PET scans (sufficient for a biomarker-based diagnosis of Alzheimer's disease) than had a clinical picture consistent with Alzheimer's disease (sufficient for a diagnosis of probable Alzheimer's disease). For example, among 85-year-olds in the study, the presence of both amyloid and tau biomarkers was found to be three times more prevalent than predicted by symptom history and cognitive tests (Jack 2019). Another study analyzed data from 1,525 participants in the Atherosclerosis Risk in Communities study and found plasma biomarkers for Alzheimer's disease (specifically, increased p-tau181 and decreased amyloid beta 42-to-40 ratio) in middle age were strongly associated with higher risk of dementia more than 20 years later (Lu 2024). Although the study did not distinguish between different types of dementia, Alzheimer's disease is the most common cause of dementia (Lu 2024; World Health Organization 2025).

A study involving 969 dementia-free memory clinic patients who were monitored for three to five years found amyloid biomarker (amyloid PET or CSF amyloid beta 42-to-40 ratio) positivity and tau biomarker (plasma p-tau217) positivity were less accurate at predicting risk of dementia in patients without characteristic symptoms of Alzheimer's-related cognitive impairment. Specifically, those without common Alzheimer's disease characteristics had a lower risk of developing dementia than those with common characteristics—even when Core 1 amyloid biomarkers and plasma p-tau217 were positive (Bouteloup 2025). Whether other tests of combinations of Core 1 biomarkers are less prone to false positive results remains to be determined.

Despite the potential value of biomarker testing, the findings described above demonstrate the ongoing importance of including clinical and cognitive assessments in the diagnostic process. Considering an individual's symptoms as an expression of the biological changes they have endured is still crucial for understanding the likely course of their condition and is key in avoiding misdiagnoses due to false positives (Bouteloup 2025). Some researchers have questioned whether defining and diagnosing Alzheimer's disease strictly biologically ignores important aspects of this complex condition, such as its psychosocial underpinnings (Hazan 2024). Other researchers have questioned the possible use of biomarker testing in people with no symptoms: Alzheimer's disease–related biomarkers may aid in identifying high-risk individuals before symptoms appear, but the broad implications of positive biomarker status for those who may be in the earliest asymptomatic stages of the condition are still uncertain (Hazan 2024; Gale 2024; Dubois 2024). Currently, the NIA-AA Workgroup does not recommend biomarker testing in asymptomatic individuals except for the purpose of research (Jack 2024;

Alzheimer's Association 2025b). Until more is known, biomarkers are most appropriate for patients with cognitive impairment or dementia as an add-on to, rather than a replacement for, clinical assessment.

Table 2: Biomarkers for Alzheimer's Disease

Biomarker	Significance	Status
PET Scans		
Amyloid PET	Used to visualize amyloid beta aggregation in specific brain regions; aids in diagnosis and possibly monitoring treatment response (Nasrallah 2025)	Clinically established and several PET tracers (flutemetamol [Vizamyl], florbetapir [Amyvid], and florbetaben [Neuraceq]) are FDA approved (Leuzy 2025; Hansson 2023)
Tau PET	Used to visualize tau aggregation and tangles in specific brain regions; aids in diagnosis and possibly monitoring treatment response (Nasrallah 2025)	Clinically established and one PET tracer (flortaucipir [Tauvid]) is FDA approved (Leuzy 2025; Hansson 2023)
CSF Tests (requiring a lumbar puncture)		
Amyloid beta 42	Low levels suggest greater amyloid deposition in brain tissue and are closely correlated with amyloid PET-positivity; thus, this test may be used as an alternative to amyloid PET (Hansson 2023; Palmqvist 2015). Changes in CSF may precede visible changes on PET (Hansson 2023).	FDA approved as part of CSF biomarker ratios (Leuzy 2025)
Amyloid beta 42-to-40 ratio	A low ratio indicates greater amyloid deposition in brain tissue and is more closely correlated with amyloid PET-positivity than amyloid beta 42 alone; this test may be used instead of amyloid PET (Leuzy 2025). Changes in CSF may precede visible changes on PET (Hansson 2023).	Individual markers are FDA approved, but ratio is a promising clinical measure (Leuzy 2025).
p-tau217	High levels are correlated with amyloid plaque load, as well as increased tau aggregates and tangles, and may provide a more accurate reflection of Alzheimer's neuropathology than other forms of p-tau; CSF levels increase before tau can be visualized on PET (Hansson 2023).	Investigational (Leuzy 2025)
p-tau181	High levels are more closely correlated with increased amyloid plaques than tau aggregates and tangles (Leuzy 2025; Ashton 2024).	FDA approved as a component of p-tau181-to-amyloid beta 42 ratio (Leuzy 2025)

Table 2. Biomarkers for Alzheimer's Disease

p-tau231	High levels are more closely correlated with increased amyloid plaques than tau aggregates and tangles (Leuzy 2025; Ashton 2024).	Investigational (Leuzy 2025)
Other p-tau biomarkers (eg, p-tau205 and p-tau235)	Tau biomarkers are generally more closely linked to amyloid beta plaques than tau tangles (Leuzy 2025; Ashton 2024).	Investigational (Leuzy 2025)
Total tau (t-tau)	A marker of neuronal injury and neurodegeneration; high levels are correlated with amyloid plaque burden in Alzheimer's disease; very high levels may indicate a non–Alzheimer's disease pathology (Leuzy 2025; Hansson 2023)	FDA approved as a component of t-tau-to-amyloid beta 42 ratio (Leuzy 2025)
Hybrid ratios (t-tau-to-amyloid beta 42 and p-tau181-to-amyloid beta 42)	High ratios are more accurate indicators of amyloid plaque burden than CSF amyloid beta 42 alone (Leuzy 2025).	FDA approved, and individual components are also FDA approved for *in vitro diagnostic* use (Leuzy 2025; Hansson 2023)
Neurofilament light chain	High levels are correlated with non-specific neurodegeneration and may help with staging, prognosis, and treatment response (Devarakonda 2024); may be more strongly related to neuropathology than plasma levels (Hansson 2023)	Experimental (Devarakonda 2024)
Plasma Tests (requiring a blood sample)		
Amyloid beta 42 (aka, amyloid beta 1-42)	Low levels are correlated with increased amyloid concentration and plaque formation in brain tissue (Hansson 2023).	Investigational; one type of test has been FDA *cleared* (this is a lower validation level than *approval*) as part of a p-tau217-to-amyloid beta 1-42 ratio calculation (Hansson 2023)
p-tau217	High levels are correlated with increased amyloid plaque as well as tau aggregates and tangles (Hansson 2023; Antonioni 2025).	Investigational; commercially available tests have been shown to be reliably accurate, and one type of test has been FDA *cleared* as part of a p-tau217-to-amyloid beta 1-42 ratio calculation (Leuzy 2025; Ashton 2024)
p-tau217-to-amyloid beta 42 ratio	A high ratio has been correlated with the presence of amyloid plaque with slightly more accuracy than plasma p-tau217 alone (Hong 2025; Piura	FDA *cleared* (Ashton 2024)

42 ratio	than plasma p-tau217 alone (Hong 2025; Pilla 2025).	

Table 2: Biomarkers for Alzheimer's Disease

Amyloid beta 42-to-40 ratio	A low value is correlated with, and may possibly precede, amyloid positivity on PET or in CSF (Hansson 2023; Klafki 2022).	Accuracy is highly dependent on lab methodology and many commonly used test methods are unreliable (Hansson 2023).
p-tau181	High levels are correlated with increased amyloid plaque and tau aggregates and tangles, but not as strongly as p-tau217 (Hansson 2023).	Investigational (Leuzy 2025)
p-tau231	Levels begin increasing while the amyloid plaque burden is low and are correlated with amyloid plaque accumulation (Hansson 2023).	Investigational (Leuzy 2025)
MTBR-tau243	High levels are correlated with tau aggregation and tangles and may be the most specific blood test for gauging tau pathology (Hansson 2023; Horie 2025).	Investigational (Hansson 2023)
Neurofilament light chain	High levels are correlated with non-specific neurodegeneration and may help with staging, prognosis, and treatment response (Devarakonda 2024).	Investigational (Devarakonda 2024)
Glial fibrillary acidic protein	High levels are correlated with non-specific neuroinflammation and may help with staging, prognosis, and treatment response (Devarakonda 2024).	Investigational (Leipp 2024)

6 Medical Treatment

Three classes of medication are available for treatment of Alzheimer's disease (Press 2024; Press 2021):

- monoclonal antibodies;
- cholinesterase inhibitors (e.g., donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon); and
- the N-methyl-D-aspartate (NMDA) receptor antagonist memantine (Namenda)

In clinical trials, all have demonstrated modest benefits of variable or uncertain clinical significance. Therefore, it is important that people with Alzheimer's disease and their caregivers discuss the benefits and risks of these medicines with their doctor to determine whether they are appropriate in each unique case. Treatment with these medicines can be initiated on a trial basis with attentive monitoring of benefits and adverse effects to assess whether longer-term continuation is warranted (Press 2024; Press 2021).

Monoclonal Antibodies (mABs)

Monoclonal antibodies (mABs) are used in the treatment of several diseases. In recent years, three mABs have garnered substantial attention following approvals for use in Alzheimer's disease. These are (AAN 2024):

- Aducanumab (Adulhelm), approved in 2021 (permanently off market since 2024)
- Lecanemab (Leqembi), approved in 2023

- Donanemab (Kisunla), approved in 2024

These drugs are all designed to target amyloid beta in the brain. The mABs are believed to work by activating microglia, a type of immune cell in the brain. Activated microglia are thought to facilitate amyloid beta elimination through a process called phagocytosis (Cummings 2024). This is a process by which a cell engulfs and digests particles, microorganisms, or foreign substances.

Prior to the approval of aducanumab, there had not been a new drug approval for Alzheimer's disease since 2003 (Servick 2021). Aducanumab was granted approval through the FDA's accelerated approval program, and is considered one of its most controversial drug approvals in recent history (Press 2021; Servick 2021; Belluck 2021). Aducanumab was taken off the market in January 2024 due to refusal of insurance coverage and lack of enthusiasm by physicians to prescribe it (Dyer 2024).

Lecanemab and donanemab, the two remaining available monoclonal antibodies drugs, differ in how they target amyloid beta. Lecanemab has a strong affinity for protofibrils of soluble amyloid beta, which are highly toxic to neurons, as compared to amyloid beta monomers or insoluble fibrils (van Dyck 2023). In contrast, donanemab targets a form of amyloid beta found only in established brain plaques (Gu 2024; Sims 2023). Both drugs are approved to treat early symptomatic Alzheimer's disease in patients with mild cognitive impairment or mild dementia and confirmed amyloid-beta pathology. They are administered viaIV infusion, every two weeks for lecanemab and every four weeks for donanemab (NLM 2024; NLM 2023).

Lecanemab was approved following the results of an 18 month, randomized, controlled, phase 3 trial (MacMillan 2023). The trial recruited a total of 1,795 people, aged 50–90 years, with early Alzheimer's disease randomized to receive lecanemab or placebo. The primary endpoint was defined as changes in Clinical Dementia Rating Sum of Boxes (CDR-SB) score at 18 months. Over the course of the study, both groups experienced a decline in cognition using this scoring system, but the decline was more severe in the placebo group. One of the secondary endpoints in this trial was changes in amyloid beta on PET scans, which was evaluated in a subgroup of 698 people. Compared with baseline, those who received lecanemab had significant reductions in brain amyloid burden, whereas the placebo group's amyloid burden slightly increased (van Dyck 2023).

Donanemab was approved following the results of a randomized controlled trial similar in design to the trial on lecanemab (Harris 2024). A total of 1,736 people, age 60–85, with early symptomatic Alzheimer's disease were randomized to receive donanemab (n = 860) or placebo (n = 876); 1,320 completed the 76-week trial. The primary outcome was twofold: change in cognitive decline, measured by the integrated Alzheimer Disease Rating Scale (iADRS) in the overall study population, and the same measurement in a subset of participants with low-to-medium levels of tau protein pathology as determined by PET scan at baseline. At the end of the trial, those in the donanemab group who had a low-to-moderate amyloid beta burden had a 35.1% slower cognitive decline, compared with placebo, based on the iADRS scale. In the overall study population that included all levels of tau pathology, there was a 22.3% slowing of disease progression in the donanemab group—again based on iADRS—compared with those who received placebo. This demonstrated that the treatment was more efficacious when administered earlier in the disease progression. One of many secondary outcomes measured was change in amyloid beta as measured by PET scan. Compared with baseline, those who received donanemab had significantly reduced amyloid burden, whereas the placebo group remained about the same. Thirteen percent of those randomized to donanemab dropped out of the trial due to adverse events (Sims 2023).

Adverse Effects of Monoclonal Antibodies

Anti-amyloid agents are associated with a significant risk of adverse effects (Press 2021). In the clinical trials leading to drug approval, the most common side effects of these two drugs were infusion-related reactions (NLM 2024; NLM 2023). The most common potentially serious side effects of the drugs are amyloid related imaging abnormalities (ARIA). Although usually asymptomatic and detected only on brain imaging, this syndrome can lead to signs and symptoms such as headache, confusion, dizziness, and seizures, and has been associated with excessive neuroinflammation. It can present as ARIA-E, which refers to edema (swelling and fluid leakage), and ARIA-H, which usually refers to small amounts of brain bleeding (microhemorrhages) or leakage of small amounts of iron-containing blood products. Less commonly, large bleeds (macrohemorrhages) or hemorrhagic stroke can occur. Both types can also occur together (Withington 2022). In both large pre-approval trials of the

two anti-amyloid therapies, incidence of either type of ARIA was two or more times as frequent in the treatment group compared with placebo (van Dyck 2023; Sims 2023).

Importantly, the greatest genetic risk factor for Alzheimer's, having two copies of *APOE-e4*, also increases the risk of developing ARIA after receiving these antibody-based therapies.

In the lecanemab trial, the rates of ARIA-H and ARIA-E, respectively, were about (Foley 2024):

- 39% and 33% among those with two copies of *APOE-e4*
- 14% and 11% among those with one copy of *APOE-e4*, and
- 12% and 5% among those without *APOE-e4*.

In the donanemab trial, ARIA-H was not reported. ARIA-E occurred in:

- 41% of those with two copies of *APOE-e4*,
- 23% of those with one copy of *APOE-e4*, and
- 16% of those without *APOE-e4*.

Importantly, these mAB therapeutics only modestly slow the progression of Alzheimer's disease, and do not restore or improve cognitive function (Press 2021). Although there were statistically significant differences in those receiving treatment compared with placebo, many experts in this field question whether these drugs produce clinically meaningful benefits, and many physicians recommend against prescribing them (Press 2021; Ebell 2024). The decision to treat Alzheimer's disease with a mAB drug should be carefully weighed against the high treatment cost and potential adverse effects.

Cholinesterase Inhibitors

Three cholinesterase inhibitors are approved for the treatment of mild-to-moderate dementia attributable to Alzheimer's disease: donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). They are symptomatic therapy; not thought to be neuroprotective or alter disease progression; and doubt persists about their benefit for long-term outcomes. Nevertheless, their use has been found to be associated with a roughly 23–40% reduction in overall mortality across numerous studies, over a follow-up period of 8–13 years. This effect appears to be more robust for donepezil and galantamine than rivastigmine. They are also known to delay the progression of cognitive decline, though this effect is small on average and of uncertain clinical importance (Press 2024; Press 2021; Truong 2022; Nielsen 2022; Zuin 2022). Response to cholinesterase inhibitors in Alzheimer's disease is highly variable, so while some patients receive no benefit, others may see significant clinical improvement. It is for this reason that individualized evaluation and management of this therapy is critical (Press 2024; NICE 2018).

Memantine

Memantine, an NMDA receptor antagonist (blocker), exhibits neuroprotective properties, and has a modest benefit in individuals with moderate-to-severe Alzheimer's disease. When added to cholinesterase therapy, it has resulted in small improvements in cognition and overall outcomes. Memantine has no benefit in cases of mild Alzheimer's disease. It is characterized by a favorable adverse effect profile (Press 2021; McShane 2019).

7 Novel and Emerging Approaches

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Evidence from population-based studies suggests beneficial effects of treatment with non-steroidal anti-inflammatory drugs (NSAIDs) in Alzheimer's disease, although these effects have not been reproduced in clinical trials (Sastre 2010). NSAIDs affect the pathology of Alzheimer's disease by inhibiting cyclooxygenase (COX) enzymes, which contribute to inflammation.

NSAIDs appear to prevent cognitive decline in older adults if started in midlife (prior to age 65) rather than late in life (Hayden 2007; Sastre 2010). Unfortunately, NSAIDs, even at normal dosages, have been associated with significant adverse effects. Long-term use of NSAIDs is associated with gastrointestinal, kidney, and cardiovascular complications (Sastres 2010; William 2011; Ejaz 2004). Low-dose aspirin, however, might be effective in reducing Alzheimer's incidence and side effects are relatively rare when only 81 mg a day are taken.

Blood Pressure Lowering Drugs

It has been hypothesized that treating cardiovascular risk factors might be an effective means of preventing or treating dementia syndromes, including Alzheimer's (Qiu 2012). Specifically, elevated blood pressure during midlife appears to be associated with Alzheimer's development in late life. This effect may be caused by a link between high blood pressure and poor amyloid beta clearance from the brain (Shah 2012).

Drugs normally used to treat hypertension, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and calcium channel blockers, have been considered as potential Alzheimer's therapies (Qiu 2010). Some research suggests that these drugs mildly reduce cognitive decline, and may reduce risk of Alzheimer's development and progression (Forette 1998; Hajjar 2008; Trenkwalder 2006). In addition to the suggested reduction in amyloid beta clearance, high blood pressure may lead to cerebrovascular changes, including reduced cerebral blood flow. Reduced cerebral blood flow may accelerate Alzheimer's disease progression. In a randomized, double-blind, placebo-controlled study, 58 participants with mild-to-moderate Alzheimer's took nilvadipine (a calcium channel blocker) or placebo for six months. In addition to reduced blood pressure, participants in the treatment group had increased cerebral blow flow in the hippocampus, an area of the brain important for forming memories and other essential tasks. These results suggest a beneficial cerebrovascular effect of using antihypertensive agents in Alzheimer's disease (de Jong 2019).

Etanercept (Enbrel®)

Etanercept (Enbrel®), a biological inhibitor of the cytokine TNF-α, is approved for the treatment of certain inflammatory conditions (e.g., rheumatoid arthritis, plaque psoriasis). When formulated as a perispinal injection and administered to Alzheimer's patients, preliminary research reports suggest that Enbrel® leads to sustained improvement in cognitive function that was evident within minutes (Tobinick 2008a,b; Tobinick 2012).

Granulocyte Colony-Stimulating Factor (G-CSF)

Granulocyte colony-stimulating factor (G-CSF) is a growth factor that stimulates production of certain white blood cells. It also supports the creation of new neurons in the brain and modulates cholinergic neurotransmission (Jiang 2010). Lower levels of G-CSF have been identified in Alzheimer's patients compared to healthy individuals (Laske 2009). An animal model of Alzheimer's found that injections of G-CSF not only rescued compromised memory and cognitive functions, but also raised levels of acetylcholine (Tsai 2007). A study at the University of South Florida seeks to evaluate the cognitive effects of administering G-CSF to Alzheimer's patients (Clinicaltrials.gov).

Brain-Derived Neurotrophic Factor (BDNF)

BDNF (*Brain-Derived Neurotrophic Factor***)**, a signaling protein active in the brain, facilitates the growth of new neurons and synapses and also reverses neuronal atrophy. Since BDNF levels decline with age and Alzheimer's disease, administration of BDNF has been suggested as a potential therapy for memory loss (Li 2009). Injecting BDNF into the brains of rodents and primates reversed synaptic damage, cell death, cognitive decline, and memory deficits (Nagahara 2009). Intensive research in rodents has led to the first promising clinical trials of intracerebral neurotrophin for AD (Schulte-Herbrüggen 2008).

Lithium

Lithium is a mineral that occurs naturally in small amounts in soil and water. Lithium-rich water has been recognized for thousands of years as a therapeutic agent for a wide variety of physical and mental disorders. More recently, high-dose lithium carbonate has become a mainstay of treatment for bipolar disorder, suicidality, and neurodegenerative conditions (Radanovic 2025).

Lithium inhibits enzymes involved in crucial cell functions: glycogen synthase kinase-3 beta (GSK-3 beta), inositol monophosphatase (IMPase), and mammalian target of rapamycin (mTOR). This stimulates autophagy (natural breakdown of cells and recycling of their useful components) and may suppress production of amyloid beta and hyperphosphorylated tau (De-Paula 2025). Lithium has been found to reduce amyloid beta and tau deposits and improve cognitive function in animal models of Alzheimer's disease (Singulani 2024). Preclinical research suggests it promotes mitochondrial function, reduces brain oxidative stress, and suppresses neuroinflammatory

signaling. It also appears to enhance growth and repair of nerves by increasing production of neurotrophic factors like brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF), as well as Beta-cell lymphoma 2 family protein (Bcl-2), which plays a role in nerve cell survival (Radanovic 2025; De-Paula 2025).

Trace-and micro-dose lithium and brain health. Lithium has a narrow therapeutic window, meaning doses used to treat mania and bipolar disorder are only slightly below amounts that can cause potentially life-threatening toxic side effects (eg, kidney damage, nerve damage, thyroid disorders, tremors, nausea, fatigue, high calcium levels, cardiac arrhythmia, confusion, vertigo, blurred vision, seizures, coma, and high white blood cell count). Early clinical research suggests **micro-dose lithium** in Alzheimer's disease patients may have beneficial effects and less toxicity. In a pilot study in 113 patients with Alzheimer's disease, those treated with 300 mcg lithium per day for 15 months experienced no change in cognitive performance while their untreated counterparts experienced significant cognitive losses (Chen 2022).

Even **trace amounts of lithium**, such as those found in drinking water, may have positive effects on brain health over long periods of time. Observational studies have noted associations between higher exposure to lithium in drinking water and lower rates of suicide, psychiatric hospitalization, violent incidents, and dementia (Radanovic 2025; De-Paula 2025; Lu 2024). One study collected lithium concentrations in drinking water in 808 cities and wards in Japan for five years (2010–2014) and found higher lithium levels were associated with lower prevalence of Alzheimer's disease in women, but not men (Huang 2024). A study that examined changes in Alzheimer's disease mortality rates in 234 counties in Texas, using records from 2000–2006 and comparing them to records from 2009–2015, found counties with drinking water lithium levels that were below the median of 40 mcg/L had greater increases in Alzheimer's disease mortality rates (Devanand 2022). Another study performed in Denmark used data from 73,731 dementia patients and 733,653 people without dementia and found those with dementia were more likely to have lower exposure to lithium from drinking water. Specifically, the incidence of dementia was higher where drinking water lithium concentrations were 5.1–10 mcg/L and was lower where lithium concentrations were > 10 mcg/L (Nunes 2013). A 2014 review reported nine of 11 studies found trace doses of lithium, mainly from drinking water, were associated with lower rates of suicide, homicide, mortality, and crime (Forlenza 2019).

Preclinical research further adds to the evidence that lithium plays a role in healthy brain function and suggests supplementation may be beneficial. A 2025 study found a low-lithium diet in laboratory mice led to increased accumulation of amyloid beta and phosphorylated tau, promoted neuroinflammation and nerve damage, and accelerated cognitive decline. Next, the researchers showed supplementing with **lithium orotate** (but not lithium carbonate) reduced neuropathologic changes associated with Alzheimer's disease in a mouse model of the condition and in aging wild-type lab mice. The same publication described findings from a study examining the concentrations of 27 trace minerals in brain tissue and blood samples from older individuals who had died with no cognitive impairment, mild cognitive impairment, or Alzheimer's disease. Those with mild cognitive impairment or Alzheimer's disease were found to have lower lithium concentrations in the prefrontal cortex, a brain region highly affected in Alzheimer's disease. There were no differences in other mineral concentrations, nor in blood levels of lithium (Aprahamian 2014). A pilot trial in nine healthy men showed small increases in brain lithium concentrations were detectable using specialized MRI after 14 and 28 days of supplementation with 5 mg lithium (as lithium orotate) (Damiano 2023). These intriguing findings, coupled with the other interesting clinical data on lithium in the context of various neuropsychological conditions, pave the way for larger randomized trials to assess the efficacy of micro-dose lithium supplementation in preserving cognitive function over time.

High-dose, medically supervised lithium therapy and brain health. Several studies have investigated the relationship between **high-dose, medically supervised lithium therapy** (typical therapeutic dose: 600–1,800 mg daily) and Alzheimer's disease risk. An observational study that used data from 29,618 patients at a mental health clinic in the United Kingdom found lithium-treated patients had a 44% lower risk of dementia, including due to Alzheimer's disease and cerebrovascular disease, than patients treated without lithium (Ishii 2021). A meta-analysis that included seven observational studies found lithium therapy was associated with a 41% reduction in Alzheimer's disease risk and a 24% reduction in overall dementia risk (Muronaga 2022). However, another meta-analysis that included data from eight studies found, after restricting the analysis to patients with bipolar disorder, lithium use had no effect on risk of Alzheimer's disease or other major neurocognitive disorders (Fajardo 2018).

One randomized placebo-controlled trial found lithium therapy may be beneficial in Alzheimer's disease patients. The trial, which included 58 Alzheimer's disease patients with high agitation and aggression scores, found 150–600 mg of lithium carbonate daily for 12 weeks improved clinical global impression scores compared with placebo without causing significantly more safety issues. Although a greater percentage of lithium-treated participants had reduced agitation and aggression scores (31.6% vs. 17.9%), this difference was not statistically significant (Kessing 2017). A 2014 review of the research reported on four older, randomized, placebo-controlled trials, all of which indicated lithium treatment resulted in some clinical or biological benefits in subjects with Alzheimer's disease. Additionally, five epidemiological studies found an association between lithium and low dementia rates (Forlenza 2019).

Findings from another clinical trial indicated lithium may also be helpful for slowing progression of mild cognitive impairment. In the double-blind, randomized, controlled trial, 52 subjects with amnestic mild cognitive impairment received lithium carbonate, at doses beginning at 150 mg and increased to reach target blood levels of 0.25–0.5 mEq/L, or placebo. (Target blood levels for treating bipolar disorder are generally 0.8–1.0 mEq/L). Cognitive and functional performance remained stable during the first two years of lithium treatment but declined significantly with placebo. The trial was extended as a single-blind study for another two years, and 40 subjects completed this phase. After a total of three years of treatment, CSF levels of the biomarker amyloid beta 42 increased by 30% in the lithium-treated participants, indicating less amyloid beta accumulation in the brain. A subgroup analysis found this lithium-related rise in CSF amyloid beta 42 occurred only in those with higher baseline levels. After four years, fewer lithium-treated subjects progressed to dementia, but the difference was not statistically significant (Mauer 2014). No changes in kidney function were detected, but lithium-treated subjects had higher incidences of weight gain, decreased thyroid function, new-onset diabetes, and abnormal heart rhythms (Aron 2025). In a follow-up study, the researchers examined long-term outcomes in a group of 36 of the original participants 11–15 years later. The study found those who received lithium in the trial performed significantly better on cognitive function tests (Mini Mental State Exam and Verbal Fluency Test) than those who received placebo (Neal 2024). Taken together, the findings suggest lithium's effect on brain function may be gradual and long-term.

Selective Estrogen Receptor Modulators (SERMs)

Selective estrogen receptor modulators are drugs that either increase or decrease estrogen signaling, depending on the tissue type (McDonnell 2002). Currently, the most studied and clinically relevant SERMs are tamoxifen and raloxifene. Tamoxifen is best recognized as a potent antagonist (blocker) of estrogen action in breast tissue. However, low concentrations of tamoxifen have been noted to protect cultured neurons from amyloid beta and glutamate toxicity (O'Neill 2004). In postmenopausal women, raloxifene, at a dose of 120 mg/day, has been linked with reduced risk of cognitive impairment and development of Alzheimer's disease (Yaffe 2005).

Vaccines

Vaccines are being developed in hopes of clearing amyloid beta from the brains of Alzheimer's patients immunologically (Upadhyaya 2010). Initial research suggests a mechanistic possibility that this approach could work (Holmes 2008), but many obstacles still impede the development of clinically effective vaccines for Alzheimer's disease (St. George-Hyslop 2008). For example, some studies suggest that simply eliminating amyloid beta may not be sufficient, and that targeting other aspects of Alzheimer's pathology in conjunction with amyloid beta vaccination may have a better chance of success (Aranda-Abreu 2011).

Anti-apoE4 Immunotherapy

The variant apolipoprotein E4 (ApoE4) gene is one of the strongest genetic risk factors for late-onset Alzheimer's disease (Kim 2012; Theendakara 2018). In mice, immunotherapy targeting human ApoE has been shown to reduce amyloid beta levels in the brain (Kim 2012). Amyloid beta can form deposits in the cerebral vasculature as well (cerebral amyloid angiopathy). In a mouse model with amyloid plaque in the brain as well as cerebral amyloid angiopathy, treatment with an anti-human ApoE antibody reduced both brain amyloid plaque and cerebral amyloid angiopathy. When the researchers used an antibody specific to amyloid beta, rather than ApoE, it reduced brain amyloid plaque but had no effect on cerebral amyloid angiopathy. In addition, the anti-amyloid beta antibody worsened brain microhemorrhages while the anti-human ApoE antibody did not. The anti-human ApoE antibody improved the function of cerebrovascular arteries and reduced pro-inflammatory genes in the cortex as well.

These findings suggest that targeting ApoE with immunotherapy may reduce amyloid beta deposits while protecting the brain vasculature (Xiong 2021), but clinical trials are needed to confirm these results.

Antibiotics

As mentioned above, the theory that Alzheimer's disease could be caused by infectious organisms is gaining traction within the scientific community. Based upon these findings, it has been proposed that antibiotics may represent a viable treatment for Alzheimer's disease (Miklossy 2011).

Early clinical trials have noted marked improvements in Alzheimer's patients following antibiotic treatment. In one such trial, 100 subjects with probable Alzheimer's disease were treated with the antibiotics doxycycline and rifampin for three months and followed for a year. At six months post-treatment, subjects who received antibiotics displayed significantly less cognitive decline than those who received a placebo, and the effect was even more pronounced at 12 months. Antibiotic recipients also showed less behavioral dysfunction at three months. The researchers concluded that "therapy with doxycycline and rifampin may have a therapeutic role in patients with mild to moderate [Alzheimer's disease]" (Loeb 2004). Another smaller trial found Alzheimer's patients treated with 100 mg daily of the antibiotic D-cycloserine displayed significantly improved scores on a standardized assessment of cognitive function (Tsai 1999).

However, subsequent trials have failed to replicate these results. The Doxycycline and Rifampin for Treatment of Alzheimer's Disease (DARAD) trial enrolled 406 patients with mild-to-moderate Alzheimer's disease and treated them with doxycycline and rifampin for a year. There were no beneficial effects seen with the treatment (Molloy 2013). Additionally, a review of four studies found that D-cycloserine did not have a positive effect on cognitive outcomes in Alzheimer's disease patients (Laake 2002). It is possible that the success of antibiotics in Alzheimer's disease treatment hinges on the presence of an actual infection, such as with *Spirochetes* (a family of bacteria) and *Porphyromonas gingivalis*. The lack of such an infection may make antibiotic treatment unnecessary and ineffective.

It has become clear that the gut microbiome plays a significant role in brain health. In fact, Alzheimer's disease may be associated with alterations in the microbiome, such as dysbiosis, which may be a source of infection and neuroinflammation. As such, modifying the microbiome with antibiotics or probiotics in Alzheimer's disease is an interesting ongoing area of research (Angelucci 2019). However, the root cause of Alzheimer's disease is still unclear, and it may be the case that different approaches should be taken depending on the individual patient. The future of antibiotics in Alzheimer's disease treatment will depend upon the results of further preclinical and clinical studies.

Piracetam

Piracetam has been studied in a wide-range of patient populations and has demonstrated small benefits in a variety of models of neurological disorders. Multiple mechanisms for the observable effects of piracetam on brain function have been proposed, though a precise description of its mode of action has yet to be elucidated. Preliminary studies suggest that piracetam may modulate the signaling of multiple neurotransmitter receptors, and improve neuronal membrane fluidity (Malyka 2010; Muller 1997).

A comprehensive review that assessed the efficacy of piracetam in older subjects suggests that the drug may provide appreciable benefits for cognitive dysfunction. The reviewers concluded that *"…the results of this analysis provide compelling evidence for the global efficacy of piracetam in a diverse group of older subjects with cognitive impairment*" (Waegemans 2002). Additionally, a piracetam analog called levetiracetam was shown to reverse synaptic and cognitive deficits in an animal Alzheimer's model (Sanchez 2012).

Zileuton

5-lipoxygenase (5-LO) is an enzyme that produces several pro-inflammatory lipid molecules, most of which are known as leukotrienes (Poeckel 2010; Hedi 2004). 5-LO and some of the leukotrienes it produces have been implicated in the inflammation that accompanies various chronic diseases, including Alzheimer's disease (Vagnozzi 2017; Joshi 2014; Chinnici 2007). These inflammatory mediators have also been implicated in other tauopathies, which are neurodegenerative conditions in which toxic protein deposits, known as tau protein, accumulate inside neurons. Alzheimer's disease is a type of tauopathy (Giannopoulos 2018a; Chu 2016).

A 2018 study suggests zileuton (Zyflo), a leukotriene inhibitor approved over two decades ago to treat asthma, may have the potential to reduce neurodegeneration associated with tau protein accumulation (Israel 1996; Watkins 2007). Using an animal model of neurodegeneration, the study tested whether inhibiting leukotriene synthesis could help after cellular damage in the nervous system has already started. Twelve-month-old mice with a tauopathy were randomized to receive zileuton or placebo for 16 weeks (Giannopoulos 2018b). As expected, at the beginning of the study memory and spatial learning were impaired in the mice with the tauopathy compared with control mice (Giannopoulos 2018b). Zileuton reduced these behavioral impairments. When the brains of the animals were examined, mice that received zileuton had about 90% fewer leukotrienes in their brains and about 50% less tau protein. The animals treated with zileuton also had decreased neuroinflammation and increased levels of three biochemical markers that reflect synaptic integrity (Giannopoulos 2018b).

Other studies also report benefits with zileuton treatment in neurodegenerative diseases. In a mouse model of Alzheimer's disease, three months of zileuton treatment significantly decreased amyloid-beta levels between the neurons and improved cognitive function (Di Meco 2014). Another study on the same mouse model of Alzheimer's disease showed that zileuton treatment led to a significant improvement in working memory and communication among brain cells (Giannopoulos 2014). Similar findings have been reported in other preclinical studies as well (Chu 2013; Chu 2011). Moreover, in rodent models of stroke, zileuton decreased inflammation, protected against brain damage, and improved neurological deficits (Tu 2016; Silva 2015). Zileuton also inhibited 5-LO activation and cell injury in a laboratory model of Parkinson's disease (Zhang, Zhang 2011). In a laboratory study, zileuton protected mouse neurons against chemical toxicity caused by exposure to glutamate (Liu 2015).

Klotho

Klotho, named after one of the goddesses of destiny in Greek mythology, is a gene encoding the Klotho protein, which plays a crucial role in promoting longevity (Prud'homme 2022). Lower blood plasma levels, which is also known to correlate with CSF levels (Kundu 2022), of the Klotho protein have been linked to various age-related diseases, including chronic kidney disease, cardiovascular diseases, osteoporosis, and cognitive decline. As a result, increasing Klotho levels through gene therapy or recombinant protein administration is being explored as a potential treatment for age-related conditions like Alzheimer's (Abraham 2022).

It was first shown in the late 1990's that mutations in the *Klotho* gene led to systemic aging and reduced lifespan in mice (Kuro-o 1997). This discovery was confirmed by numerous subsequent mice studies (Kurosu 2005; Motoko 2008). Klotho appears to modulate the aging process by regulating several key pathways linked to aging, such as insulin signaling and Wnt signaling (Kanbay 2024). In a series of experiments conducted at University of California-San Francisco, it was demonstrated that elevating Klotho levels in Alzheimer's mouse models mitigated premature mortality, cognitive impairment, and behavioral issues. Klotho appeared to increase the concentration of specific receptors at neuronal synapses, potentially boosting neural communication (Dubal 2015). In addition, it was found that overexpressing Klotho in the brain alleviated Alzheimer's-like pathology and improved cognitive deficits in mouse models (Zeng 2019). Recombinant Klotho administration also improved cognition in aged rhesus monkeys (Castner 2023).

In humans, Klotho blood serum levels are correlated with cognitive health. Researchers often employ the MMSE to screen for dementia, with higher scores indicating better cognitive function. Studies revealed that participants who scored higher on the Mini-Mental State Examination exhibited higher levels of Klotho (Kundu 2022; Linghui 2023). It was shown that older adults with Alzheimer's have lower levels of Klotho protein in their CSF compared to those without Alzheimer's, concentrations averaging 664 pg/mL versus 776 pg/mL, respectively (Semba 2014). It has also been shown that individuals with the lowest blood levels of Klotho have a significantly increased risk of severe deep white matter lesions, which are commonly associated with various neurological conditions, including vascular dementia, Alzheimer's disease, and multiple sclerosis (Kuriyama 2018).

Interventions aimed at enhancing the level of Klotho are being explored as a possible strategy to treat or prevent the onset of Alzheimer's in individuals at high risk. Several methods have been proposed, including administration of small molecule drugs, protein replacement therapy, senolytic therapy, exercise regimens, and recombinant gene therapy; however, these approaches have yet to be validated by interventional clinical studies in patients with Alzheimer's disease (Kundu 2022; Zhu 2022; Corrêa 2022).

TB006

As of mid-2024, TB006—a monoclonal antibody and investigational new drug under development by the company TrueBinding—is approved for compassionate use. TB006 targets galactose-specific lectin 3 (galectin-3), a protein involved in the formation of neurotoxic amyloid beta oligomers and plaques, and with neuroinflammation (TrueBinding 2024a; TrueBinding 2024b). Galectin-3 is associated with activation of microglia and cognitive impairment, and may play a role in several different neurodegenerative diseases, though it may be neuroprotective under certain conditions (Garcia-Revilla 2022). In addition, galectin-3 has been demonstrated to be elevated in the hippocampus, cortex, and CSF of people with Alzheimer's disease; and the presence of microglia that express galectin-3 is associated with amyloid beta plaque and tau tangles in Alzheimer's (Boza-Serrano 2022). This has led to special interest in galectin-3 as a possible treatment target.

Microglia are immune cells that play a crucial non-immune role in brain development. Later in life, in brain injuries and in diseases affecting the central nervous system, they can be harmful or helpful depending on the situation (Li 2018). This can include scavenging of amyloid beta and tau, which can be beneficial. At later stages of Alzheimer's, overactivation of microglia from chronic inflammation and excessive oxidative stress may lead to neurotoxicity (Merighi 2022).

In an early-stage (phase-1b/2) trial, safety and short-term, preliminary efficacy was assessed in a total of 157 people, aged 50 and over, with mild-to-severe Alzheimer's disease. The participants were randomized to receive a total of five intravenous infusions of TB006 weekly, as part of one of three ascending dosage groups, or a placebo for one month (Bryson 2023; TrueBinding Inc 2023). They were followed for up to 104 days. Compared to baseline, by day 36 the treatment group had significant improvements in the Mini-Mental State Examination, one of the trial's secondary outcomes. At that same time point, blood levels of a toxic form of amyloid beta, called amyloid beta-42, had also been significantly reduced in the treatment group. The trial failed to show statistically significant improvement based on the CDR-SB score. However, TB006 was shown to be safe and well tolerated over the follow-up. The most common side effect was infusion-related reactions (Bryson 2023).

Following this study, the researchers initiated a long-term open label trial, with once per month TB006 treatment and two-year follow-up. Preliminary results from the open-label trial showed that among 79 people who completed three months of treatment, 47% showed signs of disease reversal or cognitive improvement, and in 28% symptoms did not improve or worsen. Significant adverse events were not reported (Bryson 2023).

There are currently no clinical trials of TB006 enrolling new patients. To provide access to TB006 as an investigational drug, TrueBinding has launched an expanded access (compassionate use) program for interested patients who can cover the cost of their own medication and treatment (TrueBinding 2024a).

Additional Emerging Therapies

The following compounds hold promise, but more research is needed before their potential therapeutic value in Alzheimer's disease can be deciphered:

- Rapamycin (Cai 2012) – An immunosuppressive drug that also improves removal of cellular debris, including amyloid beta, via enhancing a process called autophagy.
- Secretase inhibitors (used only in preliminary human trials) (Fleisher 2008). These drugs target the enzymes that cleave amyloid precursor protein into amyloid beta fragments. In theory, blocking secretase activity would slow accumulation of amyloid beta.

8 Hormone Replacement Therapy In Alzheimer's Disease

A potential strategy to modulate factors that underlie Alzheimer's disease is to target age-related depletion of sex hormones. Following menopause, women experience a rapid loss of estrogen and progesterone. Similarly, men experience an age-related loss of testosterone, a condition known as androgen deficiency or hypogonadism. Since sex hormones have fundamental roles in neural health, hormone replacement therapy (HRT) is an intriguing therapeutic consideration in Alzheimer's disease (Barron 2012).

Pregnenolone

In humans, the steroid hormone cascade begins with pregnenolone, a hormonal derivative of cholesterol.

Subsequently, metabolic modification of pregnenolone gives rise to dehydroepiandrosterone (DHEA), which is then converted into estrogens, progesterone, and testosterone (Miller 2002; Luu-The 2010). Aging is associated with a steep decline in the production of pregnenolone and other steroid hormones. French researchers have shown that pregnenolone directly influences acetylcholine release in several key brain regions. They also demonstrated pregnenolone's ability to promote new nerve growth (Mayo 2003; Mayo 2005).

Dehydroepiandrosterone (DHEA)

DHEA has neuroprotective effects and several studies indicate that patients with Alzheimer's disease have lower levels of DHEA than those without the disease (Hillen 2000; Polleri 2002; Weill-Engerer 2002). In animal models, DHEA improved memory in rodents that overexpressed amyloid beta (Farr 2004).

Estrogen

Estrogen is an important regulator of neural function. It has been reported to protect neurons from amyloid beta-mediated toxicity as well as to reduce neuronal death in cell culture (Zhang 2003; Bailey 2011). However, the role of estrogen replacement therapy in brain protection is not entirely clear, and may be dependent upon age at initiation (Maki 2012). One research team suggested that estrogen therapy could be beneficial when neurons are still healthy, but might exacerbate Alzheimer's disease once neurological health is already compromised (Brinton 2005). The Cache County Study reported that Alzheimer's risk was reduced with long-term HRT (exceeding 10 years) compared to short-term HRT (Zandi 2002), suggesting that early initiation (near menopause) may be an important factor (Carroll 2012; Barron 2012).

Progesterone

Like estrogen, progesterone levels decline during normal aging. Declining progesterone levels are linked with increased amyloid beta, increased NFTs, increased neuron death, and impaired cognition; all of which are associated with Alzheimer's disease (Barron 2012). Therefore, some scientific evidence suggests that progesterone may be effective for the prevention of degenerative brain diseases including Alzheimer's disease (Schumacher 2004).

Testosterone

Unlike the sudden drop of female hormones that occurs during menopause, loss of testosterone is gradual in men, with bioavailable levels declining 2-3% annually from approximately 30 years of age (Barron 2012). Several studies have linked low testosterone to increased risk of Alzheimer's disease in men. In a clinical trial involving 16 male Alzheimer's patients and 22 healthy controls, 24 weeks of testosterone replacement therapy was associated with improved quality of life compared to placebo among those with Alzheimer's disease (Lu 2006).

Melatonin

Endogenous melatonin not only helps regulate the sleep-wake cycle, but is a strong antioxidant (Bubenik 2011). Melatonin secretion within the brain declines with age and lower levels are associated with a higher degree of cognitive impairment (Magri 2004). Melatonin concentration is lower in Alzheimer's patients than in healthy people of the same age (Cardinali 2011). In animal studies, melatonin improved cognitive function and reduced oxidative injury and deposition of amyloid beta (Cheng 2006). Additional studies have confirmed that melatonin protects brain cells from amyloid beta toxicity by impairing amyloid beta generation and slowing the formation of plaque deposits (Wang 2006a). Melatonin has also been shown to reduce tau tangles and amyloid beta toxicity (Srinivasan 2006).

9 Dietary and Lifestyle Management Strategies

Research suggests specific dietary patterns—generally characterized by higher intake of plant-based, minimally processed foods as in the Mediterranean diet—as well as some nutritional components of such a diet may have promising potential for preventing and treating Alzheimer's disease (Christimann 2025; Booth 2024).

Mediterranean Diet

The Mediterranean diet is associated with a lower risk of Alzheimer's disease and other forms of dementia (Nucci 2024). Its neuroprotective benefits are attributed to its rich content of essential fatty acids, polyphenols, and

vitamins, which help reduce oxidative stress and inflammation, and promote healthy changes in gut microbes that may help preserve and improve cognitive function (Siervo 2021; Solch 2022).

In a cohort study, 581 elderly people were followed for an average of about seven years before death; dietary patterns were evaluated by questionnaires. Autopsy reports revealed a connection between adherence to a Mediterranean diet or MIND diet (a combination of the Mediterranean diet and the Dietary Approaches to Stop Hypertension, or DASH, diet) and reduced amyloid-beta pathology (presence and distribution) and load (quantity). Those in the highest one-third of green leafy vegetable intake had significantly less amyloid-beta pathology compared with those in the lowest (Agarwal 2023).

A meta-analysis combining findings from multiple studies examined the relationship between MRI brain markers and adherence to the Mediterranean diet. The analysis of approximately 43,000 participants from 13 cross-sectional studies—analyzing data from a population at a specific point in time—found no significant differences in total brain volume, gray matter volume, or hippocampal volume between individuals with high adherence to the diet and those with low adherence. However, those who closely followed the Mediterranean diet showed lower levels of white matter hyperintensity, damage to the myelin sheath that is a common marker of small vessel disease and vascular risk factors. White matter, which contains the axons, or nerve fibers, that transmit nerve impulses, is essential for communication between brain regions. Increased white matter hyperintensity can disrupt this connectivity and contribute to cognitive decline (Brugulat-Serrat 2020). The meta-analysis also included seven cohort studies spanning 18 months to nine years and involving 1,938 participants. These studies also found no significant changes in total brain volume or gray matter volume associated with higher adherence to the Mediterranean diet (Wang 2025).

A meta-analysis examining the relationship between the Mediterranean diet and dementia risk in older adults included 21 studies (mostly cross-sectional and cohort studies) with a total of about 66,000 participants. The findings showed that individuals who followed the Mediterranean diet had an 11% lower probability of developing dementia compared with those who did not. When the analysis was limited to cohort studies with a total of about 55,000 participants, a 16% reduction in risk of developing dementia was observed. When only Alzheimer's disease was considered across all studies, there was a 27% reduced likelihood of developing Alzheimer's disease among those with high adherence to the Mediterranean diet (Nucci 2024).

Research on the Mediterranean diet's effects in people already diagnosed with Alzheimer's is more limited. A 2024 cross-sectional study compared the lifestyle and dietary patterns of 73 people with mild-to-moderate Alzheimer's to 73 age-matched healthy control participants. Those with Alzheimer's had significantly lower adherence to the Mediterranean diet and engaged in less physical activity. Only one person with Alzheimer's had high adherence to the diet compared with four people in the control group. Additionally, about half the people in the Alzheimer's group had at least a moderate adherence to the Mediterranean diet, while this was true for 82.2% of controls (Dominguez 2024).

Vegetarian And Vegan Diets

Limited evidence suggests that a vegetarian or vegan diet may reduce the risk of Alzheimer's or other dementias. These diets offer benefits and some drawbacks associated with varying intake of beneficial nutrients that may protect against cognitive decline. Some ways that vegetarian or vegan diets may provide brain health benefits stem from their low saturated fat content and elimination of potentially pro-inflammatory compounds. In addition, they may also result in favorable changes to the gut microbiome that could influence the course of cognitive decline (Katonova 2022).

Diets higher in unprocessed white meat, fish, or eggs have not been shown to raise the risk of Alzheimer's disease. In fact, research suggests that they are likely protective against Alzheimer's (Quan 2022; Talebi 2023; Pan 2024). Only high-fat dairy products have been linked with greater risks. However, greater total dairy intake is associated with protection (Grant 2016; Villoz 2024). Red meat may raise the risk of Alzheimer's, but the evidenced is nuanced. In observational research, reducing red meat consumption, particularly process red meet, has been associated with a reduced risk of Alzheimer's disease; however, research has not consistently shown that replacing processed and unprocessed red meat with vegan or vegetarian options results in further cognitive protection (Li 2025; Zhang 2021).

In a cohort study of about 44,000 people in the United States (mean age 78 years), the daily consumption of one or more servings of unprocessed red meat compared to less than a half a serving was associated with a 16% higher risk of self-reported cognitive decline over the course of two to four years. Within that same study, an analysis was conducted on about 134,000 people (mean age 49 years) followed for up to 43 years. It showed that replacing one daily serving of processed red meat with nuts and legumes was associated with a 19% lower risk of dementia (Li 2025). A larger cohort study followed nearly 500,000 people in the UK Biobank (ages 40–69 years) for about eight years. During that time, each 25 gram per day intake of processed meat was associated with a 44% greater risk of all-cause dementia and a 52% greater risk of Alzheimer's. Conversely, each 50 gram per day increment in unprocessed red meat was associated with a 19% lower risk of all-cause dementia and 30% reduced risk of Alzheimer's (Zhang 2021).

Studies evaluating dementia risk among vegetarians or vegans compared to meat eaters have produced mixed results (Abris 2024; Tsai 2022; Iguacel 2021). The only interventional studies on vegetarian and vegan diets in the context of dementia were done by Dean Ornish and his colleagues in 1990 (Ornish 1990) and 2024 (Ornish 2024). In both trials, multiple other interventions were added alongside the dietary changes. Therefore, it cannot be concluded that diet was solely responsible for the cognitive benefits.

In summary, convincing evidence suggests that diets lower in certain animal products, such as processed red meat, are protective against Alzheimer's and related dementias. However, complete elimination of animal products has not been shown to have further benefits. As of mid-2025, a properly designed study that controls for confounding factors, such as smoking, exercise, or processed food intake, has not been conducted on a vegetarian or vegan diet in relation to Alzheimer's.

Ketogenic Diet

The ketogenic diet, which involves a strict regimen of very high fat, moderate protein, and low carbohydrates, prompts the body to switch from its normal metabolic process of burning glucose to burning ketones. Ketones are substances produced when the body breaks down fat instead of glucose for energy. Initial research is being carried out to investigate the impact of the ketogenic diet on Alzheimer's development and progression (Jóźwiak 2011). In a transgenic mouse model, 43 days on a ketogenic diet resulted in ketone production and decreased amyloid beta levels (Van der Auwera 2005).

The ketogenic diet can cause adverse side effects (e.g., increased cholesterol levels, kidney stones, and gastroesophageal reflux) (Jóźwiak 2011).

Low-Calorie Diet (Calorie restriction)

Researchers reported that a low-calorie diet reduces the risk of mild cognitive impairment, which is the stage of memory loss between normal aging and overt dementia. Healthy study subjects between ages 70 and 89 were divided into three groups based on their normal daily caloric intake: 600-1526; 1526-2143; and 2143-6000 calories per day. Those in the highest calorie group were almost twice as likely to develop mild cognitive impairment. This association was found to be dose-dependent; the risk increased gradually with the increase in calories (Geda 2012; Pasinetti 2007).

Exercise

Regular exercise is associated with increases in brain-derived neurotrophic factor (BDNF), hippocampal neurogenesis, synaptic plasticity, brain volume, dendritic spines, and vascular function, as well as a reduction in cell death (Cotman 2007; van Praag 2009). Research focusing on Alzheimer's patients found that those who exercised had reduced brain atrophy compared with those who did not (Burns 2008). As little as three minutes of very intense exercise has been shown to sharply raise BDNF levels, as well as produce a 20% improvement in memory (Winter 2007).

The benefits of exercise may be enhanced by consumption of omega-3 fatty acids and plant polyphenols (van Praag 2009). Exercise and diets rich in omega-3 fatty acids have been shown to help normalize BDNF levels (Gomez-Pinilla 2008; Wu 2004a).

Nutritional Interventions Studied in Alzheimer's

Huperzine A

Derived from the plant *Huperzia serrata*, huperzine A is an NMDA receptor blocker than can help prevent or reduce glutamate-mediated excitotoxicity (Wang 1999). It can also help block acetylcholinesterase, the enzyme that destroys acetylcholine, which is critical for cognition and memory. This mechanism of action is similar to that of several Alzheimer's drugs, such as donepezil and galantamine (Sun 1999). Some studies show that huperzine A may penetrate the blood-brain barrier, have greater bioavailability, and have longer duration of action than some pharmaceuticals (Wang 2006b; Bai 2000). Although not all studies on Huperzine show positive effects on cognition (Rafii 2011), a review of previous studies revealed that doses of 300-500 mcg of huperzine A daily significantly improved the standardized cognitive test scores of Alzheimer's patients, and were slightly safer than some drug alternatives (Wang 2009).

Lion's Mane (*Hericium erinaceus*)

Hericium erinaceus (lion's mane mushroom) is an edible and medicinal mushroom that has been used traditionally in Asia to improve memory (Zhang 2017; Phan 2014; Khan 2013). Some of the major beneficial components found in this mushroom include beta-glucan polysaccharides; erinacine A, C, S; and sesterterpene (Tsai-Teng 2016; Khan 2013). Several laboratory and animal studies reported that compounds from *H. erinaceus* have lipid-lowering, antioxidant, anti-hypertensive, neuroprotective, anti-tumor, antibacterial, and immune-stimulating effects (Zeng 2018; Zhang 2017; Khan 2013).

In a double-blind placebo-controlled clinical trial, Japanese men and women between 50 and 80 years who had been diagnosed with mild cognitive impairment received 250 mg *H. erinaceus* tablets containing 96% of the mushroom dry powder three times daily for 16 weeks. After eight weeks, the *H. erinaceus* group exhibited better cognitive scores than the placebo group, and the improvement continued through the supplementation period (Mori 2009).

In a mouse model of Alzheimer's disease, 30 days of oral administration of an *H. erinaceus* extract reduced the production and deposition of amyloid in animals' brains and supported the growth of brain cells. Longer-term administration, for five months, helped recover cognitive decline in the same study (Tzeng 2018). The benefits of *H. erinaceus* extracts for cognition are supported by other studies on mouse models of Alzheimer's disease, which found that the extract improved nerve cell formation, decreased cellular damage, and recovered some of the animals' behavioral deficits (Tsai-Teng 2016). In another study on mice with Alzheimer's disease, a *H. erinaceus* extract increased serum and brain levels of the neurotransmitter acetylcholine, levels of which decline in Alzheimer's disease (Zhang 2016; Mufson 2008; Kelley 2007). In rats with neuronal injury, an aqueous extract of *H. erinaceus* promoted the regeneration of peripheral nerves (Wong 2016).

In a different mouse model,supplementation with a *H. erinaceus* extract blocked inflammatory signaling and reversed the depression-like behavior caused by stress (Chiu 2018). These findings are significant, considering that up to 50% of Alzheimer's patients experiencedepression (Lyketsos 2002; Chi 2014; Modrego 2010). Benefits have also been observed in healthy mice, in which oral supplementation with a *H. erinaceus* extract improved recognition memory and neurotransmission in a brain area involved in cognitive function and emotions (Brandalise 2017).

Laboratory studies revealed that extracts or compounds isolated from *H. erinaceus* support neuronal growth and survival (Zhang 2017). An *H. erinaceus* water extract was neuroprotective in laboratory experiments and decreased the accumulation of reactive oxygen species inside cells (Zhang 2016).

Benfotiamine

Benfotiamine is a fat-soluble form of vitamin B1 (thiamin) that acts on multiple metabolic pathways, including limiting the production of advanced glycation end products (AGEs). AGEs are metabolic products formed by the non-enzymatic interaction of glucose with proteins and are harmful in the body. Benfotiamine has also shown anti-inflammatory and antioxidant activity. In some preclinical models, benfotiamine has demonstrated inhibition of GSK-3, an enzyme implicated in the pathogenesis of several diseases, including Alzheimer's disease (Sun 2012;

Markova 2017). In animal models of Alzheimer's disease, administration of benfotiamine has shown promise: animals given benfotiamine have been shown to have decreased levels of amyloid beta and phosphorylated tau proteins, restored neurogenesis, and improved memory (Gibson 2020).

In a 12-month, double-blind, randomized, placebo-controlled trial, 70 participants with mild cognitive impairment or mild Alzheimer's dementia were give benfotiamine or placebo. At the end of the trial, the participants who took benfotiamine experienced less cognitive decline than those in the placebo group. Specifically, Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores and clinical dementia ratings increased 43% less and 77% less, respectively, for the benfotiamine group than the placebo. In addition, benfotiamine reduced serum levels of AGEs compared with placebo. The effects of benfotiamine appeared to be stronger in participants without the variant ApoE4 gene (Gibson 2020). In a small clinical study in five patients with mild-to-moderate Alzheimer's disease receiving 300 mg benfotiamine daily for 18 months, participants' MMSE scores increased by an average of 3.2 points by the end of the trial (Pan 2016).

Lipoic Acid

This potent antioxidant has been shown to reduce inflammation, chelate metals, and increase acetylcholine levels in animal studies (Milad 2010; Holmquist 2007). Although there have been only a few small human studies on lipoic acid in Alzheimer's, the results hold promise. In one study, nine patients with Alzheimer's or similar dementias took 600 mg of lipoic acid daily, for an average of 337 days. At the outset of the study, cognitive scores were declining continuously. By the end of the study, they had stabilized (Hager 2001). A second study extended this regime to 43 patients for 48 months and the disease progressed extremely slowly (compared with the typical disease progression rate seen in untreated patients) (Hager 2007).

Acetyl-L-carnitine

Acetyl-L-carnitine (ALC) is an antioxidant that has been shown to correct acetylcholine deficits in animals and protect neurons from amyloid beta by supporting healthy mitochondria (Butterworth 2000; Dhitavat 2005; Virmani 2001). A group of researchers combined ALC with lipoic acid and found they could reverse some mitochondrial decay in aged animals. The same research group conducted a comprehensive review of 21 clinical trials of ALC in cases of mild cognitive impairment and mild Alzheimer's disease. They found significant benefit in the ALC group compared to placebo (Ames 2004).

ALC has been noted to reduce the effects of high homocysteine levels in mice (e.g., deterioration of blood-brain barrier integrity, increased levels of amyloid beta, neurofibrillary tangle formation, and cognitive dysfunction) (Zhou 2011). Further, a small clinical trial among people with Alzheimer's disease showed that 3,000 mg of ALC daily resulted in significantly less cognitive deterioration over a 1 year period (Pettegrew 1995). Laboratory studies have found that ALC can reduce amyloid beta neurotoxicity by affecting amyloid precursor protein metabolism (Epis 2008).

Panax ginseng

Ginsenosides, steroid-like compounds in extracts of the plant *Panax ginseng (P. ginseng)*, are believed to be the active chemicals that produce memory benefits (Christensen 2009). A study that tested 200, 400, and 600 mg of *P. ginseng* on healthy patients without cognitive problems found that 400 mg produced the greatest benefit and boosted memory for 1-6 hours after dosing (Kennedy 2001). When higher dosages were tested on 58 Alzheimer's disease patients, 4.5 g of *P. ginseng* given daily over 12 weeks produced gradually increasing improvements, as compared to the 39 control patients whose cognitive abilities declined over the same period, though the improvements faded 12 weeks after discontinuation (Lee 2008).

Vitamins C and E

Vitamins C and E are well known for their antioxidant properties. Several studies have examined their combined potential in reducing the oxidative damage associated with Alzheimer's disease (Gehin 2006; Shireen 2008). One observational study showed that supplementation with vitamins C (500 mg/day) and E (400 IU/day) was associated with reduced prevalence of Alzheimer's disease (Boothby 2005). Another team of researchers found that the combination of vitamin C and E was associated with a reduced risk of Alzheimer's disease, but neither supplement alone conferred substantial protection (Zandi 2004). However, a placebo-controlled clinical trial

found that high doses of vitamin E alone, up to 2,000 IU daily, slowed the mental deterioration of Alzheimer's patients (Grundman 2000), and in an animal model, vitamin C helped reduced amyloid beta aggregation (Cheng 2011).

Deficiencies of vitamin E in Alzheimer's patients are associated with increased lipid peroxidation (oxidative deterioration of lipids), which appears to increase platelet aggregation (Ciabattoni 2007). Combination therapy with vitamins C and E has been shown to reduce lipid peroxidation in people with mild-to-moderate Alzheimer's disease (Galbusera 2004). A high intake of vitamins C and E may be associated with reduced incidence of Alzheimer's in the healthy elderly (Landmark 2006).

One method by which vitamin E might protect Alzheimer's disease has to do with its relation to apolipoprotein E4 (apoE4). Researchers suspect that, in people with the apoE4 phenotype, impaired antioxidant defense systems in neurons may increase oxidative damage (Mas 2006). Another theory suggests that vitamin E might be able to reduce the oxidative damage caused by large amounts of *inducible nitric oxide synthase*, a pro-oxidant that has been linked to progression of Alzheimer's (McCann 2005). Moreover, a recent study suggested that vitamin E may combat amyloid beta-induced oxidative stress, a characteristic of Alzheimer's disease (Pocernich 2011). (Note: Inducible *nitric oxide synthase* should not be confused with endothelial *nitric oxide synthase* that is needed to maintain healthy arterial function.)

Ginkgo biloba

Ginkgo biloba is an antioxidant that may serve as an anti-inflammatory agent, reduce blood clotting, and modulate neurotransmission (Diamond 2000; Perry 1999). In one study, *ginkgo* was tested on patients with mild-to-moderate Alzheimer's dementia. The results were inconsistent. However, in a subgroup of those patients with neuropsychiatric symptoms, 120 – 240 mg of ginkgo daily over 26 weeks significantly improved cognitive performance over placebo (Schneider 2005). Another study found that ginkgo inhibited amyloid beta production in the brain (Yao 2004).

Ginkgo, if effectively combined with other brain-supporting nutrients, appears to offer a synergistic cognitive effect, resulting partly from its ability to improve cerebrovascular function (Mashayekh 2011). Research has shown that combining *G. biloba* with other nutrients such as phosphatidylserine, B vitamins, and vitamin E can deliver cognitive benefits to both animals and humans (Araujo 2008; Kennedy 2007). In addition, a study found that ginkgo extract can rescue neuronal cells from beta amyloid-induced cell death via a mechanism distinct from its antioxidant properties (Aranda-Abreu 2011). Ginkgo also appears to protect against Alzheimer's disease by inhibiting the formation of amyloid fibrils (Longpré 2006). Finally, a review of six studies found that ginkgo benefits cognition and psychopathological symptoms, with no evidence of negative side effects (Janssen 2010).

Curcumin

Curcumin is derived from the *Curcuma longa* (turmeric) plant. Many studies have suggested that curcumin may be an effective therapy for Alzheimer's because it exerts neuroprotective actions through numerous pathways including inhibition of amyloid beta, clearance of existing amyloid beta, anti-inflammatory effects, antioxidant activity, delayed degradation of neurons, and chelation (binding) of copper and iron, among others (Begum 2008; Mishra 2008; Ringman 2005; Walker 2007).

Curcumin has been found to reduce cognitive dysfunction, neural synaptic damage, amyloid plaque deposition, and oxidative damage. It has also been found to modulate the levels of cytokines in brain neurons (Cole 2004; Mishra 2008). The anti-inflammatory effect of curcumin appears to result from a reduction of ***nuclear factor-kappaB***, a nuclear transcription factor that regulates many genes involved in cytokine production (Aggarwal 2004). Curcumin's ability to chelate toxic metals such as iron and copper and reduce their levels may also help prevent amyloid aggregation (Baum 2004). By inhibiting interaction with heavy metals (e.g., cadmium and lead), curcumin may reduce cerebral deregulation (Mishra 2008). Laboratory studies also suggest that curcumin is more effective at inhibiting accumulation of amyloid beta in animal brains than the over-the-counter NSAIDs ibuprofen and naproxen (Yang 2005). A clinical trial found that doses of regular curcumin ranging from 1 to 4 grams daily were well tolerated and exerted anti-inflammatory effects and possibly reduced amyloid beta aggregation in 27 subjects with probable Alzheimer's (Baum 2008).

Nutritional Interventions Studied in Cognitive Decline and Dementia

Docosahexaenoic acid

Docosahexaenoic acid (DHA), an omega-3 fatty acid found primarily in fish and fish oil, has been linked to cognitive function (Swanson 2012). DHA constitutes between 30% and 50% of the total fatty acid content of the human brain (Young 2005). It has been shown to reduce amyloid beta secretion (Lukiw 2005) and increase phosphatidylserine levels (Akbar 2005). Studies indicate that omega-3 fatty acids have the ability to inhibit early stages of neurofibrillary tangle formation (Ma 2009) and reduce amyloid plaque development (Amtul 2010). An animal model revealed that fish oil supplementation may combat some of the negative effects of carrying the ApoE4 gene (Kariv-Inbal 2012). In a randomized study involving 485 individuals with age-related cognitive decline, 900 mg of DHA daily for six months resulted in a marked improvement in learning and memory tests (Yurko-Mauro 2010).

One way in which DHA may exert benefits is by working synergistically with other protective compounds, such as carotenoids (Parletta 2013). An 18-month clinical trial investigated the effect of combined treatment with carotenoids and fish oil in 25 participants with Alzheimer's disease: 12 participants received a xanthophyll carotenoid supplement that provided 10 mg of lutein, 10 mg of meso-zeaxanthin, and 2 mg of zeaxanthin per day; 13 participants received the same carotenoid supplement plus 1 gram of fish oil, providing 430 mg of DHA (docosahexaenoic acid) and 90 mg of EPA (eicosapentaenoic acid) daily. Those receiving the combination of carotenoids plus fish oil experienced greater increases in blood carotenoid levels and less progression of Alzheimer's disease compared with those receiving carotenoids alone, with reported improvements in memory, sight, and mood.

Vinpocetine

Vinpocetine, derived from the periwinkle plant, has neuroprotective properties and increases cerebral circulation (Szilagyi 2005; Dézsi 2002; Pereira 2003). It also protects against excitotoxicity (Sitges 2005; Adám-Vizi 2000). Vinpocetine has been used as a drug in Eastern Europe for the treatment of age-related memory impairment (Altern Med Rev 2002). In a controlled clinical trial, 10 mg of vinpocetine three times a day improved a variety of measures of cognitive function among subjects with vascular senile cerebral dysfunction (Balestreri 1987). **Note:** Women who are pregnant or could become pregnant should not use vinpocetine.

Pyrroloquinoline quinone (PQQ)

Pyrroloquinoline quinone (PQQ) is an important nutrient that stimulates the growth of new mitochondria in aging cells, and promotes mitochondrial protection and repair (Chowanadisai 2010; Tao 2007). Mitochondrial decay contributes to many age-related diseases, including Alzheimer's (Facecchia 2011; Martin 2010). Laboratory studies indicate PQQ may inhibit the development of Alzheimer's disease (Kim 2010; Liu 2005; Murase 1993; Yamaguchi 1993; Zhang 2009). PQQ protects neurons from amyloid beta and the protein alpha-synuclein, which contributes to neurodegeneration in Parkinson's disease (Kim 2010; Zhang 2009).

Supplementation with 20 mg per day of PQQ resulted in improvements on tests of higher cognitive function in a group of middle-aged and elderly people (Nakano 2009). These effects were significantly amplified when the subjects also took 300 mg per day of CoQ10**.**

Phosphatidylserine

Phosphatidylserine (PS) is a naturally occurring component of cell membranes. In a study conducted in Japan on 78 elderly people with mild cognitive impairment, supplementation with PS for six months resulted in significant improvements in memory functions (Kato-Kataoka 2010). In another study, 18 elderly subjects with age-related memory decline took 100 mg of PS 3 times daily for 12 weeks. Tests at 6 and 12 weeks showed cognitive gains compared to baseline measurements (Schreiber 2000). A group of researchers studied the safety and efficacy of phosphatidylserine-containing omega-3 fatty acids (PS-omega-3) in eight elderly patients with memory complaints (Richter 2010). They found that PS-omega-3 had favorable effects on memory functions. Researchers are now finding that phosphatidylserine supplementation works optimally along with docosahexaenoic acid (DHA) (Shyh-Hwa 2012).

Glycerophosphocholine Glycerophosphocholine (GPC) is a structural component of brain cell membranes and a precursor to the neurotransmitter acetylcholine. In Alzheimer's disease, the concentration of GPC increases in the

CSF due to the breakdown of cell membranes during neurodegeneration (Walter 2004). Supplementation with GPC and other nutritive substances like acetyl-L-carnitine, docosahexaenoic acid, α-lipoic acid and phosphatidylserine improves cognitive functions in mice (Suchy 2009). A clinical trial on 261 patients with dementia of the Alzheimer's type showed improvement in cognitive symptoms with an acetylcholine precursor (Moreno 2003). A larger trial also revealed significant cognitive improvement when patients recovering from stroke were given 1,000 - 1,200 mg of alpha-GPC for 5 months (Barbagallo 1994).

Carotenoids

Carotenoids are red-yellow-orange plant pigments that help prevent photodamage to key components of the system through which plants convert sunlight to energy. They also extend the range of wavelengths of light that plants can utilize for energy production. Carotenoids fall into two groups based on their chemical structures: xanthophylls (eg, astaxanthin, lutein, zeaxanthin) and carotenes (eg, β-carotene). Many carotenoids are present in the diet in healthy, colorful foods such as fruits and vegetables. Some carotenoids have been shown to readily cross the blood-brain barrier and exert neuroprotective effects, including antioxidative and anti-apoptotic actions, in the central nervous system (Park 2020). Additional evidence suggests carotenoids may bind directly to amyloid beta, inhibiting aggregation of the toxic protein in the brain (Lakey-Beitia 2019).

Astaxanthin. Astaxanthin is highly concentrated in some microalgae and gives color to many crustaceans and fish. Like other carotenoids, astaxanthin has strong anti-inflammatory and free radical-scavenging properties (Grimmig 2017; Guedes 2011). Because astaxanthin has been shown to cross the blood-brain barrier, interest in its ability to protect brain tissue from age-related changes has grown. Recent evidence suggests astaxanthin promotes brain plasticity, thereby potentially preventing or ameliorating age-related cognitive impairment (Grimmig 2017; Wu 2015). Many preclinical studies have shown that astaxanthin helps preserve neurological and memory health through a variety of mechanisms (Sifi 2016; Hongo 2020; Han 2019; Wu 2014; Ji 2017; Zhou 2015; Li 2016; Pan 2017; Al-Amin 2019; Taksima 2019; Rahman 2019).

A pilot study in 10 healthy subjects with age-related memory problems demonstrated the potential benefits of astaxanthin supplementation. After 12 weeks using an algae extract providing astaxanthin at 12 mg per day, improvement was noted on cognitive performance tests (Satoh 2009). These results were confirmed in a randomized controlled trial in 96 middle-aged to older adults reporting age-related memory complaints. This trial used 6–12 mg astaxanthin per day for 12 weeks and found similar improvement in cognitive performance (Katagiri 2012). In another randomized controlled trial, astaxanthin at doses of 6 and 12 mg daily for 12 weeks inhibited the accumulation of oxidized phospholipids in red blood cell membranes of middle-aged and older adults. Abnormal accumulation of these oxidized phospholipids in red blood cells has been observed in people with dementia (Nakagawa 2011). Furthermore, in a randomized controlled trial of 21 healthy participants, astaxanthin combined with sesamin, a lignan found in sesame seeds, was shown to significantly improve psychomotor speed and processing speed compared with placebo after six weeks of treatment (Ito 2018).

Combining astaxanthin with other agents may also be a method for providing neuroprotection. In an *in vitro* study, the combination of astaxanthin and huperzine A, a cholinesterase inhibitor, resulted in increased cell survival, reduced cell membrane damage, and decreased reactive oxygen species formation in a cell model of neurologic damage (Yang 2020). Additionally, when astaxanthin was combined with another carotenoid, fucoxanthin, *in vitro* assays showed an increase in multiple measures of neuroprotection, including reduced cell death, increased neuron growth, and higher levels of antioxidant signaling (Alghazwi 2019).

Lutein and zeaxanthin. Lutein and zeaxanthin are two highly pigmented xanthophylls that are found at high concentrations in the retina and macula of humans. Therefore, lutein and zeaxanthin are often referred to as "macular pigments" or "macular carotenoids" (Lima 2016). Given the close anatomic connection between the eyes and central nervous system (Grzybowski 2020), it is not surprising that levels of lutein and zeaxanthin in the macula and blood are significantly associated with cognition. Indeed, these macular carotenoids appear to protect against the development of cognitive impairment (Min 2014; Renzi 2014; Kelly 2015).

Compared to adults with normal cognitive function, those with Alzheimer's disease have lower serum levels of carotenoids (Mullan 2017). On the other hand, high levels of lutein and zeaxanthin in the blood have been associated with a lower risk of death related to Alzheimer's disease (Min 2014). In a case-control study, levels of

macular pigments in 24 patients with mild cognitive impairment were compared with those of 24 matched controls. Among healthy controls, the level of macular pigment was only associated with visual-spatial and constructional cognitive abilities. However, in those with mild cognitive impairment, macular pigment concentration was associated with global cognition, along with visual-spatial, constructional, verbal, and attentional cognition (Renzi 2014). Furthermore, in a study that followed 1,092 elderly participants without dementia over 10 years, participants with higher lutein concentration at baseline had a 19% lower risk of developing dementia and 24% lower risk of developing Alzheimer's disease (Feart 2016).

Supplementation with lutein and zeaxanthin may also help slow Alzheimer's disease-related cognitive decline. In a preliminary uncontrolled trial of 25 patients with Alzheimer's disease treated with xanthophyll carotenoids either alone or in combination with fish oil, the combination significantly slowed progression of Alzheimer's disease. Caregivers reported improvements in memory, sight, and mood with treatment (Nolan 2018). In a randomized controlled trial, supplementation with 10 mg lutein, 10 mg meso-zeaxanthin, and 2 mg zeaxanthin resulted in significantly higher serum concentrations of lutein and zeaxanthin as well as improved visual function (Nolan 2015). Furthermore, in healthy individuals with low levels of macular carotenoids, 12 months of supplementation with lutein and zeaxanthin improved memory and cognition compared with placebo (Power 2018).

Although the precise mechanism of action of the macular carotenoids on cognition is unclear, there is evidence that lutein and zeaxanthin have neuroprotective effects similar to those of other carotenoids (Singhrang 2018).

Life Extension Study: Nutrient Complex May Positively Impact Cognitive Performance

A 2012 study conducted by Life Extension Clinical Research, Inc. assessed the impact of daily dosing of a dietary supplement containing alpha-glyceryl phosphoryl choline (A-GPC), phosphatidylserine, vinpocetine, grape seed extract, wild blueberry extract, ashwagandha extract, and uridine-5'-monophosphate on cognitive performance in forty middle-aged to elderly subjects with subjective memory complaints.

An online cognitive assessment tool (Computerized Neuropsychological Test) was used to assess the change in cognitive performance from baseline to day 30 and day 60; the Global Impression Improvement (CGI-I) scale provided an overall clinically determined summary measure.

Twenty-nine subjects completed the study with no significant adverse events being reported. Preliminary results revealed a statistically significant improvement in three tests: working Memory (N-back), inspection time, and executive function. Based on the CGI-I Scale, improvement was noted after 30 days and 60 days of product dosing.

The study was presented at the Experimental Biology 2012 multidisciplinary scientific conference in San Diego, California April 21-25, 2012.

Additional Nutritional Support for Cognition

Coffee and Caffeine

A review of several studies revealed that coffee consumption is associated with a reduced risk of Alzheimer's and Parkinson's diseases (Butt 2011). Long-term caffeine administration to mice can reduce brain amyloid beta deposition through suppression of beta- and gamma-secretase. An animal model showed that caffeine appeared to synergize with another coffee component to increase blood levels of ***granulocyte colony-stimulating factor*** (G-CSF). Both higher G-CSF levels and long-term administration of caffeinated coffee have been shown to enhance working memory (Cao 2011).

Chlorogenic acid, an antioxidant polyphenol present in coffee, has been shown to reduce blood pressure, systemic inflammation, risk of type 2 diabetes, and platelet aggregation (Cao 2011; Montagnana 2012). In one study, when mice with impaired short-term or working memory were given chlorogenic acid, their cognitive impairment was significantly reversed (Kwon 2010). Polyphenol availability varies with how long coffee beans are roasted and the roasting method itself. All roasting destroys some polyphenols, the most important being chlorogenic acid. However, there is a patented roasting process that returns polyphenol content back to the coffee beans allowing for a substantially increased polyphenol content compared to conventionally processed coffee (Zapp 2010).

Another excellent source of chlorogenic acid is ***green coffee extract*** (Jaiswal 2010).

Green Tea

The flavonoids in green tea, known as catechins, have been shown to possess metal-chelating (binding) properties, as well as antioxidant and anti-inflammatory effects (Mandel 2006). Animal studies have demonstrated that the main flavonoid in green tea, epigallocatechin gallate (EGCG), along with other tea catechins, can decrease levels of amyloid beta in the brain (Rezai-Zadeh 2005), and suppress amyloid beta-induced cognitive dysfunction and neurotoxicity (Haque 2008; Kim 2009; Rezai-Zadeh 2008). Studies propose that green tea catechins also act as modulators of neuronal signaling and metabolism, cell survival-and-death genes, and mitochondrial function. Recently, population based studies have determined that intake of catechins in both green and black tea may reduce the incidence of Alzheimer's disease and dementia (Mandel 2011).

Resveratrol

Resveratrol – a polyphenol found in Japanese knotweed, red wine, and grapes – has been shown to reduce amyloid beta levels, neurotoxicity, cell death, and degeneration of the hippocampus, as well as prevent learning impairment (Kim 2007). Several studies indicate that moderate consumption of red wine, in particular, is associated with a lower incidence of dementia and Alzheimer's disease (Vingtdeux 2008). Red wine also contains many phenolic antioxidant compounds that, research suggests, impede the pathological progress of Alzheimer's disease (Ho 2009). It has also been observed that stilbenoids – derivatives of resveratrol – lower amyloid beta peptide aggregation in Alzheimer's models (Richard 2011). Resveratrol has been shown to selectively neutralize detrimental clumps of amyloid peptides while leaving benign peptides intact as well (Ladiwala 2010).

Grape Seed Extract

Grape seed extract contains potent antioxidants called proanthocyanidins (Shi 2003). In laboratory experiments, animal neurons were treated with grape seed extract before being exposed to amyloid beta. Unlike the untreated neurons that readily accumulated free radicals and subsequently died, the cells treated with grape seed extract were significantly protected (Li 2004). In another animal study, administering grape seed polyphenols reduced amyloid beta aggregation in the brain and slowed Alzheimer's disease-like cognitive impairment (Wang 2008).

Magnesium

Magnesium is involved in the functioning of NMDA-type glutamate receptors, which are integral to memory processing (Bardgett 2005). Studies have found that imbalance of serum magnesium levels causes cognitive impairment (Corsonello 2001; Barbagallo 2011). Recently, scientists have discovered that a specially formulated magnesium compound called ***magnesium-L-threonate*** (MgT) boosts brain levels of magnesium more efficiently than other forms of magnesium. These higher brain levels of magnesium improved synaptic signaling, which is essential for proper neuronal and cognitive function, as well as enhanced long-term learning and memory. Testing of MgT on animals showed a substantial improvement in memory, especially long-term memory (Slutsky 2010).

B Vitamins

High homocysteine levels, along with low levels of B vitamins (e.g., folate, vitamin B12, and vitamin B6), have been associated with Alzheimer's disease and mild cognitive impairment (Quadri 2005; Ravaglia 2005; Tucker 2005).

- *Vitamin B12*. In a study evaluating levels of vitamin B12 in patients with either Alzheimer's disease or another type of dementia, researchers found that lower B12 levels were linked to greater cognitive deterioration (Engelborghs 2004). A population-based longitudinal study of people 75 or older without dementia found that those with low levels of vitamin B12 or folate had twice the risk of developing Alzheimer's disease over a three-year period (Wang 2001).
- *Vitamin B6*. A study found that Alzheimer's patients after age 60 consumed a significantly lower amount of vitamin B6 compared to control subjects (Mizrahi 2003). In addition, low vitamin B6 levels were associated with elevated numbers of lesions in the brains of patients with Alzheimer's disease (Mulder 2005).
- *Folate*. Folate is needed for DNA synthesis (Hinterberger 2012). In a study including 30 subjects with Alzheimer's disease, levels of folate in cerebrospinal fluid were significantly lower in patients with late-onset

Alzheimer's disease (Serot 2001). Another longitudinal analysis of people aged 70 to 79 years found that those with either high levels of homocysteine or low levels of folate had impaired cognitive function. The link to cognitive impairment was strongest for low folate levels, leading researchers to suggest that folate might reduce the risk of cognitive decline (Kado 2005).

- *Niacin*. A study of more than 6,000 people, conducted between 1993 and 2002, found that high levels of dietary niacin (vitamin B3) protected against Alzheimer's disease. The authors researched the dietary habits of initially healthy people aged 65 years or older. As the study progressed, some participants developed Alzheimer's disease and some remained healthy. Subjects with the highest intake of niacin had a 70% reduction in risk of cognitive decline (Morris 2004).

Vitamin D

The wide distribution of vitamin D receptors in the brain may be evidence for vitamin D's importance in neurological function (Eyles 2005). Studies show that clearance of amyloid beta across the blood-brain barrier is promoted by adequate levels of vitamin D. Animal tests showed 1.3 times greater rate of amyloid beta elimination with vitamin D supplementation, pointing to a potential preventive effect against Alzheimer's disease (Ito 2011). Among nearly 500 women followed for 7 years, those in the highest quintile (1/5th) for vitamin D intake had a more than **75% reduction** in risk of developing Alzheimer's disease compared to those in the lowest quintile (Annweiler 2012).

Coenzyme Q10

Coenzyme Q10 (CoQ10) has been found to improve outcomes in several neurodegenerative disorders involving loss of mitochondrial function (Galpern 2007; Manacuso 2010).

Studies have shown that levels of CoQ10 are altered in Alzheimer's disease (Dhanasekaran 2005), and supplementation has been suggested as part of an integrated approach to improve mitochondrial function in Alzheimer's disease (Kidd 2005).

In one animal study, CoQ10 counteracted mitochondrial deficiencies in rats that had been treated with amyloid beta (Moreira 2005), while in another experiment CoQ10 reduced the overproduction of amyloid beta (Yang 2008). Coenzyme Q10 was also shown to destabilize amyloid plaques in laboratory studies (Ono 2005).

Several clinical trials have evaluated the effects of synthetic CoQ10 analogs in Alzheimer's patients and shown good results. For example, a trial comparing tacrine, a pharmaceutical acetylcholinesterase inhibitor, to a CoQ10 analog among 203 Alzheimer's patients showed the CoQ10 analog was associated greater improvements on some standardized cognitive assessments (Gutzmann 2002). Another trial revealed dose-dependent improvements on cognitive assessments in Alzheimer's patients receiving a CoQ10 analog compared to placebo. This trial also showed the CoQ10 analog to be safe and well tolerated (Gutzmann 1998). Similarly, in a trial conducted on 102 Alzheimer's patients, a CoQ10 analog improved memory, attention, and behavior compared to placebo (Senin 1992).

N-acetylcysteine

N-acetylcysteine (NAC) is a precursor to glutathione, a powerful scavenger of free radicals in the body (Forman 2009; Arakawa 2007). Glutathione deficiency has been associated with a number of neurodegenerative diseases (Pocernich 2000). One study showed that NAC significantly increased glutathione levels and reduced oxidative stress in rodents treated with a known free radical–producing agent (Pocernich 2000). Another study showed that glutathione-deficient mice were more vulnerable to neuronal damage from amyloid beta (Crack 2006). An animal model of Alzheimer's found that NAC alleviated oxidative damage and cognitive decline (Tchantchou 2005).

Ashwagandha

Ashwagandha or *Withania somnifera* is a plant used in India to treat a wide range of age-related disorders (Ven Murthy 2010). A 2012 study using an animal model of Alzheimer's disease found that ashwagandha reversed accumulation of amyloid peptides and improved behavioral deficits (Sehgal 2012). Laboratory studies have shown that ashwagandha can regenerate neurites (i.e., projections from nerve cells) and reconstruct synapses in severely damaged neurons (Kuboyama 2005). In addition to its neuroprotective benefits, ashwagandha has been

shown to mimic the action of the Alzheimer's drug donepezil, an acetylcholinesterase inhibitor (Choudhary 2004).

Blueberry Extract

In 2005, scientists noted that the polyphenols present in blueberries reversed the cognitive and motor deficits caused by aging (Lau 2005). Blueberry extract stimulates neurogenesis and enhances neuronal plasticity (adaptability) in the hippocampus, the region of the brain chiefly affected by Alzheimer's disease (Casadesus 2004). In one study where researchers analyzed fruits and vegetables for their antioxidant capability, blueberries came out on top, scoring highest for its capacity to neutralize free radicals (Wu 2004b).

Luteolin

Luteolin, a flavonoid found in fruits and vegetables (e.g., green peppers, carrots, and celery), exhibited a protective effect against Alzheimer's disease in early research. When luteolin was administered to mice with Alzheimer's disease, there was a significant reduction in levels of amyloid beta. These mice also exhibited a reduction in the activity of glycogen synthase kinase 3, an enzyme that has been implicated in the development of amyloid beta and neurofibrillary tangles (Rezai-Zadeh 2009).

Multi-Nutrient Combinations & Comprehensive Interventions

Alzheimer's disease is a complex condition with various contributing factors. As with cardiovascular disease—for which it has become clear over the years that effective prevention and treatment requires a multi-faceted approach—evidence continues to accumulate that Alzheimer's disease necessitates a similarly **comprehensive strategy** (Singhaarachchi 2024; Mayo 2024; Yarns 2022).

A systematic review of 32 randomized controlled trials reported that **multi-nutrient interventions** have shown some promising effects in Alzheimer's disease, but the evidence remains inconclusive (Moreira 2020). It is important to understand that studies evaluating multicomponent interventions have used a range of therapies and differing methods, not all of which have been rigorous; therefore, more studies are needed.

The benefits of multi-nutrient supplements in Alzheimer's disease are thought to be augmented by a comprehensive diet and lifestyle approach intended to support brain function. A randomized controlled trial in 51 patients with mild cognitive impairment or early-stage dementia due to Alzheimer's disease, whose average age was 73.5 years, compared an intensive 20-week diet and lifestyle intervention to usual care (control). Both groups underwent standard of care management by their own neurologist. The intervention included:

- A **whole-foods vegan diet**, high in complex carbohydrates and low in refined carbohydrates, harmful fats, and sweeteners, with all meals and snacks provided
- One hour per day of **stress management** training (meditation, stretching, yoga-like exercises, breathing exercises, and other stress-relieving activities) supervised by a certified stress management specialist
- One hour three times per week of **group support**, including memory exercises, supervised by a licensed mental health professional
- Twelve hours of **counseling** per week by teleconference to reinforce lifestyle aspects of the program
- **Daily nutrient supplements** providing 1,680 mg omega-3 fatty acids, 800 mg curcumin, 200 mg CoQ10, 1,000 mg vitamin C, 500 mcg vitamin B12, 144 mg magnesium L-threonate, 2 grams lion's mane mushroom, a probiotic, and a basic multivitamin/mineral supplement without iron

After 20 weeks, relative to the control group, those in the intervention group improved in multiple measures of clinical function, dementia, and cognition, including Clinical Global Impression of Change and Clinical Dementia Ratings. A blood biomarker strongly suggestive of Alzheimer's disease, amyloid-beta 42/40 ratio, improved in the intervention group but worsened slightly in the control group. Improvements in the microbiomes of the intervention group were also noted (Ornish 2024).

Another randomized controlled trial was conducted in 46 patients, aged 60 to 85 years, with a diagnosis of mild cognitive impairment or Alzheimer's disease. All of the participants had amyloid pathology confirmed by PET scan. The eight-week trial had three groups: a control group, a group that received dietary supplements only, and a group that received a multifactor intervention plus dietary supplements. The multifactor program included

managing cardiometabolic risk factors, cognitive training, physical exercise, nutritional guidance, and a motivational intervention. The nutritional supplement was administered as a prepackaged drink that delivered low-potency vitamins and minerals, omega-3 fatty acids (EPA and DHA), medium-chain triglycerides, and phosphatidylserine. In the multifactor intervention group, there was improvement in a standardized measure of neuropsychological status, as well as in microbiome health, compared with nutritional supplementation alone or usual treatment (Lee 2023). The dosages of the individual ingredients in the formula used in this study were not reported.

One of the most-studied multi-nutrient supplements for Alzheimer's disease prevention and treatment is called Souvenaid, or Fortasyn Connect. It contains 625 mg uridine monophosphate, 400 mg choline, 300 mg EPA, 1,200 mg DHA, 106 mg phospholipids, 80 mg vitamin C, 40 mg vitamin E, 1 mg B6, 400 mcg B9, 3 mcg B12, and 60 mcg selenium. One randomized placebo-controlled trial included 311 subjects with mild cognitive impairment due to early Alzheimer's disease; after two years, those receiving the supplement had less worsening in their clinical dementia rating and less change in brain structure, but no improvement in cognitive performance (Soininen 2017). However, a second report of findings from 162 participants who remained in the trial for three years showed those receiving the supplement had less decline in all measures related to cognitive performance, clinical function, brain atrophy, and disease progression compared with those receiving placebo, suggesting these benefits become evident over long periods of time. This trial is expected to continue until an endpoint of six years (Soininen 2021; Hendrix 2023). As of mid-2024, Souvenaid is available in the United Kingdom, Australia, Brazil, and several European countries, but not in North America.

A preliminary uncontrolled study in 14 people with early-stage Alzheimer's disease examined the effect of a daily multi-nutrient supplement providing 400 mcg folic acid, 6 mcg vitamin B12, 30 IU vitamin E (form not specified), 400 mg S-adenosylmethionine (SAM-e), 600 mg NAC, and 500 mg acetyl-L-carnitine per day; after 12 months, dementia rating scores were found to have improved and performance on cognitive and clinical function tests were stable or improved (Chan 2009). In a randomized controlled trial that included 106 participants with Alzheimer's disease, those given the same multi-nutrient supplement for three months showed improvement on a test of executive function and on the Dementia Rating Scale compared with those given placebo (Remington 2015).

A randomized controlled trial tested a daily multi-nutrient supplement in 77 participants with mild-to-moderate Alzheimer's disease. The multi-nutrient formula used in this study included 1 gram fish oil (including 500 mg DHA and 150 mg EPA), 22 mg carotenoids (10 mg lutein, 10 mg meso-zeaxanthin, and 2 mg zeaxanthin), and 15 mg d-alpha tocopherol. Participants took the multi-nutrient formula or placebo for 12 months. The supplemented group showed improvement on standard measures of Alzheimer's disease severity (mood and memory) and marked improvement in memory as reported by caregivers (Nolan 2022).

Another randomized placebo-controlled trial involving 60 patients with mild-to-moderate Alzheimer's disease tested the effects of a supplement containing 12.35 grams L-serine, 1 gram nicotinamide riboside, 2.55 grams N-acetylcysteine (NAC), and 3.73 grams L-carnitine tartrate. The supplement was taken daily for 28 days, then twice daily for an additional 56 days (total of 84 days). After 84 days, cognitive function scores had improved by 29% in the supplement group versus only 14% in the placebo group; however, the difference between groups was not statistically significant, partly due to the small size of the trial. Further analyzing the data, the researchers found the difference in cognitive improvement between the supplement and placebo groups was significant in a subset of participants with worse baseline scores. In addition, those who received the supplement showed increases in volume and thickness of brain regions affected early in Alzheimer's disease, and in blood levels of NAD+ and glutathione (Yulug 2023).

Multi-faceted programs may also help protect people without Alzheimer's disease but at high risk. In a randomized controlled trial, 1,190 participants, aged 60 to 77 years, with an increased risk of dementia and average or slightly below expected-for-age cognitive function received either a two-year multifactor intervention or general health advice alone (control). The intervention included individual and group nutritional guidance, strength training and aerobic exercise, individual and group cognitive training, and management of vascular risk factors (hypertension, diabetes, and abnormal blood lipid levels). At the end of the trial, those who received the comprehensive intervention performed better on a neuropsychological battery of tests, regardless of their

baseline demographics, cardiovascular and cognitive health, or APOE4 carrier status (Ngandu 2015; Rosenberg 2018; Solomon 2017). After an additional follow-up period averaging 7.4 years, the risks of coronary events, strokes, and transient ischemic attacks (TIAs) were found to be lower in the intervention group than the control group (Lehtisalo 2022). Based on these findings, an international network of researchers is currently collaborating to investigate the applicability of this comprehensive approach to dementia prevention in more than 20 other countries, including the United States (Kivipelto 2020). Another randomized controlled trial in 172 elderly participants at increased risk of dementia found a two-year intervention including health coaching, regular nursing care, and personalized risk reduction strategies was more effective than health education alone for improving cognition, reducing dementia risk factors, and increasing quality of life (Yaffe 2024).

Wild Green Oat Extract

Extracts of oat (*Avena sativa L.*) contain bioactive components that exert antioxidant and anti-inflammatory properties (Lee 2015). Oat extracts contain flavonoids, saponins, and compounds unique to oat species, avenanthramides (Wong 2012; Dimpfel 2011).

Increased monoamine oxidase B (MAO-B) activity decreases dopamine levels in the brain and increases oxidative stress in neurons (Nagatsu 2006; Mallajosyula 2009). Analyses of brain tissue from deceased individuals with Alzheimer's disease was found to contain up to three times the amount of MAO-B activity than brain tissue of healthy, age-matched controls (Saura 1994; Jossan 1991).

Monoamine oxidase inhibitors are considered promising therapeutic targets for the treatment of Alzheimer's disease because of their ability to reduce accumulation of beta amyloid and improve cognition and memory deficits (Cai 2014; Delumeau 1994; Finali 1991). Wild green oat extract is able to inhibit MAO-B activity (Wong 2012; Moccetti 2006).

Elderly patients with mild cognitive impairment performed substantially better on cognition tests after a single 1600 mg dose of wild green oat extract (Berry 2011). Healthy, middle-aged adults participating in a double-blind placebo-controlled trial improved their performance on multiple cognitive tests after a single 800 mg dose of wild green oat extract (Kennedy 2015).

Nicotinamide Riboside

Nicotinamide riboside is a source of vitamin B3 that the body uses as a precursor for nicotinamide adenine dinucleotide (NAD), a molecule involved in a range of biological processes. NAD+, a biologically active forms of NAD, is necessary for the activation of sirtuins, proteins that modulate cellular metabolism and DNA transcription (Houtkooper 2010; Chi 2013; Imai 2014). NAD+-dependent sirtuins appear to be involved in such fundamental cellular activities as energy metabolism, DNA damage response, stress resistance, proliferation and differentiation, survival, and aging, and in animal research have been shown to modulate brain connectivity and memory formation (Gao 2010; Srivastava 2016). NAD+ levels decrease with age, which may cause dysfunction in cell nuclei and mitochondria, ultimately contributing to a range of age-related disorders, including cognitive decline and Alzheimer’s disease (Srivastava 2016; Imai 2014). In experimental cellular models of neurodegenerative processes, NAD, NAD+, and nicotinamide riboside have prevented the breakdown of neurons and neuronal connections (Deleglise 2013; Sasaki 2006). Restoration of NAD+ with supplemental nicotinamide riboside has been shown to reverse age-related cellular dysfunction, which contributes to many neurodegenerative diseases, while models of Alzheimer’s disease indicate nicotinamide riboside may be neuroprotective (Imai 2014; Canto 2012; Chi 2013).

In a six-month controlled trial in 26 individuals with probable Alzheimer’s disease, those who received the NADH form of nicotinamide adenine dinucleotide had no progression in cognitive decline and significantly better scores on a dementia rating scale compared with the placebo group (Demarin 2004). In rodents, NADH administration in older animals resulted in improved performance on cognitive tests (Rex 2004). In a mouse model of Alzheimer’s disease, three months of nicotinamide riboside supplementation led to increased brain levels of NAD+, prevented cognitive decline, and reduced levels of neuron damaging amyloid-beta proteins (Gong 2013).

Colostrinin (Proline-rich peptide complex)

Colostrum—the first breast milk secreted after childbirth—is known for its high levels of antibodies and other

factors with immune-activating effects (Godhia 2013). Findings from preclinical and clinical studies suggest colostrinin, a proline-rich polypeptide complex in colostrum, may help prevent the progression of Alzheimer's disease (Janusz 2013; Stewart 2008). A number of studies have found a range of possible mechanisms for colostrinin's beneficial effects, including modulating immune activity; preventing oxidative stress, including oxidative damage to DNA; anti-inflammatory activity; inhibiting overproduction of nitric oxide; and decreasing age-related mitochondrial dysfunction (Boldogh 2008; Janusz 2010; Zablocka 2010; Zablocka 2012; Bacsi 2007; Bacsi 2006).

A double-blind placebo-controlled trial compared colostrinin to placebo in 105 subjects with mild-to-moderate Alzheimer's disease. The colostrinin group received 100 micrograms colostrinin every other day for three weeks, followed by two weeks with no treatment, for three 5-week cycles. After the first 15-week period, all subjects received colostrinin for a second 15-week treatment cycle. Colostrinin treatment had a stabilizing effect on cognitive function and ability to perform activities of daily living. Participants with mild cognitive impairment responded better to treatment than those with more advanced decline (Bilikiewicz 2004). Another trial used the same dosing schedule for 16 to 28 months in 33 Alzheimer's patients and found it resulted in stabilization or improvement in health status (Leszek 2002). An earlier double-blind placebo-controlled trial was conducted in 46 patients with Alzheimer's disease and mild-to-moderate dementia. Subjects received either 100 micrograms colostrinin, 100 micrograms selenium, or placebo every other day in three-week treatment cycles, followed by two weeks of no treatment. Eight of 15 colostrinin patients improved, while seven of them experienced stabilization of their condition; in contrast, none of the patients in the selenium or placebo groups improved (Leszek 1999). Studies reported colostrinin was well tolerated with mild side effects that passed quickly (Leszek 2002; Leszek 1999).

Studies in which cultured nerve cells were treated with colostrinin or a nanopeptide fragment of colostrinin have demonstrated their potential to disrupt amyloid beta fibrils and prevent further accumulation and neurotoxic effects of amyloid beta (Janusz 2009; Douraghi-Zadeh 2009; Bourhim 2007; Schuster 2005).

Cannabidiol

The phytocannabinoid cannabidiol (commonly referred to as CBD) has been shown in preclinical studies to possess neuroprotective, anti-inflammatory, and antioxidant activity, as well as to prevent the accumulation of amyloid beta and hyperphosphorylated tau protein (Karl 2017). In addition, CBD may block the amyloid beta-mediated hyperphosphorylation of GSK-3 (Li 2020). In a mouse model of early onset familial Alzheimer's disease, treatment with CBD improved disease symptoms and cognitive function. CBD also increased expression of IL-33 and TREM2, two proteins involved in modulating neuroinflammation and synaptic plasticity and which may be dysregulated in Alzheimer's disease (Khodadadi 2021).

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