Non-pharmaceutical Treatments for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is defined as a progressive disease that disrupts brain function, most notably impacting memory and cognition. At present, most treatments act to mitigate symptoms rather than address the root cause or reverse existing damage. As there is currently no known cure, preventive methods of care may delay the onset of symptoms for those predisposed to Alzheimer's disease. Over the years, non-pharmaceutical treatments such as diet, exercise, and sleep paired with cognitive therapies have been studied for their effectiveness in treating those with AD. This allows discussion into whether pharmaceutical approaches are perhaps not the only viable solution to treating AD. This review will discuss potential non-pharmaceutical treatment options and how they vary in treatment structure and efficacy in patients at risk or currently suffering from AD symptoms. The ultimate goal for the future is not just to slow cognitive decline but to address the root cause driving disease progression altogether.

Introduction To Alzheimer's Disease

The healthy human brain contains tens of billions of neurons—specialized cells that process and transmit information via electrical and chemical signals. They send messages between different parts of the brain and from the brain to the muscles and organs of the body. In Alzheimer's disease, this communication is disrupted, resulting in loss of function and cell death leading to characteristic cognitive symptoms. As AD progresses, anatomical changes in the brain also occur, as shown in **Figure 1**.

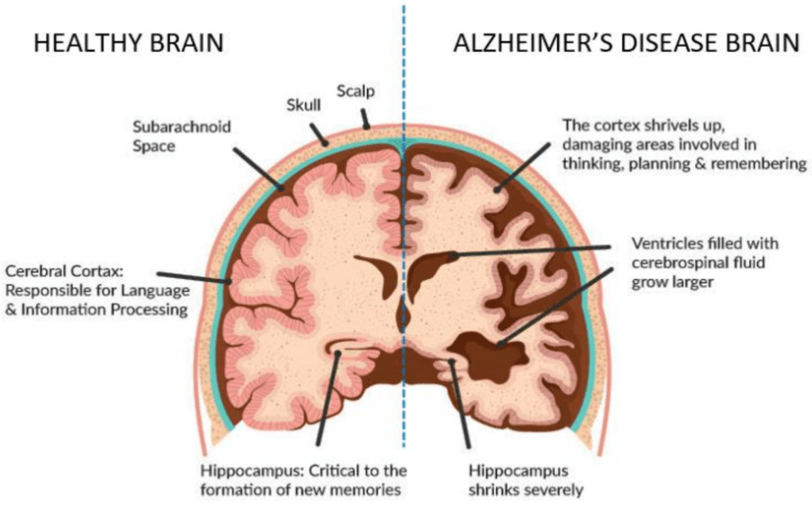

Figure 1: Anatomical differences between a healthy brain and an AD brain. (Dan et al, 2021)

The pathology of Alzheimer's disease is characterized, in part, by extracellular Amyloid Beta (Aβ) deposits, commonly referred to as plaques, as well as intracellular tau neurofibrillary tangles (NFTs) (Castellani et al., 2014). Aβ is formed through the breakdown of a larger protein, called amyloid precursor protein (APP). One form, beta-amyloid 42, is thought to be especially toxic. In the AD brain, abnormal levels of this naturally occurring protein clump together to form plaques that collect between neurons and lead to cellular dysfunction (NIA, 2017). Tau is another protein involved in AD that normally helps stabilize the internal skeleton of neurons (Avila et al., 2004). Internal skeletons have a

tube-like shape through which nutrients and other essential substances travel to reach different parts of a neuron. In AD, an abnormal form of tau builds up and causes the internal skeleton to fall apart. These abnormal forms of tau cling to other tau proteins inside the neuron and form “tau tangles” (Alzheimer’s Association, 2021).

As a result of these cellular changes, symptoms of Alzheimer’s disease typically begin with mild memory difficulties that evolve into various cognitive impairments which can disrupt complex daily activities and several other aspects of cognition (Kelley et al., 2007). There is a transitional period between normal aging and dementia as the disease progresses, called mild cognitive impairment (MCI). MCI is characterized as either amnesic, which primarily affects memory, or nonamnesic, which primarily affects cognitive function (Csukly et al., 2016).

The sooner a patient is diagnosed with MCI, the sooner symptom mitigation can begin. Earlier diagnoses increase an individual’s eligibility for different types of treatment and approaches, thus providing the best chances of delaying cognitive decline (Alzheimer's Association, 2022). Additionally, earlier diagnoses have been linked to improved emotional and social states as the individual generally has lessened anxiety about the symptoms they are experiencing (NIH 2021).

Treating Alzheimer’s Disease

Over the years, understanding the causes driving Alzheimer's disease has greatly evolved. A number of risk factors including genetics and lifestyle have been correlated with AD progression, but commonly fall within two main theories: the amyloid cascade hypothesis and the cholinergic system theory. The amyloid cascade hypothesis states that the over-deposition of amyloid beta forms plaques and drives the formation of neurofibrillary tau tangles, leading to neuron degeneration and death. It has been established that genetic predisposition or risk for Alzheimer's can be identified fairly easily through genetic testing for specific mutations. One mutation connected to an increased risk for AD is found within the APOE-e4 allele (Sienski et al., 2021), a gene whose role is to control the production of apolipoprotein E which forms lipoprotein molecules (NIH, 2021).

The cholinergic system theory proposes the dysfunction of neurons regulating sensory processing, attention, sleep, and arousal, which are regulated by cholinergic neurons in the brain, and are directly related to memory (Narayan et al., 2021). Therefore, as the body ages, this system slowly deteriorates and impacts an individual’s memory.

Despite the general consistency within the main ideas surrounding treatment targets, methods used to preserve and improve cognitive skills have varied. Treatment for AD first began with a short-term goal: to improve the patient’s quality of life and mitigate symptoms for as long as possible. Currently, treatment has evolved to prevent cognitive decline by temporarily disrupting and preventing the further progression of amyloid beta plaques and neurofibrillary tangles. Aducanumab, an IgG1 monoclonal antibody, was a giant leap forward, considering it can target AB plaques, which according to the Amyloid Cascade hypothesis, cause a large part of the cognitive decline associated with AD. This is a stride forward as it seeks to address the root cause rather than merely mitigating symptoms. (Beshir et al., 2022). Research has also progressed for possible vaccines, including active vaccines targeting AB (Lacosta et al., 2018) and tau (Novak et al., 2017), in which phase I trials are underway.

Additionally, physicians have turned to non-pharmaceutical approaches including changing the patient’s diet and exercise routine (NIH 2013). Pharmaceutical approaches are

perhaps not the only viable treatment solution and are currently being investigated. Changes in the brain of an Alzheimer's patient begin to occur years before symptoms present themselves. Therefore, if brain scans occurred frequently enough to catch or identify the early stage of the disease, there is a window of opportunity to possibly prevent or delay AD through non-pharmaceutical options such as proper nutrition and physical and cognitive exercises. These approaches would also be a useful preventative measure for individuals who are genetically predisposed or otherwise concerned about developing AD.

Diet

A healthy diet is incredibly important when it comes to brain health (Harvard Health Publishing, 2021). Several foods are important in maintaining the structure and upkeep of the brain. For example, omega-3 fatty acids have been shown to be vital in maintaining a clean and well-functioning mind. Omega-3s, which can be found in foods like fish, have demonstrated detoxifying properties, cleaning out excess of the previously mentioned proteins beta-amyloid and tau (Harvard Health Publishing, 2021). On top of this, omega-3s also improve clean arteries and blood circulation, which enable oxygen, glucose, vitamins, and other nutrients to travel to the brain and promote its overall health.

A poor diet can also affect sleep, which is another preventative measure pertaining to AD that will also be discussed in detail. For example, high-carb diets have been shown to cause insomnia and prevent the body from easily entering deep sleep (St-Onge et al., 2016). Additionally, it has been found that the consumption of foods high in fat, as well as processed foods in general over a long period, has been linked to poor brain, cardiovascular, and mental health (Sabbagh et al., 2022).

Diet is also the fuel to give your body energy for its activities throughout the day. Without proper nutrition, the quality of something like exercise, another important practice, can be greatly affected. Eating a healthy diet can also limit risk factor conditions for AD such as type 2 diabetes and cardiovascular disease, further mitigating factors that may facilitate disease onset and progression. (Fernández-Sanz et al., 2016; Clinical trial ID: NCT02817074; Harvard Health Publishing, 2021).

Currently, as there is no means to completely reverse the cognitive decline that accompanies AD, healthy diets consisting of leafy greens, lean proteins, and foods with omega 3, vitamin E, and whole grains, are extremely effective in sustaining brain health. (Fernández-Sanz et al., 2016; Clinical trial ID: NCT02817074; Harvard Health Publishing, 2021). Therefore, the introduction of healthy dietary habits could not only support overall health but potentially stall AD progression and preserve the quality of life in AD patients.

Exercise

Exercise is a promising treatment strategy to slow cognitive decline. It has shown great results in animals, with indirect evidence of it working in humans (Ahlskog et al., 2011). In a study conducted on mice with a higher concentration of amyloid beta in their brains, all mice that underwent exercise on treadmills and running wheels obtained much higher scores on memory and object recognition tests than control mice. A majority of findings from this study revealed a lower concentration of Aβ in the brain as well as a reduction in tau phosphorylation. The results of this study in human AD patients showed improvement in cognitive scores for active adults in

29 randomized, controlled trials compared to their baseline before they started exercising. Functional MRIs (fMRIs) that highlight particular areas of brain function noted significant improvement in the cortical connection and activation of active seniors' brains compared to their brains at the beginning of the study. Furthermore, a study of current AD patients showed that those who maintained physical activity had a reduced risk of mortality (Ahlskog et al., 2011). Aerobic exercise in particular has proven to be very beneficial for maintaining brain health, even in people who are at risk for developing dementia and Alzheimer's, and making a difference in one's cardiac health can also greatly influence brain function as well.

A study published by Nature Medicine in 2019 found that changes in protein expression in the brain after exercise could rescue synaptic plasticity destroyed by AD (Peng et al., 2022). FNDC5, the precursor protein of irisin, is a glycoprotein secreted from muscles during exercise. Increased concentrations of FNDC5 result in increased neurogenesis in the hippocampus, an area of the brain important for memory (Young et al., 2019). In turn, this could rescue the memory impairment which is the hallmark symptom of AD.

The underlying mechanism of physical activity might be due to cross-talk between muscles and the brain (Basso, Suzuki, 2017). Exercise enhances circulating levels of myokines to enable this process, affecting neuronal proliferation and differentiation, synaptic plasticity, memory, and learning (Forbes et al., 2015). Myokines are important to brain functions such as mood and learning and build relationships between muscles and the brain (Scisciola et al., 2021).

Additionally, depression is rather common among Alzheimer's patients. Exercise could also address this (Aguera-Ortiz et al., 2006) through the production of endorphins, which are opioid neuropeptides able to block the presence of pain and consequently produce a sense of pleasure. (Chaudry, Gossman, 2022) .

Sleep

Sleep is another important aspect of brain health. Studies have shown that poor sleep during adulthood has been linked to dementia later on in life (Sabia et al., 2021). Furthermore, a lack of sleep as early as adolescence has been linked to decreases in cognitive performance, sustained attention span, working memory, executive function, and positive mood (Lo et al., 2016). Adults in their 50's and 60's that get less than 6 hours of sleep are 30% more likely to develop dementia (NIH, 2021). For those predisposed to Alzheimer's, maintaining a healthy and consistent sleep cycle is therefore crucial. When people do not sleep enough, Aβ and tau can build up in the brain, and when pathology becomes severe enough, it contributes to disrupting cell function and causes cell death. During deep sleep, low-frequency electrical waves are produced in the brain. These wave patterns can induce a cerebrospinal flush to enter the brain and clear away these toxins, including beta-amyloid. (Lewis, 2019). Therefore, forming fixed sleep patterns and maximizing the hours of deep sleep per day would preserve brain health for as long as possible, and specifically support AD patients.

Cognitive Therapy

Cognitive therapy has been shown to aid with perception, thinking, and remembering, and could therefore be beneficial when utilized in patients with AD. It includes mental exercises relating to arithmetic, words, and puzzles (NIH, 2013) offered in either one-on-one or group

sessions lasting 30 to 90 minutes up to twice weekly. Another component is reality orientation training, which improves space and time orientation by repeatedly giving people with Alzheimer's basic information such as their name, the date, or the time. However, there are caveats to this technique. It can be overwhelming for people, making them feel even more confused, and some specialists are critical of this training because it repeatedly points out the obvious, which people with Alzheimer's might consider patronizing (NIH, 2013).

Another variation of cognitive therapy, known as Computerized Cognitive Training (CCT) has generated considerable attention as a safe, relatively inexpensive, and scalable intervention that aims to maintain cognition in older adults. It involves guided drill-and-practice on standardized tasks designed to load on specific cognitive processes such as problem-solving, and identifying associations between items or tasks. Additionally, it also adapts task difficulty to individual performance (Hill et al., 2016).

One final method is reminiscence therapy (RT), which aims to evoke memories, stimulate mental activity and improve well being through showing individual memories like videos and pictures. Individuals that underwent RT individually scored higher on cognitive tests immediately after treatment, but not necessarily weeks to months after that. RT in community settings, however, positively affects the communication and interaction of the subject immediately after the end of treatment and persists for weeks after. (Woods et al., 2018).

Concluding Remarks

Since AD has no established cure to date, it is in the best interest of patients and their physicians to act preventatively. Treatment plans that include non-pharmaceutical options can be adapted to the individual patient and have been shown to be more cost-effective than other treatment methods. As shown through a study done in Finland, non-pharmaceutical approaches such as family programs greatly decreased the cost of care (Rosenvall et al., 2020).

For individuals with genetic mutations associated with AD or direct family members with Alzheimer's, genetic testing can help identify potential risks for developing AD. If they do carry an associated genetic mutation, non-pharmaceutical treatments could be beneficial in monitoring or attenuating disease onset. Yearly brain scans (similar to annual mammograms from women to screen for breast cancer) could detect changes in the brain years before symptoms begin as well as determine whether selected treatment approaches are efficient. In general, the sooner treatment begins, the more effective it is, so early intervention is critical. These minimally invasive non-pharmaceutical options are therefore an accessible starting point for the prevention and intervention of AD progression in addition to supporting overall brain health.

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