

# Non-pharmaceutical Treatment for Alzheimer's Disease

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**Abstract.** Alzheimer's disease (AD) has grown to be a serious issue for human health. It has overtaken cancer as the world's fifth leading cause of death. People have invested a lot of time, effort, and money in the process of Alzheimer's disease treatment, but there hasn't been much progress in pharmaceutical treatment for AD over the years. People can start with non-pharmaceutical therapies in addition to drugs. This paper discusses several effective non-pharmaceutical therapies for Alzheimer's disease. Sixteen articles were analyzed and used to analyze different treatments for Alzheimer's disease. The research examines nine non-pharmaceutical treatments, which included the removal of A $\beta$  burden, stimulation of the hippocampus or entorhinal cortex, cognitive therapy, exercise, mental stimulation, reminiscence therapy, diet therapy, caregivers, and life care. A large amount of data is analyzed, and the results, benefits, and disadvantages of these treatments are compared. This research proves that non-pharmaceutical therapies are feasible ways to treat Alzheimer's disease and play a very important role in the treatment process.

**Keywords:** Alzheimer's Disease, Non-pharmaceutical Treatment, Research Progress.

## 1. Introduction

Alzheimer's disease is a neurodegenerative disease that often influences persons over 65 and is fairly complex and brought on by a variety of different factors [1]. All aspects of the patient's psychological clinical manifestations often decline, for example, in life often forget what has just been done, forget to eat or can not find the way home, or even mistaken identity or forget relatives. Without timely intervention, patients may be completely unable to take care of themselves, and even their life may be shortened rapidly. Around 50 million people worldwide suffer from the disease, a number that is expected to double every five years to reach an estimated 152 million cases by 2050 [2]. A variety of factors may lead to the occurrence of AD, and the pathogenesis is not completely clear at present. The recognized pathogenesis, such as A $\beta$  and tau protein, is the main treatment target for AD. Acetylcholinesterase inhibitors and non-competitive N-methyl-D-aspartate (NMDA) antagonists, two widely used drug families that are currently available on the pharmaceutical market, these drugs only relieve the symptoms of the disease and are suitable for the dementia stage of Alzheimer's [3]. However, medical therapy has limitations and, for some patients, adherence is poor, and some may have side effects, such as headaches, falls, and allergic reactions.

In recent years, with the continuous development of medical science, some non-pharmaceutical therapies have gradually come to people's attention. For example, there is the removal of A $\beta$  burden, stimulation of the hippocampus or entorhinal cortex, cognitive therapy, exercise, mental stimulation, reminiscence therapy, diet therapy, caregivers, and life care. The advantage of non-pharmaceutical therapy is that the damage to the human body is small. The patients have not induced drug dependence, allergic reaction, or withdrawal reaction. At present, the evidence-based evidence of non-pharmaceutical therapy for AD is not perfect. This study intends to explore the treatment of AD mainly from the perspective of non-pharmaceutical therapy, to provide a more theoretical and evidence-based basis for diagnosing and treating AD.

## 2. Removal and reduction of A $\beta$ burden

Alzheimer's disease's pathophysiology has been linked to the Amyloid- $\beta$  (A $\beta$ ) peptide. According to Gerhard Leinenga and Jürgen Götz, they describe a nonpharmacological strategy for getting rid of A $\beta$  and recovering memory function in a model of a mouse with AD where Amyloid- $\beta$  is accumulated inside the brain. They regularly used scanning ultrasound (SUS) to remove A $\beta$  from the brain of mice rather than the use of any additional drugs, like an anti-A antibody (4). Mice tested for SUS safety showed no edema, neurodegeneration, or ischemia damage (5). SUS-treated AD mice had lower plaque burdens than sham-treated animals, and 75% of the SUS-treated mice had removed plaques. Three memory tests—the active place avoidance task, the novel object recognition test, and the Y-maze—showed increased performance in treated AD mice as well [4].

Sadly, the most effective treatments are costly, as is the case with immunotherapy. Additionally, because of the possibility of immune system damage, thicker skull, and significantly bigger brain size, translating to human trials necessitates careful consideration [5].

## 3. Stimulation of the entorhinal cortex or hippocampus

The capacity to turn ordinary experiences into long-lasting memories depends on the medial temporal structures, which include the entorhinal cortex and the hippocampal formation, which may affect memory function.

According to Nanthia Suthana, etc., in order to pinpoint the areas where seizures begin in seven participants for upcoming epilepsy surgery, they implanted intracranial depth electrodes. The participants went through a spatial learning exercise where they learned about locations in virtual worlds. For half of the learning trials, focal electrical stimulation was used at levels down those that result in an afterdischarge (i.e., a firing of neurons that takes place after the stimulation has ended). When individuals were learning the locations of landmarks, entorhinal stimulation was applied to help them remember these positions later. The subjects reached at the landmarks faster and by smaller roads than when the locations were remembered without stimulation [6].

## 4. Cognitive stimulation therapy

The term "cognition" is used as a general term for all things related to an individual's mental abilities, such as perception, thinking, and memory [7]. Cognitive decline is common in people with dementia. And cognitive training can help them improve their memory to some extent. Cognitive therapies come in a variety of forms for those with mild to moderate Alzheimer's. They might include calculation problems where patients have to complete a series of numbers or exercises where they have to remember and recognize images. There are also some exercise activities like words and puzzles, at the same time, there are treatments where people practice doing things such as going shopping [7].

Memory training, processing speed training, and reasoning training were the three cognitive training programs that older persons were randomly allocated to in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study. Individuals in the ACTIVE research evaluated their functional abilities by rating how well they could carry out essential daily tasks after the training session. Reasoning training and speed training were found to improve a variety of cognitive and functional skills about the received training types, even after 10 years, while memory training was found to improve memory up to 5 years after training. Cognitive training can enhance both cognitive and functional abilities, according to ACTIVE research [8]. Research has indicated that cognitive stimulation is a very successful non-pharmacological therapy among several attempts to assess its usefulness. Participants experienced immediate improvements in cognitive function, life quality, and well-being compared with those receiving anti-dementia drugs [9]. However, the possible disadvantages of cognitive therapy cannot be excluded. For example, if people with AD cannot

complete exercise time and time again, they may become very frustrated due to multiple repetitions [7].

## 5. Exercise

A potential approach to halt cognitive deterioration is exercise. Mild cognitive impairment (MCI) and community-dwelling healthy older persons can both benefit from aerobic and resistance exercise [10]. Dementia is more likely to develop in those with MCI, making this a prime opportunity for intervention [8].

According to Lindsay S. Nagamatsu, et al., 86 community-dwelling women between the ages of 70 and 80 were randomly assigned to three groups for a six-month randomized trial called Exercise for Cognition and Everyday Living: resistance training abbreviated as RT, and n=28; aerobic training abbreviated as AT, and n=30; and balance and tone training abbreviated as BAT, and n=28; which served as the control group. If a participant's score on the Montreal Cognitive Assessment 8 was less than 26 out of 30 and they reported having subjective memory issues, they were considered to have likely mild cognitive impairment. 77 of the 86 participants (RT: 26, AT: 24, BAT: 27) finished the 26-week experiment. Their fMRI analysis comprised 22 people (RT = 7, AT = 7, and BAT = 8). In contrast to twice-weekly balance and tone exercises, resistance training for six months enhanced regional patterns of associative memory, selective attention/conflict resolution, and functional brain plasticity in older women with subjective memory impairments. At the same time, physical function was enhanced after six months of twice-weekly aerobic exercise. Exercise like resistance training can benefit people at high risk of dementia in multiple areas. In women in their study who had probably mild cognitive impairment and had only been followed for six months, there was an improvement. Training may therefore have larger effects on selective attention and conflict resolution in people who are more possibly to develop dementia [10].

## 6. Mental stimulation

People with Alzheimer's often lack social interaction because of lapses in memory. More social interaction improves the life quality of patients with dementia and their families. They can help avoid the lack of caring and social interaction associated with Alzheimer's disease. They can also reduce patients' need for medical care [7].

A Cochrane review of 15 randomized controlled trials (RCTs) found that cognitive stimulation programs helped individuals with mild Alzheimer's or moderate Alzheimer's disease preserve their cognitive skills and self-reported life quality [11]. Besides, Another investigation had 718 men and women who had mild AD, moderate AD, or other types of dementia. Researchers looked at 15 research. Puzzles, communicating, and word games were among the enjoyable activities the Alzheimer's patients engaged in. These activities helped them think more clearly and retain information. Additionally, there is music and practical pursuits like cooking or gardening. These activities are led by qualified staff members who meet with a small group of Alzheimer's patients for around 45 minutes, four to five at a time, twice a week. In other situations, family carers pushed their Alzheimer's-affected relatives to take part in intellectually stimulating activities at home. Ultimately, the researchers discovered that the stimulation of mental increased AD patients' memory and thinking test grades, which is comparable to a six to nine-month delay in the progression of symptoms. According to several research, participating in these activities improves the life quality and happiness of persons with Alzheimer's disease, including their ability to communicate and connect with others [12].

## 7. Reminiscence therapy

Reminiscence Therapy involves talking about old events and things. It usually include the use of old things, such as old books, music, and gifts. People with Alzheimer's often struggle to recall

memories, but some representative objects may help them improve their condition. The recall is a good way to improve patients with AD's mood, but results are mixed in terms of definite cognitive benefits. Interventions were carried out either on an individual basis in the context of a focused life review or in a group setting, often once per week, with an emphasis on the free recall of memories [9].

In the Turkish city of Konya, one study—a randomized controlled single-blind study with two groups and an experimental pretest–posttest design—was conducted. It was decided to add 60 older persons altogether. The researcher created an information form that assessed the sociodemographic traits and medical past of participants in the interference and control groups. The information was gathered using the Standardized Mini-Mental State Examination (SMMSE), the Cornell Scale for Depression in Dementia, and the Quality of Life in Alzheimer's Disease (QOL-AD) Scale. Reminiscence treatment was employed once a week for eight weeks. Each meeting lasted for 60 minutes. Each group has six members. Following the implementation of the program, the elderly in the intervention group's mean scores for depression, the Mini-Mental test, and quality of life rose, and the difference was statistically significant ( $P < 0.05$ ). In the intergroup comparison, older people's mean scores on the post-test depression, Mini-Mental Test, and quality of life were substantially different from those of younger adults' ( $P < 0.05$ ). The conclusion shows that frequent memory treatment should be acknowledged for inclusion in normal medical care for the improvement of cognitive abilities, dismal symptoms, and life quality in older AD patients [13].

## 8. Diet therapy

Diet is a possible cause of Alzheimer's disease. A lot of researches have shown that the diet of people eating affects the abilities of aging brains to remember and think. Eating a certain diet may affect the biological mechanisms of Alzheimer's, such as oxidative stress and inflammation.

The ketogenic diet is an effective way to cope with AD. Matthew C. L. Phillips claims. Out of the 26 patients who were randomly allocated to the ketogenic diet, only one withdrawal was associated with it; 21 of them (81%) completed the program. By maintaining physiological ketosis (12-week mean beta-hydroxybutyrate level:  $0.95 \pm 0.34$  mmol/L), patients who followed a ketogenic diet. The mean within-individual ADCS-ADL scores ( $\pm 3.13 \pm 5.01$  points) with  $P = 0.0067$  of patients on the ketogenic diet increased, the QOL-AD scores ( $+ 3.37 \pm 6.86$  points) with  $P = 0.023$  increased, and ACE-III scores ( $\pm 2.12 \pm 8.70$  points) with  $P = 0.24$  increased, but not significantly. The majority of the changes in cardiovascular risk variables were positive, while the negative consequences were minimal. According to the results of this study, administering a 12-week modified ketogenic diet to Alzheimer's disease patients appears to be doable with excellent retention, adherence, and safety rates. When compared to patients on a conventional diet plus low-fat healthy eating advice, ketogenic diet's patients had gains in daily function and life quality [14].

The Mediterranean diet should have benefits on memory and cognition. This diet consists mainly of large amounts of poultry, legumes, fish, olive oil, vegetables, fruits, nuts, and whole grain products [7]. Besides, in Traditional Persian Medicine (TPM), there are a variety of dietary guidelines that can prevent and mitigate dementia and memory disorders. In pharmacological studies, the bulk of the dietary supplements suggested by TPM were found to have anti-amyloidogenic, etc., and memory-improving characteristics. There are some that have been discovered to have greater anti-AD properties, including ginger and its 6-gingerol and 6-shogaol, saffron and crocin and crocetin, raisins, garlic, rose petals, S-allyl-cysteine, and diallyl-disulfide, and seafood [15].

## 9. Pay more attention to the caregivers

Clinically, not only looking at the people with Alzheimer's but also the caregiver. AD Patients require a lot of time, effort, and resources every year from their families and the medical community, and as the illness worsens, they require an increasing amount of assistance. Support for unlicensed

caregivers has been provided through educational programs. These classes are designed to teach participants how to help persons with Alzheimer's retain as much of their mental capacity as possible [7]. According to research, Alzheimer's patients can remain in their homes for a longer period of time if their carers participate in training programs. Additionally, there is some proof that specialized instruction on how to handle difficult behaviors is beneficial [7].

However, family caregivers may find it challenging and stressful to care for a patient with severe AD. The most frequent issues for carers are depression and exhaustion since many of them believe they must always be available, which puts them under a lot of stress. Family caregivers may have to reduce job hours or even leave their works generally because they need to care patients. Some people who care for someone with AD may feel release when the patient dies. People need to realize that this feeling is normal [17].

## 10. Adjust the life style

Patients with Alzheimer's may no longer be capable of making decisions or judgements on their medical treatment and health care at the end of life due to a progressive loss of thinking, memory, and reasoning skills. If there is no pre-established documentation of a care plan, or if the family is unaware of the patient's wishes, the caregiver may need to make difficult decisions about care and treatment methods on behalf of the patient.

When making health care decisions for patients with Alzheimer's disease, the first thing to think is the life quality of patients. For example, there are medications that can be used to delay or prevent the continued progression of the disease, or also help control some of the symptoms of mild-to-moderate Alzheimer's patients. But if the side effects are excessive or even outweigh the benefits, some caregivers may not want to prescribe drugs to people in the advanced stages of these diseases. As a result, in addition to the disease itself, it is necessary to consider the goals of care and weigh the benefits, drawbacks, and side effects of any proposed therapy. Caretakers also need to consider the patient's level of comfort while making treatment decisions. Sometimes it is preferable to remain with Alzheimer's patients as they near the end of their lives rather than trying to prolong their life or keep them functional for longer. Sensory connections can be made to calm the patient, such as listening to some piece of music, watching movies, or noises from nature [16].

## 11. Conclusion

With the age of population aging, the incidence of AD patients will increase year by year. In a mouse model of AD where A is stored inside the brain, Gerhard Leinenga and Jürgen Götz applied scanning ultrasound to the brain of mice to remove A $\beta$  and regain memory function. Also, entorhinal cortex or hippocampus's stimulation may change memory function. Additionally, cognitive activities like arithmetic problems, word searches, and puzzles, as well as therapies where people constantly practice things like shopping, can assist Alzheimer's sufferers somewhat improve their memory. Moreover, A promising approach to halting cognitive deterioration is exercise. Active older persons who reside in their communities and those with modest cognitive impairment can benefit from both aerobic and resistance exercise. A promising approach to halting cognitive deterioration is exercise. Older people with mild cognitive deterioration who live in the community can benefit from both aerobic and resistance training. Alzheimer's patients frequently live socially isolated lives as a result of their illness. According to research, social engagement improves the life quality for AD patients and their relatives. They can aid in avoiding the apathy brought on by Alzheimer's. Talking about previous occasions is a part of reminiscence therapy. Typically, props like photos, sentimental items, or music are used. Alzheimer's patients frequently have trouble remembering events, but a few symbolic items might help them.

Alzheimer's disease may have a diet-related etiology. Numerous studies have revealed that diet has an impact on how well people think and remember as they age. persons with Alzheimer's disease

can live at home for longer if their caregivers take part in training programs. Additionally, there is some proof that specialized instruction on how to handle difficult behaviors is beneficial. Lastly, the advanced patient's quality of life often should be taken into account before anything else when making decisions about their medical and life care.

Throughout the history of human illness, Alzheimer's disease has become one of the most concerning health issues since it was discovered. Whether pharmaceutical or non-pharmaceutical treatment has its advantages and disadvantages, people should take the advantages and disadvantages, integrate the advantages of each treatment method and combine them with other treatment methods. Although there is no specific pharmaceutical or non-pharmaceutical treatment for Alzheimer's disease, it is believed that AD will be conquered with the development of science in the future.

## References

- [1] Ju Y, Tam KY. Pathological mechanisms and therapeutic strategies for Alzheimer's disease. *Neural Regen Res.* 2022;17(3):543-549.
- [2] Uwishema O, Mahmoud A, Sun J, et al. Is Alzheimer's disease an infectious neurological disease? A review of the literature. *Brain Behav.* 2022;12(8): e2728.
- [3] Behl T, Kaur I, Sehgal A, et al. The road to precision medicine: Eliminating the "One Size Fits All" approach in Alzheimer's disease. *Biomed Pharmacother.* 2022; 153:113337.
- [4] Leinenga G, Götz J. Scanning ultrasound removes amyloid- $\beta$  and restores memory in an Alzheimer's disease mouse model. *Sci Transl Med.* 2015;7(278):278ra33.
- [5] Hane FT, Robinson M, Lee BY, et al. Recent Progress in Alzheimer's Disease Research, Part 3: Diagnosis and Treatment. *J Alzheimers Dis.* 2017;57(3):645-665.
- [6] Neuhaus AH, Bajbouj M. Memory enhancement and deep-brain stimulation of the entorhinal area. *N Engl J Med.* 2012;366(20):1945-1946.
- [7] Non-drug interventions for alzheimer's disease. NIH.2020. <https://www.ncbi.nlm.nih.gov/books/NBK279355/>
- [8] Hane FT, Robinson M, Lee BY, Bai O, Leonenko Z, Albert MS. Recent Progress in Alzheimer's Disease Research, Part 3: Diagnosis and Treatment. *J Alzheimers Dis.* 2017;57(3):645-665.
- [9] Berg-Weger M, Stewart DB. Non-Pharmacologic Interventions for Persons with Dementia. *Mo Med.* 2017;114(2):116-119.
- [10] Nagamatsu LS, Handy TC, Hsu CL, et al. Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment [published correction appears in *Arch Intern Med.* 2013 Aug 12;173(15):1477].
- [11] Epperly T, Dunay MA, Boice JL. Alzheimer Disease: Pharmacologic and Nonpharmacologic Therapies for Cognitive and Functional Symptoms. *Am Fam Physician.* 2017;95(12):771-778.
- [12] Mental stimulation slows alzheimer's progression. Fisher Center for Alzheimer's Research Foundation. Published November 12, 2014. <https://www.alzinfo.org/articles/mental-stimulation-slows-alzheimers-progression/>
- [13] Bademli K, Selçuk-Tosun A. The effect of reminiscence therapy on cognitive functions, depression, and quality of life in Alzheimer patients: Randomized controlled trial. *Int J Geriatr Psychiatry.* 2019;34(1):47-53.
- [14] Phillips MCL, Deprez LM, Mortimer GMN, et al. Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease. *Alzheimers Res Ther.* 2021;13(1):51.
- [15] Iranshahy M, Javadi B. Diet therapy for the treatment of Alzheimer's disease in view of traditional Persian medicine: A review. *Iran J Basic Med Sci.* 2019;22(10):1102-1117.
- [16] End-of-life care for people with dementia. National Institute on Aging. <https://www.alzinfo.org/articles/mental-stimulation-slows-alzheimers-progression/>