

Advances in Comprehensive Treatment of the Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is one of the most popular and deadly disease. In order to deal with Alzheimer's disease, thousands of researches, studies and experiments have been done to seek out the ways can prevent or even cure the disease. This paper will discuss some initiative and effective methods that deal with Alzheimer's disease. The Paper is first going to look at the pharmacological treatments which are treatments that involves drugs or chemical substance that are proven by experiments or theoretically proven to be effective to the patients and focus on use of mixing Vitamin E plus memantine, Lecanemab, aducanumab and Epigallocatechin gallate. Secondly, non-pharmacological treatments that includes the treatments without using drugs and chemical substance. Instead, it is going to look at the treatments that train the patient's physical and mental strength. Physical treatment, cognitive treatment, music treatment and dancing treatment will be discussed in this part. Prevention of Alzheimer's disease will be briefly gone over. Since correlation between some potential causes and Alzheimer's disease has long been discovered and talked about, this paper will not extend each of these potential causes in detail, which in resulting in providing data reference for further study of AD.

Keywords: Alzheimer's disease, Pharmacological Treatments, Non-pharmacological Treatments, Prevention.

1. Introduction

Alzheimer disease has currently been discovered for more than one hundred years. Through those one hundred years, countless researches and experiments worldwide are conducted to deal with it. Yet, the breakthrough to completely overcome Alzheimer disease, curing the severe patients, have not been made. The patients who have Alzheimer disease suffer from memory lost, dementia and even completely lost the ability to manage their body due to the damage in brain neuron and synapse which are the basic functioning unit of brain. As a people's age increase and their neurodegeneration intensify, the probability that they will get Alzheimer's disease significantly increases. In China, the country that has the greatest amount of Alzheimer's disease, for the old people whose age is above 55, the possibility of getting Alzheimer's disease will increase approximately one times in average as their age increase by 5 [1].

Since the first case was reported in 1907, great progress has been made in understanding AD, but the understanding of its pathogenesis, pathophysiology, clinical process and treatment methods is still unclear. This paper aims to introduce some recent discovery in prevention and treatment of early Alzheimer's disease to further discuss the effectiveness in these treatments. The paper will basically discuss from pharmacological treatments, non-pharmacological treatments, and the prevention of the AD.

2. Pharmacological treatments

Pharmacological treatments are basically providing the patients with the drugs or chemical substances that the researches and experiments find to be effective in the lab that can decrease the symptom of Alzheimer's disease. The use of drugs and chemical substance on the participants has to be carefully used while the drug or chemical substance used on the participants should be proven to have no negative effect on human body.

2.1. Memantine and Vitamin

Memantine treatment for 6 months promoted non-amyloid cleavage of amyloid precursor protein (APP) and subsequently reduced soluble A β 42. Thus, long-term enhancement and cognitive impairment are prevented. In contrast, hyperphosphorylated endogenous tau levels remained unchanged, indicating that long-term memantine treatment was ineffective in inhibiting tau lesions induced by APP processing [2].

Mixing use of two substances called Memantine and Vitamin E are discovered to be effective in dealing with Alzheimer in clinical trials. Both of these two substances are known to be useful to moderate severe Alzheimer Disease. However, E-vitamin, or alpha tocopherol, is known to have no effect on mild cognitive impairment while memantine is proved to have little to no benefit on patients with mild Alzheimer Disease.

An experiment was designed by the department of Veterans Affairs Cooperative Studies Program. The experiment trial is set to be double-blind and placebo controlled with parallel-group RCT. During the study, the researchers used a stratified sampling method and randomly assign the patients to for different blocks with identical size. Each block of participants will receive a different treatment while there are four different kinds of treatments: alpha tocopherol with matching placebo for memantine, memantine with a matching placebo for alpha tocopherol, alpha tocopherol with matching placebo for memantine, alpha tocopherol with memantine and matching placebo for alpha tocopherol with matching placebo for memantine. ADCS-ADL inventory score is a unit to measures the ability of the Alzheimer's disease patients to perform daily activities. The range of it is from 0-78; the lower the score is, the worse the ability that the patients are able to perform activities. All three experiment groups show a better result than the placebo group. In the first 12 month, the decline of 8 unit in the ADCS-ADL inventory score of the Placebo group is the most significant while that decrease in vitamin E group of around 4 units is the least significant. The decrease of memantine and mixed group is similar, both groups have a decrease around 7 units. After 24 months, the decreases in units of ADCS-ADL in vitamin E, memantine, Vitamin E plus memantine, and control group are around 12,14,13 and 16 correspondingly. For the 36th month, the decreases for vitamin E, memantine, memantine plus vitamin E memantine, Vitamin E plus memantine, and control group are around 20, 19, 19, and 25 correspondingly. For the 48th months, the decreases for vitamin E, memantine, memantine plus vitamin E memantine, Vitamin E plus memantine, and control group are around 26, 25, 29 and 27 correspondingly. Due to the result, the researchers conclude that both alpha tocopherol and memantine group has a significant benefit comparing to the placebo group They suggest a possibility that alpha tocopherol and memantine interfere the effect of one another, but they claim that it is only their guess while they did not find out the causation of this phenomena or investigate it. This hypothesis still needs future investigation that follows up to justify [3].

2.2. Lecanemab

Lecanemab is an IgG1 monoclonal antibody, which is a kind of antibody that is produced by the fusion of myeloma cells and solenocytes from a immunized mouse. It will be active in oligomers, protofibrils and insoluble fibrils able to target the soluble aggregated amyloid beta, a substance accumulated in human brain in early stage of Alzheimer's disease, as the preference. In a multicenter, double blinded, placebo-controlled Bayesian design experiment that lasts for eighteen months and test on patients with early Alzheimer's disease, they randomly assign all the participants into six different groups that takes lecanemab in different amount and different frequency while including one placebo group. The result is measured by the reduction of amyloid PET SUVR that is caused by the dose. The change of least squares from the baseline in amyloid PET SUVR is 0.004, -0.094, -0.131, -0.197, -0.225, and -0.306, for groups of 2.5mg/kg biweekly, 5mg/kg monthly, 5mg/kg, 10mg/kg, and 10mg/kg biweekly, correspondingly. Individuals in the experiment group have a significant reduce in the brain amyloid than the placebo group. Particularly for the 10mg/kg biweekly experimental group, its result also shows the difference on ADCOMS and ADAS-Cog14 versus the placebo group [4].

2.3. Aducanumab

Aducanumab is also a monoclonal antibody which is derived from a process of reverse transcription. It directed to the N-terminus of the amyloid beta peptide. Its effectiveness for the patients in early stage of Alzheimer's disease has been measured, however, its effectiveness for the patients with severe Alzheimer's disease remains unknown. In an double-blind, placebo-controlled experiment that aims to investigate the level of safety, tolerability of taking aducanumab, for the patients with mild Alzheimer's disease, randomly selected participants are randomly assigned to placebo group and groups that takes different number of doses of aducanumab for one year. The result is measured through florbetapir PET imaging, The baseline is set at 1.44 score of PET standard uptake value ratio. After the period of 54 weeks, the 3, 6 and 10 mg kg⁻¹ group shows significant ($P < 0.001$) reduction in standard uptake value ratio. The result shows that the participants in groups treated with aducanumab has reduced brain amyloid beta plaques [5]. Currently, the aducanumab has been identified as a treatment for Alzheimer's disease by the US Food and Drug Administration.

2.4. Epigallocatechin gallate

Epigallocatechin gallate is a natural substance found in green tea that the people drink in daily life. It can bind to beta-amyloid through hydrophobic interactions or form hydrogen bonds with each other. This binding will immobilize 1-20 amyloid beta peptide residues which will then lead to the inhibition of characteristic beta sheet formation. However, the greatest limitation and disadvantage of Epigallocatechin gallate in treating Alzheimer's disease is that it cannot be effectively absorbed by intestine while it has a low stability. As a result, nanocarriers, substances with antioxidant and anti-inflammatory property have been used to enhance the efficiency of Epigallocatechin gallate efficiency [6]. Although being a potent molecule to treat many neurological diseases including Alzheimer's disease, more clinical trial has to be done to prove the true effectiveness of this molecule against those diseases.

2.5. Curcumin

Curcumin is a kind of polyphenol substance widely existing in the rhizome of the herb *Curcuma longa*. Because of its anti-amyloid protein formation and aggregation, anti-inflammatory, antioxidant and immune related effects in the nervous system, curcumin plays a neuroprotective role and plays a certain role in the prevention and treatment of AD. Curcumin inhibition A β The aggregation mechanism may be in A β The specific mechanism of a link after generation needs to be further studied. In general, animal studies have shown promising findings on the physiological and behavioral enhancement of cognition [7]. The effectiveness in human body needs to be further explored.

2.6. Icariin

Icariin (ICA) is one of the main active components of the *Epimedium*. Many pharmacological studies have found that ICA has extensive pharmacological activities. A large number of studies have confirmed that peripheral administration can produce obvious central effects, including neuron protection, prevention and treatment of various AD models, and anti-aging effects.

In 2023, the new animal experiment found that ICA can improve the damage of brain insulin signal transduction, increase the expression of the glucose transporters, and hinder the formation of pathogenic Alzheimer's disease proteins, like the A β Accumulated and hyperphosphorylated tau. ICA treatment protects neurons and synapses from brain insulin signaling disorders and glucose hypometabolism, and improves memory impairment in AD mice. Icariin with low toxicity may bring new hope to AD patients [8].

3. Non-pharmacological treatments

Besides the pharmacological treatments of Alzheimer's disease, the researchers start to pay more attention on the non-pharmacological treatments which is also proven by be effective especially to patients with mild or moderate Alzheimer's disease. Most of the non-pharmacological treatments are available during our daily life and easy to be done outside the lab.

3.1. Physical activity treatment

Researches has discovered that among people who are diagnosed as the having mild cognitive impairment, the people who engage in aerobic exercise program have been discovered to experience improvements in brain memory, executive functions and the cognitive test. Exercising will not only change our body by making our muscles stronger and giving us a better health, but also change our brain in anatomic, cellular and molecular levels by the activation of angiogenesis, neurogenesis, synaptogenesis, and stimulation of neurotrophic factors that can enhance the ability of learning and memorizing. It is also found that there is a negative correlation between physical activity levels and the level of plasma and A-beta protein, which is a protein commonly found in patients with Alzheimer's disease, in the old people who does not have Alzheimer's disease [9].

3.2. Cognitive treatments

Cognitive treatments are generally the more effective in dealing Alzheimer's disease than pharmacological treatments in several researches. In one of those researches, the researchers randomly assigned the participants into four groups: memory, reasoning, speed and control group. The participants receive treatments that is corresponding to their group. Measured in mean memory score, obtained from the 10-year-long research, all three training are shown to be 2-10 units higher than the treatment of control group before Year 10. However, in year 10, no significant difference between experiment group and control group can be found. Through training the patience with reasoning, speed of processing and memorizing, the researchers are able to improve the patients' cognitive and functioning ability in things that is similar to what the training content while the effect will last until 10 years after the training has been done. The neural circuits of the patients will be stimulated which will help the patience to effectively keep their past memory and obtain new memories [10]. By applying cognitive trainings, the brain circuit of the patients will be stimulated which consequently leads to the improvement in their brain function.

3.3. Music therapy

Music is usually recognized only as a way of entertainment. However, it can also conduct sensory and emotional stimulations to the patients. There are two techniques of music therapy: active music therapy which includes the use of music instruments or anything that produces sounds, and receptive music therapy that simply play the music to the patients [11]. Yet, in most of the music therapies, two techniques are combined and used together. In experiments, the researchers will offer the patients with mild to moderate Alzheimer's disease the music therapy. The result of the experiment found that there are significant improvements in memory, orientation, depression and anxiety while the significance can be found after only four music therapy sessions [12].

3.4. Dancing therapy

Dancing is an normal activity in daily life. In an experiment investigating the effeteness of the dancing therapy, they investigate and compare the patients who receives no treatment, standard caring or other kinds of treatments with patients who was given one of the types of dancing therapy from several different types. Comparing to physical treatment, dancing is discovered to be more effective in enhancing social and behavioral factors like self-motivation while most of the benefit of normal physical therapy can also be found during the dancing therapy. It is also a common practice to combine dancing therapy and music therapy to treat the patients in the same time. The combined use

of two therapies is proved to produce more dopamine, a substance that stimulates the sense of happiness in human brain, and gives the patients a better mood in day-to-day life [13-14].

4. Prevention

Alzheimer's disease develops over a long period of time, it will be significantly. In early stages of Alzheimer's disease, it is much easier to treat the patients than during severe stages. Since Alzheimer's disease is so prevalent among old people, it seems to be more effective to prevent the disease from happening than treating it after it has already occurred. In particular, it is necessary to do a good job in the primary prevention of AD, improve the understanding of the population to prevent diseases, popularize the related knowledge of prevention, increase the ability of active prevention, develop good living habits, ensure health, happy mood. According to US National Institutes of Health, diabetes mellitus, smoking, depression, mental and physical inactivity and poor diet are main have a positive association with the possibility of getting Alzheimer's disease while many past researches and paper has found and concluded many statistically significant results [15]. By changing one's life style and increase the amount of physical and mental exercise that is taken. Not only will the possibility of getting Alzheimer's reduce significantly, but also own a healthy body that can prevent an old person from suffering the pain brought by diseases other than AD.

The latest research shows that health guidance for AD patients through telephone can also reduce the risk of AD to a certain extent, especially during the current COVID-19 pandemic. This method has just the right space to play, and at the same time, the economic cost is low, which is more suitable for elderly patients with low income during the COVID-19 pandemic [16].

5. Conclusions

As one of the most popular and deadly disease that mostly threaten old people over 55 years old over more than 100 years, Alzheimer's disease is still an obstacle for human. Since Alzheimer's disease is closely related to human brain, the most intricate and important organ in human, researches on Alzheimer's disease is relatively slow. Ethic problems of using human brain in the experiment is a great challenge for the researchers because they do not have the chance to totally study the human brain.

Currently, there are three popular approaches that deal with the Alzheimer's disease: pharmacological treatment, pharmacological treatment and prevention. For pharmacological approach, the using of drugs and chemical compound in the experiment helps the treatment to be target-specific. Pharmacological treatments can be investigated through discoveries of theories in the lab. It is a very promising control because their still remain countless of substance that people can test to see the effectiveness on curing Alzheimer's disease. However, drug treatment will lead to safety problem of the participants and user. Sometimes, it is hard to 100% make sure the chemical substance that you provide the participants will be safe to use on every participant. Pharmacological treatments also require way more cost to test and develop than the non-pharmacological treatment.

Non-pharmacological treatments is mainly the use of physical and mental training on the patients. These treatments, unlike most pharmacological treatments, are easy to perform, especially for physical treatment, music treatment and dancing treatment. However, it is hard to prove the effectiveness of the non-pharmacological treatments in theoretical way.

Since a large number of old people will get Alzheimer's disease, it becomes important to focus on the prevention of Alzheimer's disease. The future studies of Alzheimer's disease are very likely to be based on prevention of Alzheimer's disease because limited positive results in the experiments done on pharmacological and non-pharmacological that can completely cure the disease. So, not letting the disease to happen seems to be a short-cut for human in our fight with the Alzheimer's disease.

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