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Treatment of Alzheimer's disease based on new drugs

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Abstract. It is well-known that Alzheimer's disease (AD) is a chronic neurodegeneration characterized by memory impairment, cognitive complexity, language impairment, mood swings, and behavioral abnormalities. The AD is related to a variety of factors and has been associated with circumstances, genes, generations and genders. The mechanism of pathogenesis is also unclear, and there are several hypothesis theories. The more convincing one is the deposition of amyloid. Although there is no one drug that can cure the AD completely, there are approved drugs that alleviate the development of the AD by preventing the breakdown of acetylcholinesterase and increasing the nerve cells that transmit messages. The development of new drugs and their use in the treatment of AD has received increasing attention. In this research, six drugs will be focused on, which are aduhelm, aricept, exelon, leqembi, namenda, and namzaric. Compared with single-target drugs, multi-target drugs can target different physiological aspects of the disease and have the advantages of fewer adverse effects, lower clinical doses and significant efficacy. Because their therapeutic mechanisms are different, patients can select the most appropriate drugs for different conditions of the AD according to the symptoms of the disease. Based on the current treatments, there is no way to cure the AD, hoping people could find a full cure for AD in the future.

Keywords: Alzheimer's disease, mechanism, drug therapy.

1. Introduction

Neurological disorders can cause a diverse of different problems in the central nervous system. The neurological disorder that cause dementia is the Alzheimer's disease (AD). Alzheimer's is not something that comes naturally when you grow old, but getting older is currently the most significant cause for this disease [1]. Most of the Alzheimer's patients are in their 60s. As time goes by, some symptoms of AD like dementia get worse and worse dur to the progressive disorder of the AD. In the early stages of the disease, patients will gradually loose some parts of their memories. But when the disease develops into its later stages, people are going to find communicating or engaging with their surroundings very difficult. After diagnosed with Alzheimer's, patients could live about 4 to 8 years. There are some exceptions, depending on some other factors, some could live up to 20 years. Although the probability of an increased risk is small, some gene that could increase the risk of getting the disease may be inheritable, which patients could get from their parents [2].

Our body changes as we age, the same goes to our brain. Some processing delays and frequent memory issues are things that the majority would eventually be aware of. If patients brain cells start failing, there are some symptoms that might occur. For example, their mental functioning may change

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significantly, disorientation and great memory loss. The symptoms of Alzheimer's are found in the learning related region of the brain, and they include randomly suspecting the people around patients, their family and friends. As the disease distribute further into the brain, more symptoms start to appear, such as memory loss and change in behaviors, having trouble to walk, speak and swallow. These are what most people are scared of experiencing when diagnosed with the AD. It's not easy to spot the symptoms when the patient themselves are in the situation.

Although different treatments have been used to treat AD, there is no cure for such disease. Researchers don't yet fully understand the mechanisms of the disease, such as how it causes memory loss or behavioral problems in humans [3]. The goal of their research is to be able to reverse these changes in hopes of one day preventing or stopping the disease from its origin. As the study progressed, the researchers found that there were treatments that could ease the symptoms of Alzheimer's and help patients recover over a long period. Due to the disease can develop new symptoms, the treatments need to be modified. And with new treatments, new problems arise. Medication is the most widespread therapy for the AD at this stage [4]. In this society, the treatment of the AD can be mainly separated as two types: environmental treatment and the medication. The environmental treatment means that the people around the patients need to create a safe and supportive environment for the patients. However, although this method can minimize the pain of AD, it requires a large amount of labor and financial resources. While current treatments for AD have more or less their own drawbacks, drug-based treatments are still receiving attention. For example, aduhelm is the first targeted treatment for Alzheimer, and it is essentially an antibody that targets the amyloid protein. For the treatment of the AD, aduhelm can slow the progression of the AD by reducing the amount of amyloid protein that aggregates. However, in clinical trials, aduhelm has been found to cause allergic reactions and fluid accumulation in the brain.

Aricept is an oral drug marketed by Eisai cooperates with Pfizer. Aricept belongs to a class of cholinesterase inhibitors that inhibit the production of acetylcholinesterase in the brain. The disruption of message transmission caused by a decrease in acetylcholine may contribute to the development of Alzheimer's. Hence aricept alleviates the AD by preventing acetylcholinesterase from breaking down acetylcholine. By the way, aricept has more side effects, including insomnia, nausea, and loss of appetite. Exelon is made by Novartis, a Swiss company, which is also a cholinesterase inhibitor drug. Leqembi is responsible for targeting beta-amyloid in the brain, which is an antibody therapy that is injected intravenously into the body. It is a useful way to slow the onset of the AD. Side effects of leqembi include headaches and amyloid-related imaging abnormalities. Namenda is marketed by the American company Allergan and is used to treat patients with moderate or severe the AD. Namenda's side effects include feeling tired, constipated, and dizzy. Namzaric is a combination of two treatments, aricept and namenda, that simultaneously inhibits acetylcholinesterase, enhances intercellular communication, and controls the amount of calcium entering brain cells. Namzaric has demonstrated effectiveness in 677 patients with the AD and has also ensured the safety of patients taking the drug [5]. However, it can also have side effects such as dizziness and diarrhoea. All those therapies do not cure the AD, and they can only delay or relieve the symptoms of the AD. The specific analysis of those drug treatments will be presented subsequently.

As a result, this research will analyze the six drug treatments for the drug therapy of the AD, including aduhelm, aricept, exelon, leqembi, nuedexta, and namzaric. For each medication, this research will firstly study if it has any side effects since some patients may not accept the medication with any side effect. Also, some side effect will cause serious health problem. Besides, this research will focus on the medications' therapeutic result and the principle of how they work. In short, developing the treatment of the AD is crucial to the whole world for several reasons. Firstly, the increasing number of patients means that the AD is developing as a serious disease for all human being. Secondly, researches reflect that the AD will cause a series of safety problems such as the patient may get lost, or the patient may get into an accident. In some worse cases, the patients might hurt themselves due to the lack of the consciousness caused by the AD. At last, the AD has the heredity

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which means that the patient's child will have a higher possibility of getting this disease. Therefore, having an exact treatment of AD is very important.

2. Analysis of new drug treatments

A distinctive feature of the AD is the deposition of protein structures in brain called amyloid plaques. Amyloid plaques and neurofibrillary are closely associated with AD. Studies have shown that the formation of neurofibrillary tangles and amyloid plaques can cause nerve cells in the brain to degenerate. Neurofibrillary tangles are twisted states of brain cells, which are insoluble fibres. Neurofibrils are made up of microtubules, which are normally responsible for transporting nutrients within nerve cells. However, in the case of the AD, the microscopic structures do not work properly. In addition, amyloid is actually a soluble protein that is naturally produced by the body. Normally, the human brain breaks down and eliminates these protein fragments. However, in the case of the AD, the same protein fragments accumulate and combine together to form a number of insoluble protein plaques known as β-amyloids, which are insoluble fibres formed when amyloid proteins are combined together. They clog the communication system in the brain, damaging synapses and organelle membranes, causing abnormalities in the transmission of information in the brain and manifesting the symptoms of the AD.

Aduhelm works by destroying amyloid clumps. Aduhelm is a monoclonal antibody that binds to amyloid clumps and helps the immune system in the body to find and target the amyloid clumps, then immune cells can break them down. Aduhelm has been shown to be effective in breaking down amyloid plaques, but has not shown a significant reduction in clinical symptoms such as cognitive decline. In the meantime, Aduhelm can cause some severe side effects. Some people may also develop small bleeding spots within the swollen brain or on the surface of the brain. More than 20 percent of patients in clinical trials suffered from headaches associated with brain swelling. In addition, dizziness that changes in vision, nausea and seizures were also side effects of taking aduhelm. And now aduhelm has opened up a new path for the treatment of the AD [6].

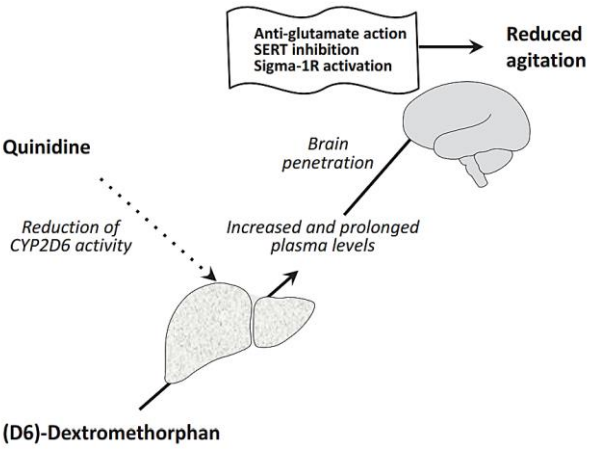

Figure 1. The underlying mechanism of anxiety in AD patients with quinidine [7].

Aricept can be used to help alleviate the symptoms of the AD. One reason is that AD causes damage to the brain is as the disease gets worse. It will destroy brain cells, and when brain cells are reduced, then less amount of acetylcholine is produced. Acetylcholine is a neurotransmitter produced by neurones to transmit chemical messages between brain cells. In other words, a decrease in the number of cells responsible for transporting acetylcholine means a blockage in the transmission of essential information. Aricept is a drug that belongs to the group of cholinesterase inhibitors. Therefore, aricept can temporarily alleviate dementia associated with the AD. Unfortunately, all kinds of cholinesterase inhibitors cannot reverse Alzheimer's or repair the destroy of neurons. As a result, aricept cannot cure or stop the progression of the AD. Some common side effects of aricept include

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diarrhoea, vomiting, and nausea. There was research data suggests that starting treatment at a low dose and steadily reaching higher doses can help reduce side effects.

Nuedexta is comprised of a combination of quinidine and dextromethorphan. Quinidine is a drug that is used to treat ventricular arrhythmia and malaria. And such drug has been used to treat AD, as shown in Figure 1 [7]. Dextromethorphan is an antitussive agent comparably effective chronic, nonproductive cough. The mechanism behind how exactly nuedexta work is still not clear. This will relieve PBA agitation, which is a neurological condition where patients start laughing and crying uncontrollably. These emotional responses do not follow your internal emotions. Enhancing the drug benefits, quinidine raises the level of dextromethorphan in our blood. It is well-known that all drugs have side effects, and thus nuedexta is not an exception. Some side effects that you can get from taking nuedexta is sudden dizziness, short of breath, bleeding gums, fever, liver problems as well as muscle and joint pain. It could also cause a symptom called the serotonin syndrome, which includes hallucinations, agitation, shivering, fast heart rate and diarrhea. If patients ever find themselves experiencing the serotonin syndrome, they need to find medications and stop taking nuedexta right away. People with heart failure and hepatitis, which people could get from taking mefloquine and should not take nuedexta.

Namzaric is comprised of a combination of memantine and donepezil. Unlike nuedexta, namzaric's mechanism behind its therapeutic effects is very clear. Memantine regulates the neurotransmitter glutamate, neurotransmitters are chemical messengers that the brain utilizes to transfer signals between nerve cells. The functions of various neurotransmitters vary. Glutamate, for instance, has a role in memory and learning. The NMDA receptor, which is present on the surface of nerve cells and which glutamate typically interacts with, allows the calcium to enter the cell. Because excessive intake of calcium can be toxic and cause cell damage, it is crucial to precisely regulate how much calcium enters the cell. Damage to brain nerve cells in AD results in a loss in memory, thinking, and learning abilities. It is thought that some injured nerve cells begin to emit too much glutamate. Increased glutamate results in excessive calcium entry into cells, which further damages cells and disturbs the closely regulated memory and learning process. Memantine prevents excessive calcium from entering cells and harming them by blocking glutamate's access to NMDA receptors. In addition, namzaric can cause various serious side effects including seizures, vomiting, nausea, headache, dizziness. As well as slow heart beat and faint which is common for people that has heart problems. People with lung diseases and asthma could get their disease worsened after taking namzaric. This drug has been used to treat AD and has achieved good results. As shown in Figure 2, this is mainly through the 11 cognitive subscales of the AD assessment scale (ADAS-cog 11), which is the main efficacy measurement [8].

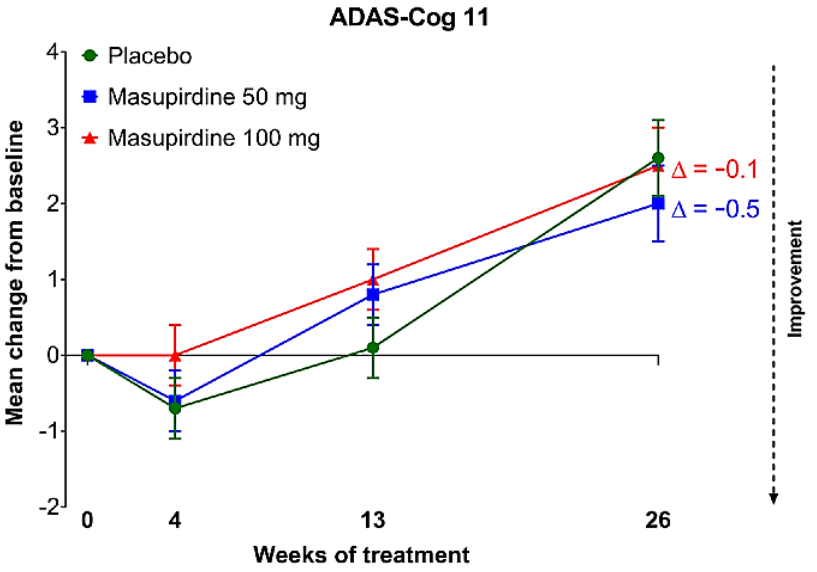

Figure 2. The main efficacy measurement for AD [8].

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Donepezil enhances communication between the brain's still-healthy nerve cells, providing a brief relief from the symptoms of Alzheimer's. It prevents the enzyme acetylcholinesterase from degrading the neurotransmitter acetylcholine. The brain employs a substance called a neurotransmitter to convey impulses between nerve cells. Reduced acetylcholine communication in the brain is one of the theories for why memory and judgment are affected in Alzheimer's. As shown in Figure 3, donepezil can be used to treat mice with AD [9]. Donepezil improves communication between brain cells by raising acetylcholine levels by inhibiting acetylcholinesterase. The research had stated that the AD can be used to produce a neurotransmitter called acetylcholine. This neurotransmitter is used to memorize, think, and detect. After being used, it will be broken down by acetylcholinesterase. If the level of acetylcholine is too low, there will be some symptoms of AD reflected on a person. Exelon was invited to solve this problem. It can reduce the level of acetylcholinesterase in people's brain. In this case, the acetylcholine will not be broken down. At the last, the communication between the nerve cells in the brain will be promoted and the symptoms of AD will get an anesis in a certain extent. However, in the long run, Exelon is not the best choice for AD as it is not able to stop AD growing or cure it.

Exelon, which is also called rivastigmine tartrate, had been proved to be a good choice of treating the symptoms of the AD (10). In the worldwide clinical trials, no matter oral-taken or the patch form had already been found that patients can get a better therapeutic result than taking placebo. However, another clinical trials of exelon illustrated that the side effects of this medicine are also unignorable since they affect the patients in different forms. Some patients may have a severe vomiting or diarrhea. They will continuously have a head-lighted feeling. Other patients may not be able to control well their body since the medicine can affect the muscle movement. Moreover, the patients who use the exelon patch may get a severe skin redness with itching or irritation. The diagram (drugs) had shown that patients who take Exelon had a higher rate of discontinuation. In short, the good therapeutic result of exelon is coming with the severe side effects, and it still cannot be the best choice for curing AD.

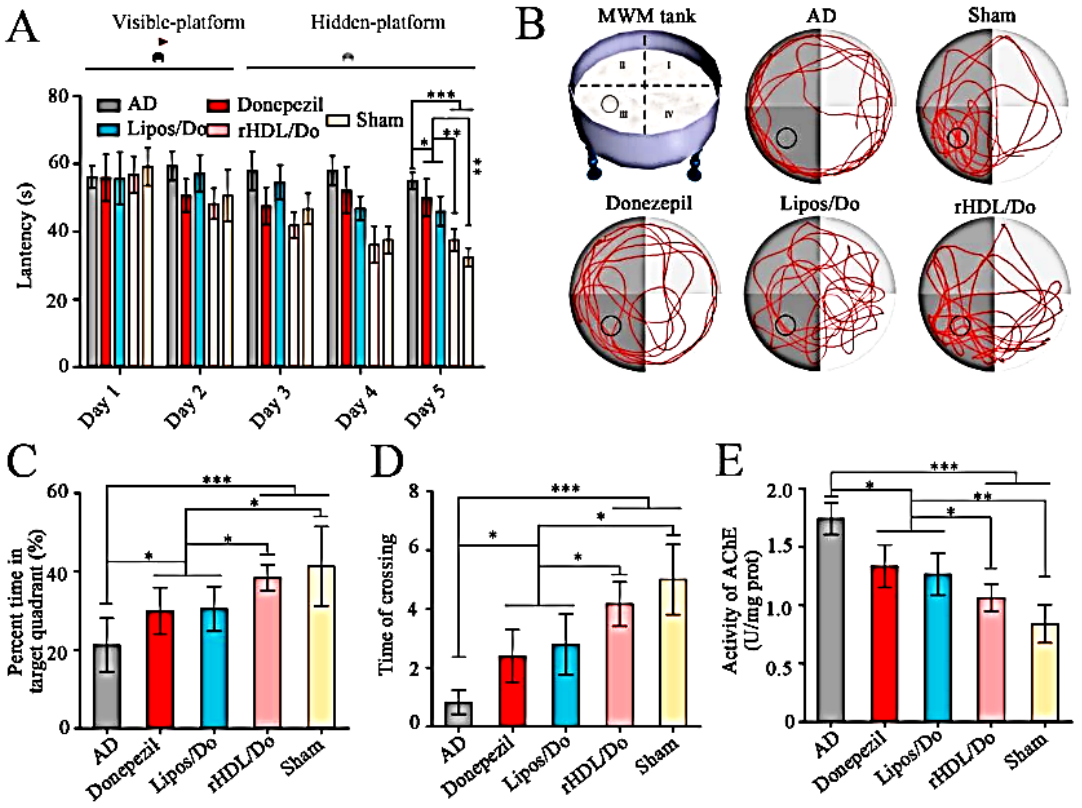

Figure 3. Treatment of donepezil for AD mice with relieving memory deficiency [9].

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Patients with the AD had been found that there was a clump in their brain. Scientists found that the clumps were caused by the accumulation of a kind of beta-amyloid protein [10]. These clumps can affect the function of the neurons and finally destroy them in the patients' brain. Therefore, a treatment called leqembi was invited in order to solve the problems caused by the beta-amyloid protein. Leqembi is an antibody which is designed to bind to and neutralize a soluble, toxic version of beta-amyloid. It will tag the protein, and let the immune system of the body to clean it before it reaches the toxic level. In this trend, the treatment had been defined as a way to slow down the Alzheimer's progression. After being checked that there is beta-amyloid protein in brain, the patients will be required to take an intravenous infusion once every two weeks. Every infusion will take about an hour. Study 201 was formed to study the effectiveness and the safety of the leqembi. Over 800 AD patients participated in this trial. The result illustrated that the benefits of leqembi had reflected on the patient 6 months after the trial began. Infrequently, there will be a large area of bleeding occurs in brain. This effect will not always cause negative impact on the patients, but sometimes it will. When that happens, the patients will feel headache or confused. They may get a change of vision or walking difficulty. Besides, during the infusion, the patients may also have side effects such as fever, nausea and vomiting. These are all the normal reflections of taking this treatment. In short, compare with other treatments, leqembi has a lower side effect, but also cannot cure the AD completely.

3. Conclusion

In conclusion, the research mainly focused on the drugs-based treatments for AD, and it analyzes the basic characteristics, treatment mechanism, advantages and disadvantages of each drug. The research also analyzes and demonstrates the principle of how the treatments work, the therapeutic result and the side effects of each method. By comparing different drug treatment methods, this research found that there is not any exact medication which can cure the AD completely. In the research, the documents acted an important role to show the basic information of every treatment. According to those documents, it can compare the effects and the draw the conclusion of the advantages of each treatment. Although there had already been many research articles written to show the information of the treatments, the research made a crucial comparison of the advantages of the six different medication treatment. In future, this research can be a possible document for people to understand the different medication treatment of AD.

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