Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 7
MISBP 2024

Analysis of drug treatment methods for Alzheimer's disease

Ruihan Liu*

The Affiliated International School Of Shenzhen, Shenzhen, China

* Corresponding Author: gabriellaliu@outlook.com

Abstract. Alzheimer's disease (AD) has attracted attention from scientists since every year thousands of patients are suffering from this. AD, as the primary cause of dementia, holds 60%–80% of all cases and is associated with deficient cholinergic neurotransmission. The path of discovering methods to tackle it is still a long way to go, because there is not such a method to completely heal this disease and as for drugs therapy. There are some drugs including tacrine, donepezil, galantamine and rivastigmine, which are officially being used and are proved to be slightly effective. This research will discuss the etiology of AD, the development of AD related drugs, the functions and dosages of drugs, as well as their advantages and disadvantages. It can be avoided in the early stages, by gaining a better understanding of the current different drug treatment methods and the changes made in the process, in order to improve the efficiency and prediction after fixation, and thus provide direction for the future development of AD drugs.

Keywords: Alzheimer's diseases; Cholinesterase inhibitors; Memantine; Neurodegenerative disorder; Drug treatment.

1. Introduction

Alzheimer's disease (AD) has been regarded as one of the very common diseases, which is especially found in old people and started to be observed on many young adults. However, there is no thorough therapy to cure it. It is a progressively neurodegenerative disorder with many causes like genetic factors, increasing age, influencing mental and neurocognitive function [1], where the main feature is degraded memory. There are many hypotheses for the causes of AD, such as Tau hypothesis. Tau is a genre of protein that works to stabilize microtubules inside cytoskeleton, and hyperphosphorylation is the main reason for accumulation of it in the nerve cell bodies and tangles with cellular proteins which impeding them from functioning normally. Poisonous tau can even increase formation of Amyloid-beta (Aβ) [2]. Amyloid cascade hypothesis says that the unusual process of amyloid precursor protein (APP) results in production of Aβ. Aβ produced aberrantly will trigger a cascade which results in synaptic damage as well as loss of neuron and ultimately leading to neurodegeneration [2].

Many researches are carried out to investigate methods to cure AD, and those treatments are stem cell-based therapy, drug therapy and calcium signaling [1]. This research mainly focusses on the drug therapy which control the symptom instead of change the course of AD while this therapy is developed by using trial methodology with three phases included [2, 3]. There are two divided types of drug-using remedies for AD, which are targeted therapy and combination drug therapy with the second one most frequently used in curing AD [2]. Currently, there are only two treatments-cholinesterase inhibitors and memantine that are put into use and more than ten are expected to be carried out in the future. Relatively less clinical practice related to AD have been made in the past few decades with 99.6% of them failed.

Taclin and donepezil are two acetylcholinesterase inhibitors that have the best effects on cognition and memory in AD patients, and they have varying degrees of action [2]. However, mixing use of drugs which has been proved to be quite beneficial to mid-stage AD compared to those influence single treatment can bring. Potential therapies are been developed such as anti-amyloid therapy which involves enzymes, immunisation or monoclonal antibodies and Tau targeted therapy [2]. The

following content will mainly concentrate on the present drug treatments and future directions of this method.

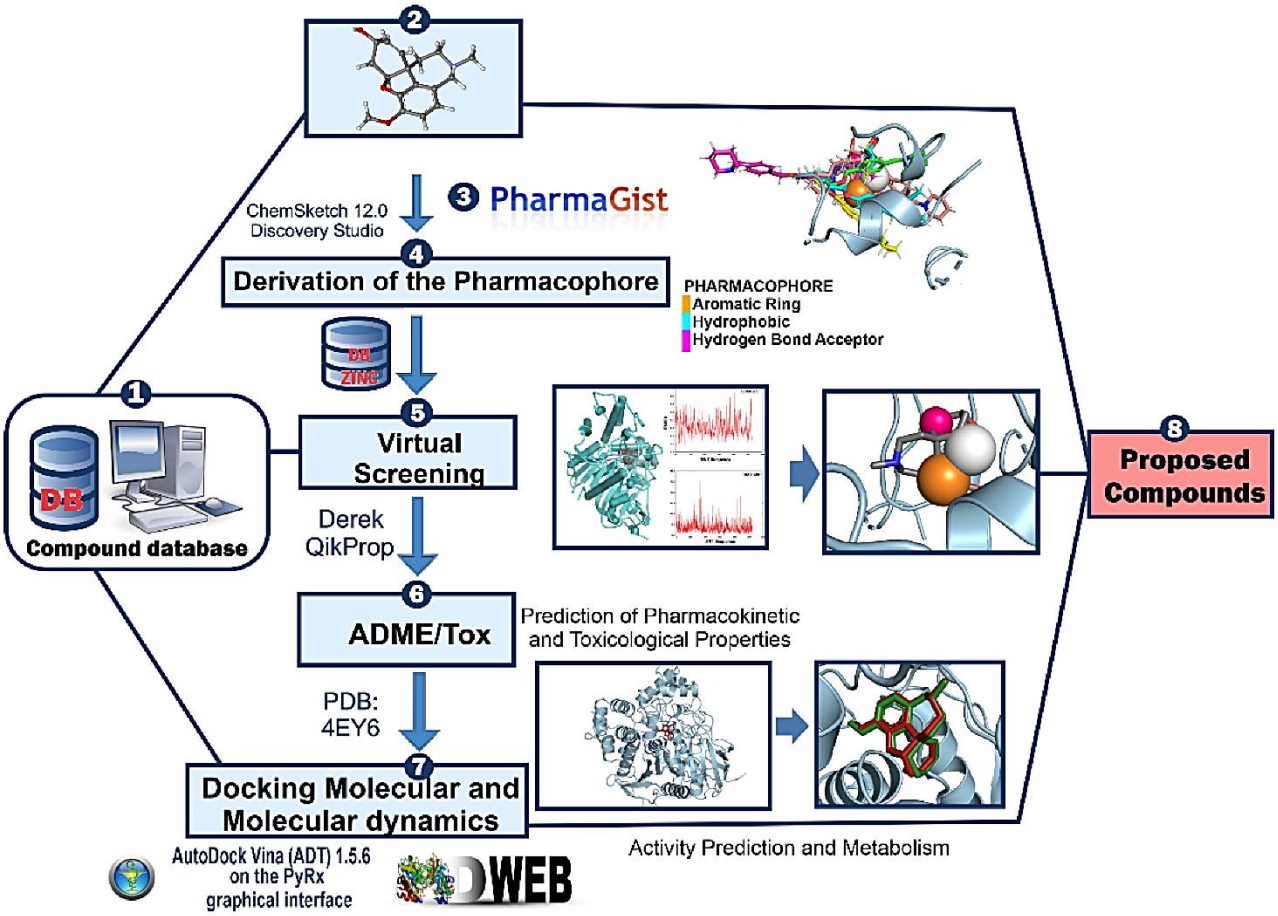

Figure 1. The process of choosing new AD drugs [4].

2. Drug treatments

In 1990, there are ideas that has been said that anti-inflammatory drugs may have protection on AD. It has leading effects on treating methods [2]. AD agents needed to go through several phases. It takes approximately 13 months to go through Phase 1, followed by Phase 2 at about 28 months, and Phase 3 at around 51 months, then the regulatory review took nearly 18 months [3]. Including preclinical development, it will take a total of more than 9 years. Nevertheless, almost all potential drugs developed can't be successful beyond phase II/III trials [1].

Focusing on drug invention and development, efforts are moved toward drug-modifying therapy (DMTs) in the past few decades. AD drug failure is common, and this is partly the reason of insufficient target engagement or the existence of toxic effects in drug test. Bringing new AD drugs to the market are facing many challenges, such as insufficient knowledge related to AD mechanism, the polyfactorial aetiology and complicated pathophysiology of AD, the slow gradual characteristics of AD and many diseases happen accompanied in old people. Moreover, symptoms of AD are not easily noticed until obvious change happens in the brain. Establishing and adjusting the clinical trial networks globally as well as recruiting participants for the trial are very hard and are time- and cost-intensive since suitable outcome measures haven't been agreed upon widely. In order to accelerating the AD drug development, many improvements are made and some obstacles are overcomed. Changes are made on aspects such as clinical trial environment with the invention of more effective measures. Currently, there are some potential AD drug treatment are been testing such as anti-amyloid therapy immunization, as shown in Figure 1. And research nowadays proved that it is more effective to use drug treatment in pre-cliniacal stage when early diagnosis of SCI or MCI are made.

Loss of cholinergic transmitter and acetylcholine in the brain is the main reason for the successive cognitive degeneration. Tacrine is a pharmacological action originally discovered and tested by Shaw and Bently in 1946 [5]. It was released as the first reversible acetylcholinesterase inhibitor to the market for AD treatment. It is an acridine that has pKa of at about 9.85 and a 2D structure, and with three rings while a few replacements of an amino group in the fifth position is white crystalline powder. This drug was first put into use in clinical trials to treat mental disorder caused by detoxicator and for upgrading the relief of muscle of succinylcholine. Initially, tacrine was used to neutralize the respiratory depression due to a drug called morphine [5] and has absorption availability at 10% to 30%, but were later discovered to be used as inhibitor. However, it was withdrawn soon since it has drawbacks of having hepatotoxic side effect. There are three other cholineterase inhibitors which are those currently been used to slow the loss of cognitive functions-donepezil, galantamine and rivastigmine.

As for donepezil, it restrains acetyl choline (ACH), which is an essential neurotransmitter for memory, from been decomposed by cholinesterase, increasing ACH in synapse. Even AD damage the brain, synaptic functions can still work for a period and it ranked the greatest prescribed drugs in the United States.It has approximately 6 million prescriptions in 2020 [6]. It also has been reported to make improvement on cognitive disability by many mechanisms. Initially, it started by gradually increase the dose in evening and after one month raise to 10 mg if acceptable. This is detected by gauging if the patient's memory or behavior started to rise to higher level or toward the normal level. If no reaction is observed after three months of use, dose-giving would be stopped. Its side effects cannot be ignored, usually related to gastrointestinal, fatigue, and muscle discomfort. Whether the patient had history of digestive or some intestinal related disease is decisive for determination on whether care should be taken. Once the situation of the patient is getting worse on the cognition aspect, the drug would be stopped immediately. Tacrine and donepezil are cholineterase inhibitors with different levels of effects but overall quite similar to each other—at a modest effect with only 1/3 patients showing low positive benefit [2].

Galantamine is a tertiary alkaloid, with a synthetically complex structure involving an intense tetracyclic framework and three stereocenters [7], was initially separated in the 1950s from the plant Caucasian snowdrop [7]. Using a dose of 24 mg/day of galantamine slowed the development of symptoms of the disease and the cognition and everyday activities of patients are maintained. Placing mouse pups in a high oxygen chamber can lead to neuroinflammation and a range of other symptoms. After injecting 5mg/kg/dose of galantamine into mouse pups for 7 days, the results can be observed. Galantamine ameliorated the symptom of neuron loss and differences are significant when compared group that with galantamine injection with the control group, as shown in Figure 2 [8].

As the only cholinesterase inhibitors that inhibits both acetylcholinesterase and butyrylcholinesterase enzymes in the brain, rivastigmine, a semi-synthetic derivative of physostigmine, demonstrates the most significant effect on patients, with great safety and fewest side effects accompanied. It can be available as a skin patch, so that patient adherence is upgraded [9]. Nevertheless, it faces several challenges such as limited bioavailability due to its hydrophilic property, hard to penetrate from blood-brain barrier which results in eliminated plasma half-life [10]. A recently clinical trial was aimed to prove the impact of rivastigmine as a cholinesterase inhibitor on cognitive impairment. The result showed that rivastigmine treatment is way more effective by shown a significant drop on the number of populations with cognitive impairment.

From 2000 to 2010, 244 new drugs are been put into trials but only memantinewere permitted entering the market. Memantine is the only clinically uncompetitive NMDA acid receptor antagonist that can upgrade neuron synthesis and regulate burning. People have no complete understanding toward memantine until 1982, when its core nervous activity was found by Merz then in 1986, it entered clinical practice as a dementia treatment [11].

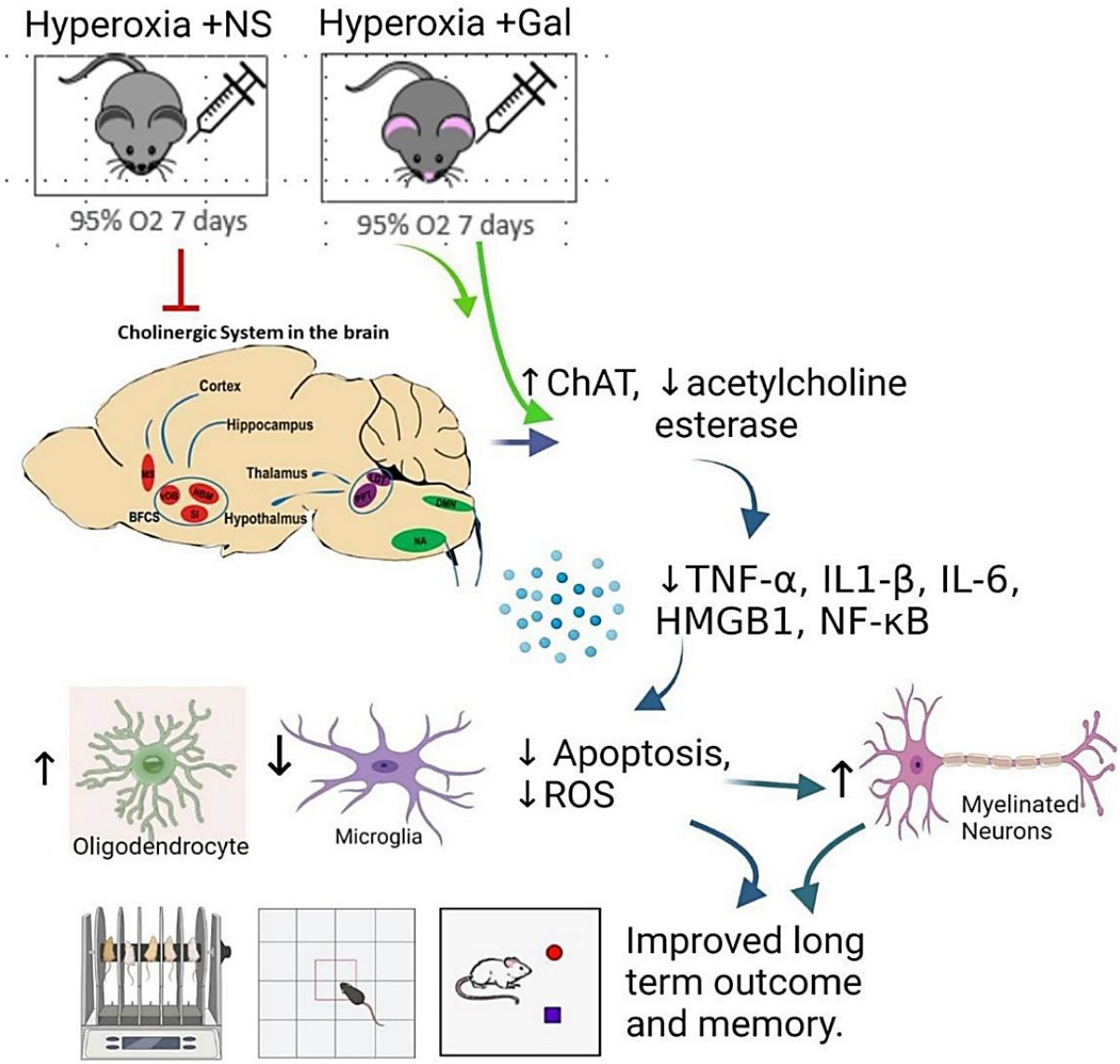

Figure 2. The process of how galantamine works on mouse pups [8].

A clinical trial was carried out to prove the effectiveness of memantine. 188 participants were divided into two separated groups-the control group with only donepezil and another with donepezil and memantine. Participants in the experiment group was requested to gradually raising the dose of memantine 5 mg/day per week for the previous 28 days and were increased and then at 20 mg/day until practice ends. The result shows that the combination in the test group are slightly more effective when used to treat moderate to severe AD [12].

Memantine is a medicine that involved in amantadine classification [11], and it is similar to donepezil that can reduce the symptom for some times. Memantine blocks the NMDA receptors, avoiding neuron loss and restore the function of damaged neurons. It also increases the dose gradually from 5 mg initially, 5 mg more every week until 20 mg. Although it is more adaptable, it can be accompanied with some side effects such as dizziness and somnolence. It can be used to treat severe AD while few examples on mild AD. It can be used with cholinesterase inhibitors, functioning on glutamate, protecting neurons from glutamine-mediated excitotoxicity.

3. Conclusion

Though these two medical treatments are the only two that shows enough safety and efficacy, overall, they generally having milder average effect. Using one drugs solely may not be very effective and may leads to greater harm, so combination of different AD drugs is a more suitable for successful

treatment of AD. With the removal of obstacle from development of new drugs, it is hoped that they will be more effective drugs permitted to be into the market for AD. In the prosperous future, hopefully, not only in the drugs treatment field, but also in AD healing regions, more new therapeutic methods and progress can be developed and some advertisement about intervention in the early stage can be promoted so that less people and their family will be suffering from the dilemma brought. Methods such as ReCODE treatment that are recently been invented and are proved to be more useful may be more developed in the future and are wished to cure AD more effective or even completely.

References

[1] S. Srivastava, R. Ahmad, S. K. Khare, Alzheimer's disease and its treatment by different approaches: A review, European Journal of Medicinal Chemistry 216 (2021) 113320.

[2] R. Briggs, S. P. Kennelly, D. O'Neill, Drug treatments in Alzheimer's disease, Clinical medicine 16(3) (2016) 247-253.

[3] J. Cummings, P. S. Aisen, B. DuBois et al. Drug development in Alzheimer's disease: the path to 2025, Alzheimer's research & therapy 8 (2016) 1-12.

[4] L. B. Silva, E. F. B. Ferreira, Maryam, et al. Galantamine based novel acetylcholinesterase enzyme inhibitors: A molecular modeling design approach, Molecules 28(3) (2023) 1035.

[5] S. Mitra, M. Muni, N. J. Shawon, et al. Tacrine derivatives in neurological disorders: Focus on molecular mechanisms and neurotherapeutic potential, Oxidative Medicine and Cellular Longevity 2022(1) (2022) 7252882.

[6] T. Nham, M. C. Garcia, K. L. J. Tsang, et al. Proarrhythmic major adverse cardiac events with donepezil: A systematic review with meta-analysis, J Am Geriatr Soc. 72(8) (2024) 2552-2565.

[7] B. Cheng, Q. Wang, Y. An, et al. Recent advances in the total synthesis of galantamine, a natural medicine for Alzheimer's disease, Natural Product Reports 41 (2024) 1060-1090.

[8] N. Zaghloul, N. S. Cohen, K. R. Ayasolla, et al. Galantamine ameliorates hyperoxia-induced brain injury in neonatal mice, Frontiers in Neuroscience 17(2023) 890015.

[9] Ç. B. Apaydın, Ö. Soylu-Eter, P. Eraslan-Elma, et al. Synthesis and molecular modeling studies of 1-benzyl-2-indolinones as selective AChE inhibitors, Future Medicinal Chemistry 14(23) (2022) 1705-1723.

[10] T. amshidnejad-Tosaramandani, S. Kashanian, I. Karimi, et al. Synthesis of a Rivastigmine and Insulin Combinational Mucoadhesive Nanoparticle for Intranasal Delivery, Polymers 16(2024) 510.

[11] B. C. Tang, Y. T. Wang, J. Ren, Basic information about memantine and its treatment of Alzheimer's disease and other clinical applications, ibrain 9(2023) 340-348.

[12] H. J. Kim, Y. S. Shim, H. J. Han, et al. A Multicentre, Randomised, Open-Label, Prospective Study to Estimate the Add-On Effects Of Memantine as Ebixa® Oral Pump (Solution) on Language in Patients with Moderate to Severe Alzheimer's Disease Already Receiving Donepezil (ROMEO-AD), Neurology and Therapy 12(4) (2023) 1221-1233.