

Current drug treatments in Alzheimer's disease

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Abstract. Alzheimer's disease (AD) is a long-lasting, degenerative neurological condition that causes deterioration of memory, cognitive and mental decline, it is the most prevalent and leading cause of dementia. Alzheimer's disease currently has symptomatic therapies, but there are still ongoing studies looking for ways to treat the illness itself. Deposition of A β and tau, inflammation, oxidative stress, and neuronal fiber tangles are the main causative mechanisms leading to Alzheimer's disease, therefore the prevention on them can effectively alleviate symptoms. To date, existing treatments have only been symptomatic, attempting to balance the neurotransmitter disorders of the disease. This review systematically summarizes and discusses a range of drugs that are currently available on the market, including cholinesterase inhibitors and glutamate receptor antagonists, natural medicines with anti-antibody, antioxidant, and anti-inflammatory properties, such as Chinese medicines "Di Dan Decoction", Ginkgo biloba, and Huperzine A, as well as promising therapeutic modalities that are currently undergoing clinical trials.

Keywords: Alzheimer's Disease, Treatments, Natural Medicines.

1. Introduction

The most prevalent form of dementia in senior people is Alzheimer's disease (AD), a neurocognitive condition that is age dependent. Neuronal plaques, neurofibrillary tangles, amyloid β peptide buildup, and loss of neurons are some of its histological characteristics, among others.

Alzheimer's disease has emerged as one of the biggest public health issues in the globe because of the significant development in the aging population in recent years. Dementia primarily affects adults over the age of 60. Given that AD is thought to affect 25–50% of individuals over 85, it is becoming more widely acknowledged that AD is one of the most significant medical issues affecting the elderly [1]. Recessive episodes of memory loss and cognitive impairment, as well as a reduction in mental and daily living independence, are all clinical signs of AD. The cholinergic hypothesis and the amyloid hypothesis are the two most well-known theories for the multifaceted nature of AD. In addition, age, risk factors like genetics, head trauma, infections, and environmental variables all contribute to the disease's onset [2].

The diagnostic phases of Alzheimer's disease are divided into four main stages: (1) The preclinical asymptomatic phase, during which time patients do not notably display clinical symptoms of AD. (2) Patients in the mild stage of AD start to exhibit some loss of focus and memory, changes in mood, and the emergence of depression. (3) In the moderate stage of AD, the disease affects the cerebral cortex and causes memory loss as well as impairments in learning capability. (4) Intense AD stage, in which when the entire cortical region has been affected and there has been a serious buildup of neuronal plaques and neurofibrillary tangles, causing the patient to suffer from severe functional and cognitive impairment. The patient may also become bedridden, which can lead to complications and death [2].

The neurotransmitter imbalance in AD is the focus of all currently used therapies [3]. There are currently no effective therapy options to treat this illness, despite the numerous current research efforts on AD-based medications. Only two drug classes have been licensed for the treatment of AD up to this point, and they are only useful for reducing the severity of the disease's symptoms, not for curing it entirely. Acetylcholinesterase inhibitors (AChEIs) have a cholinergic basis, such as donepezil, galantamine, and rivastigmine. Additionally, the NMDA antagonist, which comprises the low to medium affinity receptor antagonist: memantine, is another medication authorized for the therapy of mild to severe AD.

This article's intention is to provide a comprehensive overview of the many kinds of medications that are available on the market, natural compounds, and new potential treatments for Alzheimer's disease that are now being investigated in Phase I-IV trials.

2. Approved drug treatments

The cholinergic hypothesis of AD states that the early phase of Alzheimer's disease influences the cholinergic system of the basal forebrain. This includes acetylcholine synthesis, loss and degradation of acetylcholine neuron enzyme activity, leading to amnesia and deterioration of other cognitive and non-cognitive functions [4]. Three cholinesterase inhibitors, galantamine, rivastigmine and donepezil, have been approved for pharmacological remedy of varying severity of Alzheimer's disease (AD), and they are largely regarded as the gold standard and first-line therapies [4-6].

2.1. Acetylcholine inhibitors

Acetylcholine (ACh), a key neurotransmitter connected to memory, plays a role in a number of physiological processes in the brain, including learning, memory, attention, and sensory processing. It has been discovered that AD is characterized by cholinergic neuron degeneration, which alters cognitive function and impairs memory [2]. Despite having slightly different pharmacological properties, all these drugs function by preventing acetylcholinesterase from performing its function that influence the clinical signs and symptoms of AD. Use of CIs can successfully postpone the acetylcholine's degradative process between synaptic clefts, improving cholinergic transmission and reversing the decrease in cognitive performance. According to studies, individuals on cholinesterase inhibitors (Cis) often experience a slight improvement in their cognitive function in the first three months of treatment. Over the subsequent 3 to 9 months, the average rate of decrease in cognitive function progressively slows. Attention, thinking, memory, practice, language comprehension, and communication are among the symptoms that become improved [4,5].

Based on the three cholinesterase inhibitors' effects on patients with different degrees of dementia brought on by Alzheimer's disease. According to results, patients receiving CIs experienced more overall adverse events than those receiving a placebo. There were many different kinds of adverse effects, but the frequencies of sicchasia, vomiting, and diarrhea was considerably higher in the CIs therapy set than those in the placebo set. Overall, the three CIs were effective in treating light to severe Alzheimer's disease and did not differ significantly in efficacy despite having slightly distinct mechanisms of action. Evidence from a sizeable trial, however, revealed that donepezil was linked to fewer adverse events than rivastigmine [5,7].

2.1.1. Tacrine

During 1993, Tacrine (tetrahydroaminoacridine) become the first approved acetylcholinesterase inhibitor to treat Alzheimer's disease. Tacrine was first created in 1945 as part of a study looking for an antibacterial medication to treat troops' infected wounds. Interestingly, later research has demonstrated that tacrine functions as an acetylcholinesterase inhibitor. Tacrine was later utilized alone to treat acute anticholinergic syndromes since it could be injected in higher doses without inducing respiratory depressions when combined in ampoule with morphine. After finding that Tacrine was particularly efficient in dealing subacute anticholinergic syndrome and was generally safe in reversing induced coma, Dr. William Summers put forth the theory that Tacrine could treat early Alzheimer's dementia [8]. It is the most potent and therapeutically successful acetylcholinesterase and increases ACh in muscarinic neurons to function; nevertheless, due to the high prevalence of adverse effects, including hepatotoxicity and raised serum alanine aminotransferase levels, it was quickly taken off the market [2].

Tacrine has been extensively employed in studies to create compound passageways that are hybrid or multi-targeted. Tacrine's powerful acetylcholinesterase inhibitory activity is combined with other pharmacological features to generate a novel design without hepatotoxicity while maintaining other advantageous cholinergic qualities by attaching tacrine to other pharmacologically bioactive

constituents. Tacrine derivatives have been the subject of numerous reports, including Bis (7) tacrine dimer (Fig. 1A), Tacrine-ferulic acid hybrid, Cystamine-tacrine dimer, Tacrine-silibinin co-drug, and others [9].

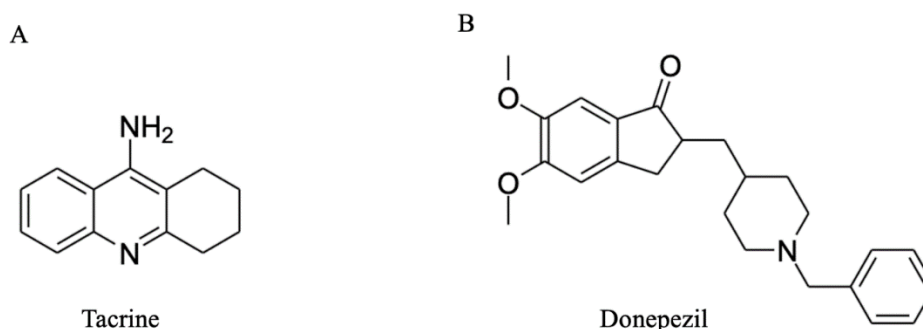


Figure 1. Structure of current approved drugs
(A) Tacrine, (B) Donepezil.

2.1.2. Donepezil

Donepezil (Fig.1B) is one of the most predominantly used cholinesterase inhibitors which has a license for the therapy of slight to intermediate Alzheimer's disease. Since AD is thought to be caused, in part, by a shortage of acetylcholine, acetylcholine insufficiency is considered to play a significant role in the disease's clinical presentations. Donepezil can facilitate brain nerve conduction and improve memory by increasing the level of the neurotransmitter acetylcholine in the brain. Evidence from numerous clinical trials suggests that it has a good safety profile, is long-term tolerable, and can stably improve cognitive ability in patients with slight to intermediate AD. Although there are many novel drug therapies in various stages being developed, but donepezil will likely remain a major treatment option for of Alzheimer's disease for years to come [10].

2.2. Glutamate receptor antagonist

Extracellular amyloid beta proteins and intracellular nerve fiber tangles made of hyperphosphorylated proteins are two features of Alzheimer's disease. Acetylcholine production is decreased in AD patients, and cortical cholinergic function is compromised. By blocking cholinesterase in the synaptic cleft and boosting cholinergic transmission, cholinesterase inhibitors used to treat dementia (such as donepezil, rivastigmine, and galantamine) can reduce symptoms. Memantine, however, acts differently from cholinergic medications and is thought to have a neuroprotective impact [11].

The NMDA receptor is one of the receptors that glutamate activates. It is a key excitation neurotransmitter in the central nervous system of the brain. When it comes to glutamatergic neurotransmission and synaptic plasticity, the NMDAR's excitability is essential. However, excessive NMDAR activation results in excitotoxicity and encourages cell death [11], damaging neurons and triggering a range of acute and long-term neurological conditions, including dementia. But appropriate neuronal function also requires physiological NMDA-receptor activation [12]. Synaptic NMDAR activation can start plasticity and promote cell survival. Activation of extra-synaptic NMDARs, on the other hand, encourages cell death and hence conduce to the pathogenesis of AD [13].

A medium affinity, non-competitive antagonist of glutamate NMDA receptor, Memantine is a medication endorsed as a therapy for intermediate to sever Alzheimer's illness (AD) [2]. It can both permit typical glutamate receptor activity and inhibit the excessive activation of glutamate receptors associated for AD-related neurotoxicity. Through effective NMDA-glutamate receptor subtype blocking, Alzheimer's disease-related neurotoxicity can be slowed down. When the receptor-associated ionic channel is over-opened, memantine has the capacity to enter it preferentially because of its function as a non-competitive, low-affinity blocker that does not obstruct regular synaptic transmission. As a result, it shields the brain from further harm caused by excitotoxicity-induced

neuronal cell death. Magnesium ions block the voltage-gated cation channel known as the NMDA receptor when it is not being activated. Magnesium ions that have been stimulated are displaced, allowing calcium ions to enter and activate. The AD receptor becomes persistently activated due to overstimulation. Memantine aids in reducing this excessive stimulation, it can be used to serve AD either alone or in conjunction with acetylcholinesterase inhibitors since it is well tolerated, safe, and has a low affinity for excitatory receptors, which allows it to block them without impairing normal synaptic transmission [2].

3. Natural medicines

Along with the clear association between the quantity and intensity of $A\beta$ aggregates and the severity of AD, numerous other neurodegenerative processes, including neuroinflammation, oxidative stress, hereditary, and environmental variables, also have significant pathogenic factors. As a result, it is crucial to find efficient therapeutics that address the numerous pathogenic pathways linked to AD, but the available medications can only be used to manage the disease's early-stage symptoms [14].

Natural substances have long been used as medicinal agent molecules. Various natural substances are said to be useful in prevention and treatment of neurological illnesses, AD being one of which [15]. As a result, numerous natural substances are currently now in clinical trials [2].

3.1. Vitamin

Due to their defense against inflammatory processes and oxidative stress - induced, Vitamins C, E, and D are of particular importance when it comes to using vitamins as chemotherapeutic drugs for AD [15].

Using AD mice in vivo experiments have demonstrated that vitamin C, which is primarily obtained from vegetables and fruits, is helpful in lowering $A\beta$ production and tau phosphorylation, alleviating behavioral decline, and improving learning and memory. Due to its antioxidant activity, vitamin C is effective in preventing oxidative damage and neuroinflammation in the brain. In addition, vitamin E has shown powerful in vivo antioxidant and anti-inflammatory effects and can be effective in reducing $A\beta$ levels [15].

Vitamin D is an anti-inflammatory compound that is mainly derived from food and from the action of light on the skin. It can reduce the generation of $A\beta$ and amyloid plaques and increase $A\beta$ breakdown by inhibiting the activity of beta and gamma secretase enzymes. Studies have revealed that vitamin D treatment dramatically improved AD mice 's learning and memory functions. Also, findings in clinical trials further illustrate that vitamin D elevated plasma $A\beta$ in patient with slight cognitive impairment $A\beta$ Level, which contrasted with decline in $A\beta$ elevation in the brain. Thus, supplementing with vitamin D has been shown to be helpful in patients with AD-related early cognitive impairment [15].

3.2. Traditional Chinese medicines

Over 2,000 years of usage of traditional Chinese medicine (TCM) in the Chinese medical system have resulted in the identification of numerous potent pharmacological substances from herbal remedies [1]. According to TCM theory, dementia has numerous causes in addition to being caused by one organ, making it a complex condition. Although dementia's pathological location is in the brain, TCM claims that the disease is strongly linked to functional abnormalities in other organs and may be brought on by an energy deficiency in the kidney, heart, or spleen, as well as blood and/or phlegm stagnation [16]. The fundamental TCM method for AD therapy is "dissolve phlegm in order to open orifices"[17]. This is because in TCM theory, the symptom of "phlegm obstruction of orifices" (PTOO) is regarded to be one of the key causal reasons of AD.

3.2.1. “Di-tan decoction” (DTD)

To "resolve phlegm in order to open the orifices", renowned TCM doctor Dong Su created the traditional TCM formula "Di Tan Decoction" (DTD) in 1449. In the clinical application of TCM, it was utilized to serve AD signals extensively, and it still is. Studies have revealed that mice given DTD had significantly higher values of acetylcholine transferase (ChAT) and acetylcholine (Ach) in their brain tissue., whereas acetylcholinesterase (AChE) levels were decreased, and memory impairment was significantly improved in AD animals under the action of DTD [17].

3.2.2. Ginkgo Biloba

Ginkgo biloba extracts was used broadly applied in Chinese medicine for countless years to serve conditions like circulation issues, dizziness, asthma, weariness et al. The extract EGb761 in ginkgo exhibits antioxidant activity and has positive effects on the muscarinic cholinergic system, cerebral circulation, and nerve cell metabolism. In addition to possessing neuroprotective qualities against Abeta and NO-induced toxicity in vitro, it lowers apoptotic both in vitro and in vivo. In a number of investigations, it was found that Ginkgo biloba extract therapy increased memorization in rats in varies age as well as decreased scopolamine-induced amnesia in mice [1].

3.2.3. Huperzine A

A powerful and specific inhibitor of acetylcholinesterase, Huperzine A (HupA) is an extract of Huperzine, it has been long used in China to cure blood abnormalities, edema, and fever excreta. According to a study, HupA treatment had neuroprotective effects and significantly reduced the loss of density in dendritic spines and synaptic protein values in brains of APP/PS1 transgenic mice. Additionally, it decreased levels of oligomeric beta-amyloid (Abeta) and the load of amyloid plaques in the cortex and hippocampus. In triple transgenic mice, HupA increased learning, memory, and a few emotional indicators without causing any significant negative side effects [1].

4. Promising treatments currently undergoing clinical trails

Galantamine, donepezil, rivastigmine, NMDA antagonists, and memantine are examples of current medications that improve memory and relieve symptoms yet could not halt the evolution of AD. As a result, current treatments for AD remain symptomatic and do not alter the prognosis of the disease. The first-line treatment for AD patients, according to some research, can lessen AD without medical intervention by making adjustments to lifestyle factors including diet and exercise. The use of treatments and combination therapies targeting tau pathology has the potential to be effective in reducing the course of AD pathology. AD treatment's effectualness relies on prophase pharmacological intervention and tracking the patient's health progress, therefore, to treat AD patients and those at risk of contracting the disease, an efficacious medicine must be developed immediately [2]. The following table (Table 1) summarize the currently progressed/in-progress treatments for Alzheimer disease and their phases.

Table 1. Promising treatments currently undergoing clinical trials [14].

Promising Drug treatments	Mechanism	Phases
MK-1942	Replaces A β oligomers that are bonded to synaptic receptors, induce oligomer clearance into CSF, and boosts the synapses quantity and the proteins expression in neurons [18]	I
CT1812	Removal of A β oligomers from synaptic receptors	II
Riluzole	Glutamate modulator agents, reduce glutamate-mediated excitotoxicity [2]	II
BIIB092	Monoclonal antibody that is humanized and targets N-terminal tau	II
Bexarotene	RXR agonist that reduced A β in the brain	II
Semagacestat	γ -secretase inhibitor that reduces secretion by the γ -secretase enzyme complex	III
Carvedilol	Reduce the workload on the heart and help it to beat more regularly	IV

5. Conclusion

Alzheimer's disease (AD), a chronic developmental neurodegenerative disorder which is the main cause of dementia, is associated with a loss of cognitively and daily life independence. This condition, which primarily affects people in their middle years or early old age, is impacted by several risk factors, including such aging, genetics, head trauma, inflammation, as well as environmental factors. In this article, we summarize the drugs currently available and those in development for AD. The current AD treatments are based on a variety of processes, which includes faulty tau metabolism, beta-amyloid, inflammation response, and cholinergic transmission. to treat AD symptoms. Many medications, including MK-1942, CT1812, Riluzole, BILB092, Bexarotene, Semagacestat, Carvedilol, and others, have entered clinical studies with the goal of targeting the A β route to prevent the spread of AD; however, there had not been successful cases in the final clinical phase. A multifaceted mechanism incorporating inherent and environmental factors contribute to the genesis of AD, but natural medicine with anti-antibody, antioxidant, and anti-inflammatory properties is thought to be a novel and promising source of possible anti-AD therapies, it is clear that this field has a lot of untapped potential that deserves additional investigation in the future. It will be critical in the future to develop a medicine that is powerful and specific for AD patients.

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