



Review of Alzheimer's Disease Treatment and Potential Future Therapies

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that leads to decline in cognitive functioning and ultimately loss of social independence. The complete pathology of this disease is not yet understood. However, the mechanisms currently proposed include formation of neurofibrillary tangles, deposition of β -amyloid plaques, and decreased cholinergic neurotransmission. There are no definitive causes of this condition, but age appears to be a risk factor. This article will review current treatments that are used in practice, highlighting the medication class, mechanism of action, and common or serious side effects. Areas of future drug development will also be reviewed. As new information regarding the pathophysiology of AD is uncovered, researchers will continue to develop new potential therapies.



Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder resulting in memory impairment, ultimately leading to changes in thinking and behavior. This neurologic disorder is a form of dementia that causes a long-term decline in cognitive function, leading to decreased ability to perform activities of daily living and loss of social independence.¹ According to the Alzheimer's Association, AD is the most common form of dementia and affects approximately 5.5 million individuals within the United States. It is most commonly seen in those over the age of 65, with approximately 5.3 million Americans with AD being 65 years or older. Since the year 2000, mortality due to AD has increased by 89%.² As the population in the United States continues to age, the number of AD cases is expected to rise, with an expected prevalence of 13.2 million Americans by 2050.³ Currently, there is no single laboratory test that is able to definitively diagnose AD; the diagnosis of AD requires a comprehensive medical assessment. This may include the patient's medical history, mental status testing, physical or neurological examination, and serum tests as well as brain imaging to rule out other causes of dementia.⁴ As a result, this disorder may be difficult to diagnose accurately.

There are no definitive causes of this condition, but there are certain factors that contribute to increased risk. The most significant risk factors for AD are age and family history. Individuals age 65 or older are at an increased risk of developing AD, as well as those with a first-degree relative that has

the disease.² Variations in certain genes may also play a role in development of the disease. The one gene that has currently been found to have the strongest impact is APOE-e4, the e4 isoform of apolipoprotein E. Those inheriting the e4 allele of this gene are at an increased risk of AD and may develop symptoms at a younger age.⁵ Mutations in the genes coding for amyloid precursor protein, presenilin-1 and presenilin-2, have also been implicated in development of autosomal dominant early-onset AD.⁶ Other risk factors include female gender, serious head injury, and lack of stimulating mental activity.² Unfortunately, there is currently no cure for AD and the presently available therapies are unable to reverse the condition. However, there are medications that have some usefulness in delaying the progression of AD and future therapies are currently being investigated to develop agents with greater effectiveness.

There are several key pathologic features of AD. One of these is accumulation of neurofibrillary tangles of the tau protein within neurons in the brain. This protein forms part of the microtubule structure, which is integral to maintaining the shape of the neuron and transporting nutrients from one part of the cell to another. In AD, the tau proteins are hyperphosphorylated and as a result, the microtubules disassemble.⁷ The tau proteins then precipitate and form tangles with each other. Another distinguishing feature of AD is the accumulation of β -amyloid plaques between neurons in the brain. These plaques form from the abnormal processing of amyloid precursor protein, resulting in overproduction of β -amyloid protein.⁷ The accumulation of these neurofibrillary tangles and amyloid plaques leads to the neuronal degeneration that is





characteristic of AD. Decreased levels of the neurotransmitter acetylcholine are also thought to play a role in the progression of Alzheimer's. Acetylcholine is thought to have some effect on learning and formation of new memories, and it has been hypothesized that destruction of cholinergic neurons in the basal forebrain contributes to the manifestation of AD.⁸ Medications that increase the brain levels of acetylcholine have been the primary means of treatment, though their limited effectiveness calls for the need to investigate other pathways.

Symptoms

Symptoms of AD typically start to manifest in the mid-60s, with recent memory being affected first. As the disease progresses, the cognitive impairment becomes more severe and patients will require greater assistance with daily living. AD progresses in several stages. Those with mild AD begin to have some memory impairment but are still largely able to maintain independence. Symptoms in this stage may include misplacing items, taking longer to complete daily tasks, a worsening sense of direction, and repeating questions. In moderate AD, the patient begins to require more frequent supervision and care. In this stage, patients may exhibit increased memory loss, confusion, trouble understanding and/or forming words, difficulty performing routine multi-step tasks, and behavioral changes such as agitation, anxiety, or depression. In severe AD, the patient becomes completely dependent on others for their care. Those in this stage commonly exhibit mutism, long-term memory loss, difficulty swallowing, double incontinence, and are bed-ridden.⁹

Early detection of symptoms is important so that treatment may begin as soon as possible, with a greater chance of slowing the progression of AD to preserve the patient's overall health and quality of life.

Current Pharmacologic Treatments

Since none of the currently available therapies for AD are curative or reverse the disease process. The present goal of treatment is to treat the symptoms and preserve cognitive functioning for as long as possible. The first-line agents for treatment of AD are acetylcholinesterase inhibitors. These drugs inhibit the enzyme acetylcholinesterase, which is responsible for metabolizing acetylcholine. As a result, use of these medications causes an increase in the acetylcholine concentrations and this has been associated with mild improvements in cognitive function, behavior, and activities of daily living in those treated for a period of at least 6 months.¹⁰ The currently available acetylcholinesterase inhibitors include donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne).

Donepezil is a reversible and noncompetitive inhibitor of centrally acting acetylcholinesterase, and is approved for use in mild, moderate, and severe AD. It is available as a tablet and an oral disintegrating tablet (ODT). Rivastigmine is a reversible and noncompetitive inhibitor of both acetylcholinesterase and butyrylcholinesterase, and is approved for mild to moderate AD, as well as dementia related to Parkinson's disease. It is available as a capsule and transdermal patch. Only the patch formulation is indicated for severe AD and may be a preferable option for patients





with difficulty swallowing or those experiencing adverse GI effects from the oral formulation. Galantamine is a reversible and competitive central acetylcholinesterase inhibitor that also has a sensitizing effect on nicotinic cholinergic receptors. It is approved for mild to moderate AD and available as a tablet, extended release capsule, and oral solution. All the agents in this class show similar efficacy, and choice is generally based on patient preference and tolerability. The most common side effects of the acetylcholinesterase inhibitors are GI related. These include nausea, vomiting, diarrhea, and decreased appetite. However, these adverse effects are typically mild and the medications are generally well tolerated.¹¹

Another agent that is approved for AD is memantine (Namenda). Memantine is an NMDA receptor antagonist indicated for moderate to severe Alzheimer's. In AD, there is thought to be an overexposure of NMDA receptors to the excitatory neurotransmitter glutamate. Overstimulation of these receptors leads to excitotoxicity and contributes to neuronal cell death.¹² By blocking NMDA receptors, memantine reduces the amount of glutamate that can bind to these receptors. A Cochrane review found that treatment with memantine for a 6 month period showed a slight improvement in cognition and ability to perform activities of daily living for those with moderate to severe AD.¹⁰ It is available as a tablet, extended release capsule, and oral solution. Memantine may be administered as monotherapy or combined with an acetylcholinesterase inhibitor for a potentially synergistic effect. Side effects of this drug may include headache, dizziness, confusion, hypertension, constipation, and diarrhea.¹²

There is also a combination of extended release memantine with donepezil (Namzaric) that was approved in 2014 for moderate to severe AD. In an observational study involving 382 AD patients with mean follow-up of 30 months and mean treatment duration of 22.5 months, those receiving this combination showed significantly lower rates of deterioration on measures of cognition and function compared with those on acetylcholinesterase inhibitor monotherapy.¹³ Another observational study involving 943 patients with a mean follow-up time of 62.3 months showed that those patients on the combination of memantine and donepezil were significantly less likely to be admitted to a nursing home compared with those on acetylcholinesterase inhibitor monotherapy.¹³

Future Pharmacologic Therapies

Due to the significant prevalence of AD and the minimal effectiveness of current therapies, many clinical trials are assessing new treatment options for the disease. One class of medications that is currently being developed are inhibitors of the beta-site amyloid precursor protein cleaving enzyme (BACE inhibitors). These compounds inhibit the enzyme β -secretase, which is responsible for producing the β -amyloid protein that is responsible for the plaque formation in AD. Results of phase I trials showed these drugs were able to demonstrate 45-95% reductions in β -amyloid protein within the cerebrospinal fluid. However, it is still unclear what degree of reduction is necessary to see clinical benefit, and at what point in the AD process these drugs should be initiated.¹⁴ There are currently 10 phase II or III clinical trials





being conducted involving these molecules.¹⁴ One phase III trial compares lanabecestat 20mg and 50mg versus placebo in patients with early AD. The primary outcome is change from baseline score on the 13-item AD Assessment Scale-Cognitive Subscale (ADAS-Cog13) at week 104. The trial is expected to be completed in September 2019.¹⁵ Another similar phase III clinical trial is being conducted with elenbecestat, which is another BACE inhibitor with the same mechanism as lanabecestat. This trial is expected to be completed in December 2020.¹⁶

Another class of agents being evaluated are monoclonal antibodies (mAbs). There are currently 16 such antibodies being investigated in 31 clinical trials. These agents target either the tau protein or various forms of β -amyloid, leading to increased clearance of these proteins.¹⁴ Solanezumab is an antibody that targets soluble β -amyloid. In a previous phase III efficacy trial involving 2100 patients with mild AD, this drug failed to separate from placebo. Aducanumab targets multiple forms of β -amyloid aggregates and has shown promising results in phase I/II trials.¹⁴ A previous study in patients with prodromal and mild AD found that one year of monthly IV infusions of aducanumab reduced brain levels of β -amyloid in a dose and time-dependent manner. This was also reflected in a slowing of clinical decline as measured by Clinical Dementia Rating-Sum of Boxes (CDR-SB) and Mini Mental State Examination (MMSE) scores.¹⁷

Solanezumab is now being assessed in a phase III trial for the prevention of AD in older subjects with confirmed brain amyloid deposits. The planned treatment duration is

240 weeks and the primary outcome is change from baseline of the ADCS Preclinical Alzheimer Cognitive Composite (ADCS-PACC). The study is expected to be completed by July 2022.¹⁸

Aducanumab is now continuing in several phase III trials, both expected to conclude in 2022. Both trials have an expected treatment duration of 78 weeks, with primary outcome of change from baseline in CDR-SB score.^{19,20}

Crenezumab is an IgG₄ antibody that targets both soluble oligomeric and fibrillary β -amyloid. The phase III CREAD study has begun enrolling patients with prodromal to mild AD. The study is expected to conclude in July 2021, and the primary outcome is change from baseline to week 105 in CDR-SB score.²¹

Gantenerumab, an antibody targeting β -amyloid aggregates, is currently being studied in several phase III clinical trials in patients with mild AD. One such trial has a planned treatment duration of 104 weeks, with several primary outcomes. These outcomes include mean change from baseline in ADAS-Cog13 and Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scores. The study is expected to conclude in July 2020.¹⁸

BAN2401 is an antibody that binds to the amino terminus of large soluble β -amyloid aggregates.¹⁴ It is currently in a phase II trial involving subjects with early AD, and is expected to be completed in November 2018. The primary outcome measure is change from baseline in the Alzheimer's Disease Composite Score (ADCOMS) at 12 months.²²

ABBV-8E12 is a tau targeting antibody. It is currently in a phase II trial of





patients with early AD, with anticipated completion in June 2021. The primary outcome is change from baseline to week 96 in CDR-SB score.²³

RO7105705 is another antibody targeting the tau protein. It has completed a phase I trial in mild to moderate AD and is now undergoing a phase II trial in prodromal to mild disease. This phase II trial is expected to be completed in September 2020 and the primary outcome is change from baseline to week 72 in CDR-SB score.^{24,25}

There are also clinical trials in AD focusing on insulin therapy and drugs that affect insulin release.²⁶ Proteins involved in insulin signaling have been found in neurons of many brain regions that are affected in AD, such as the temporal lobes and hippocampus. In addition, autopsy examination of brain tissue from AD patients showed impaired neuronal insulin signaling.²⁶ Insulin-related therapies that are currently being studied include intranasal insulin, liraglutide, and pioglitazone.¹⁴

Intranasal humulin insulin is being evaluated in a phase II/III trial involving 240 patients with mild cognitive impairment or mild AD. There is a 12 month treatment period, and the study is expected to conclude at the end of 2018.²⁷ Intranasal insulin glulisine is being investigated in a phase II trial also involving patients with mild cognitive impairment or AD. The treatment duration is 6 months, and completion is targeted for September 2018.²⁸ Intranasal insulin aspart is undergoing a phase I trial in patients with mild cognitive impairment or AD. This trial has a 3 month treatment duration and expected study conclusion in July 2018.²⁹

Liraglutide is a glucagon-like peptide-1 (GLP-1) analog that binds to GLP-1 receptors on pancreatic β cells to stimulate insulin secretion. It is being studied in a phase II trial in patients with mild AD for a 12 month treatment period, with expected study conclusion in March 2019.³⁰

Pioglitazone is a peroxisome proliferator-activated receptor-gamma (PPAR- γ) agonist, which contributes to increased insulin sensitivity via modulating transcription and translation of various genes. Pioglitazone is also thought to decrease the expression of β -secretase, thus reducing synthesis of β -amyloid. A phase III trial of pioglitazone is currently being conducted in patients with mild cognitive impairment due to AD. The treatment duration is 24 months, and the expected completion date is April 2021.³¹

In addition to the agents discussed above, there are compounds with other mechanisms that are being assessed as well. Some of these include histamine-3 (H3) receptor antagonists, which target histamine heteroreceptors on cholinergic neurons to increase acetylcholine release.¹⁸ Serotonin-6 (5-HT₆) receptor antagonists, which are thought to enhance cholinergic neurotransmission, are also being studied. Active vaccines are being investigated to allow formation of an antibody that can help clear the β -amyloid and tau protein from the body. Anti-inflammatory agents, such as the microglial activation inhibitors, are being investigated to reduce the neuronal inflammation thought to contribute to AD progression.¹⁸





Conclusion

Alzheimer's is a multi-faceted disease that continues to increase in prevalence, mortality, and healthcare costs. Unfortunately, the current therapeutic options have shown only modest benefit and there is currently no method to reverse the progression of this disease. With the urgent need for more effective therapies, there are a variety of new compounds being investigated. As the results of more clinical trials become available, it should become clear as to whether any of these new agents are able to make a significant impact and what role they might play in the management of AD. With the number of targets being evaluated in the treatment of AD, the hope is that continued research will identify a treatment that will provide clinically meaningful advances in the management of Alzheimer's Disease.



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