

# Alzheimer's Disease: The Review from Pathophysiology to Future Direction

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## Abstract

According to estimates from 2021, dementia, which affects 52 million people worldwide, is primarily caused by Alzheimer's disease (AD). Over 65 million individuals in India are 65 years of age or older and dementia is more common as people age. Moreover, the neurotransmitter acetylcholine deficiency and oxidative stress brought on by the aggravation of glutamatergic transmission are linked to AD. This number of new cases is over 30% higher than the incidence reported in the WHO. Even after over a century of research, the pathophysiology of Alzheimer's disease remains a mystery, and there is no treatment that causes natural recovery. Beta fragments and neurofibrillary tangles as previously established are crucial markers for Alzheimer's disease. These deposits arise as a result of native proteins folding incorrectly Alzheimer's disease is linked to inflammatory processes. Tacrine, donepezil, memantine and thiazolidines drugs are used in the treatment of this disease to control the symptoms.

## Keywords

Alzheimer's disease, Pathophysiology, Therapy.

## INTRODUCTION

The primary cause of dementia is AD, which has as its clinical hallmarks the emergence of episodic memory issues and a gradual, all-encompassing deterioration in cognitive function. According to estimates in 2013, approximately 44 million people worldwide suffer from dementia [1]. By 2050, it is expected to increase significantly to approximately 136 million [2] [3]. This is an important factor in AD. For example, when the glucose level is low, the glucose level in the brain will rise. Consumption occurs decades before the onset of cognitive dysfunction and is a constant symptom of AD [4]. The removal of neuronal energy is assumed to be the root of A-42's well-documented neurotoxicity, which starts off a series of pathogenic processes. Reactive oxygen species are released more frequently as a result of the interaction between A-42 and mitochondrial enzymes. With the build up of damaging molecules, this reactive oxygen species impact glycolysis, TCA cycle and the function of the mitochondrial respiratory chain [5] [6] [7]. AD symptoms include cognitive, language impairment, confusion, behavioural issues like paranoia and delusions, as well as psychosocial issues [8] [9] [10].

Moreover, a lack of the neurotransmitter acetylcholine (Ach) and oxidative stress brought on by an increase in glutamatergic transmission are linked to AD. According to the 2011 census, 5.5% of the country's population, or 65 million people, are 65 years of age or older. There are 2.7% dementia cases in India, according to reports. The likelihood of developing dementia rises with age. For instance, dementia affects roughly 20% of individuals over the age of 80.

## EPIDEMIOLOGY

Dementia affects roughly 46.8 million individuals globally, according to estimates from 2020. This number of new cases is over 33% (10.2 million) higher than the incidence reported in the World Health Organization (WHO) report from 2020. Asia (47%), Europe (27%), and America (26%) had the greatest incidence rates [11] [12].

According to projections, the population would increase by 74.7 million by 2030 and 136 million by 2050. According to the World Alzheimer Report 2020 East Asia and Africa had the highest number of dementia sufferers followed by Western Europe with 9.5 million [11].

The AD increasingly gets worse with age, according to the Diagnostic and Statistical Manual of Mental Disorders [13]. As a result, getting older is seen as a risk factor. [14]. This means that the prevalence rate doubles every five years. According to the World Alzheimer Report the largest incidence of Alzheimer's disease occurs in Europe and the Americas between the ages of 80 and 89. In Asia between the ages of 75 and 84, and in Africa between the ages of 65 and 74. Each year, the prevalence of Alzheimer's disease rises among military veterans who have had traumatic brain injury, post-traumatic injuries related to military service in the United States [15]. The growing number of ill war veterans tends to increase hospital costs since they require more medical attention and prolonged hospitalisation. [16]. People who have had a moderate to severe TBI are two to four times more likely to get Alzheimer's disease later in life [17]. There was apparently a link between dementia development in boxers [18]. Other sports with a lot of contact and strength, such American football and hockey, cause TBI in athletes (approximately 1.6 to 3.8 million in the US per year) [19] [20] [21].

According to the 2012 census, the elderly population in the country has increased significantly. The ageing index, which is the number of adults over 60 for every 100 people under the age of 15, is one indicator in this regard. In Brazil, the percentage is around 51.8 percent, which means that for every two people under the age of 15, one person aged 60 or older exists. When Brazil's statistical bases from the 2000s were compared to data from other locations the results showed that the country had a prevalence of 1.4 million cases and an annual incidence of 150,000 new cases [22] [23]. Nonetheless, there is a need to enhance data search and registration because Alzheimer's disease may go untreated or underdiagnosed [24] [25].

### **PATHOPHYSIOLOGY**

Even after over a century of research the pathophysiology of Alzheimer's disease remains a mystery and there is no treatment that causes natural recovery. Nonetheless, macroscopic and microscopic markers are known to be associated with it and may aid in its characterisation, knowledge of illness pathophysiology and development of potential therapies [26] [27]. At the macroscopic level, there is hippocampal and cerebral cortex atrophy which is more pronounced in AD due to age [28] [29]. The production of amyloid plaques also known as senile plaques, which are amorphous Aβ structures as well as the build up of hyperphosphorylated Tau protein which indicates the creation of neurofibrillary tangles and widespread neuronal death, may be seen under a microscope [26] [27] [30] [31] [32] [33]. Recent studies have uncovered additional mechanisms including genetic imprint variables like family history and mechanisms involving apolipoprotein the mechanism of oxidation processes leading to the neurodegenerative process [34] [35] [36].

Clinical signs and symptoms are used to make a diagnosis of dementia. Procedures used to diagnose dementia may involve neuropsychological testing, laboratory tests, brain scanning, and genetic testing after a medical history and physical examination, including a neurologic and psychiatric assessment. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are techniques for identifying changes in brain physiology and function [37]. The use of computed tomography (CT) and structural and functional magnetic resonance imaging (MRI) is also occasionally possible. Family medicine doctors but more frequently neurologists, geriatric psychiatrists and geriatricians are educated to diagnose dementia in the US and Canada. A clinical diagnosis is necessary to ascertain the prognosis, clinical management, genetic repercussions for family members and enrolment in clinical trials [38].

The early diagnosis of the risk of acquiring AD disorders before the dementia stage depends on the biomarkers. These indicators can now be used clinically and as a reference for other alternative biomarkers found in bodily fluids of humans. The National Institute on Ageing and Alzheimer's Association's 2018 research framework, which updates

earlier protocols for AD diagnostic guidelines to focus on biomarkers rather than initial symptom evaluation, provides the foundation for the recently used biomarkers for AD diagnosis [39].

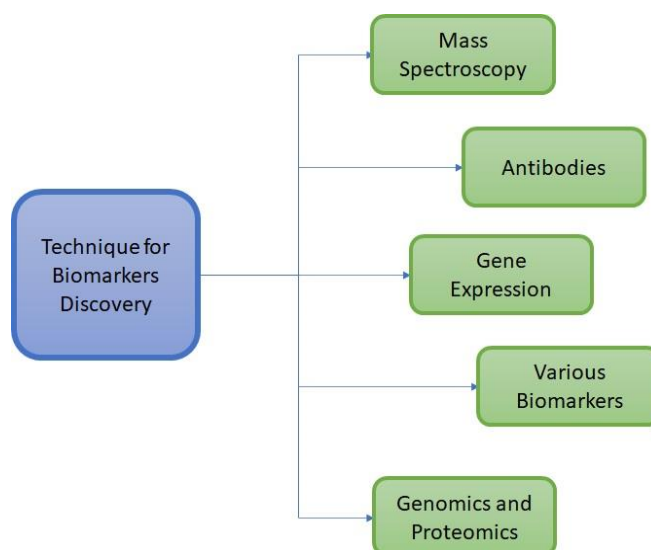
Researchers from around the world have universally agreed on the following criteria for a potential powerful biomarker for Alzheimer's disease reflect the brain's ageing.

- Describe the pathophysiological functions of the brain.
- Extremely perceptive and precise.
- Reproducible outcomes as time passes.
- Clearly defined cutoff values with at least a twofold change.
- Cheap tests and easily collectable findings.

Beta-Tau protein amyloid Phosphorylated tau indicators provide results that are >95% sensitive and >85% specific which together strengthen the validity for diagnosis [40].

### **Bioinformatics Tools for Biomarker Discovery**

Incorporating systems biology into the process of finding biomarkers has led to the development of a number of online databases and 'omics' tools based on various data mining techniques including Decision Trees, Clustering, Regression, Association Rules, Artificial Intelligence, Neural Networks, Genetic Algorithm, Nearest Neighbour method, Classification, and other pattern-based searches [41] [42] [43]. Figure 1 shows several tools for biomarker discovery.



**Figure 1.** Various tools for Biomarker Discovery

### **Genetic Mechanism**

Rare mutations in the APP gene, which causes the well-known AD [36], and allele 4 of apolipoprotein E, which has been established in recent research to be the strongest genetic risk factor associated to the development process of AD. There is no dominant hereditary aetiology for the vast majority of AD cases which means that they are sporadic.

About one in five individuals are human ApoE carriers. These people account for about 65 percent of cases of the problem which is revealed when it is discovered that ApoE

promotes the development of Alzheimer's disease [34] and that ApoE carriers have a threefold greater chance of getting Alzheimer's. The processes that link the existence of ApoE to Alzheimer's disease are yet unknown, although it's thought that there's a decrease in Abeta clearance in the brain in such circumstances [35] [43].

Studies reveal a high association between the presence of preselinin alleles (PSEN 1 and PSEN 2) in AD patients and persons who are predisposed to being carriers of AD or other connected illnesses, in addition to the ApoE-related mechanism [44].

Although the PSEN 1 and PSEN 2 genes are not frequently found in Alzheimer's patients, their association with ApoE is a significant determinant when the illness is inherited [44] [45] [46] [47]. The mechanism of preselinin's link with APP cleavage control has yet to be fully explored [48].

### **Inflammatory Mechanism and Mitochondrial Dysfunction**

Inflammatory processes are connected to Alzheimer's disease. Moreover, numerous studies have discovered that acute and ongoing inflammatory processes significantly worsen Tau abnormalities [49]. Pro-inflammatory cytokines, microglial activation prior to the development of neurofibrillary tangles and microglial clusters around the densest areas of Abeta plaques all play a role in mediating these inflammatory processes [50]. Benevento was able to more clearly deduce that Abeta peptides can directly harm neuronal mitochondria as a result of his research on the existence of these peptides [51] [52].

### **Oxidative Stress**

Because it is present as both a cause and a result of general inflammatory processes which are common in neurodegenerative illnesses studies show that oxidative stress caused by Abeta is significant in the onset and progression of AD [53] [54] [55] [56]. The mitochondrial oxidative phosphorylation which can lead to the creation of highly reactive oxygen species provides the brain's high energy needs. Overproduction of these species leads to oxidative stress [57] [58]. This mechanism, however is reliant on Abeta fragments which, when aggregating promote the reduction of iron and copper in the brain both of which are critical for inducing oxidative stress which in this situation leads to DNA damage [59].

### **Cholinergic Hypothesis**

The cholinergic hypothesis which was the initial explanation connected to AD pathogenesis is one of the most investigated mechanisms related to the development and evolution of AD [60]. In general AD carriers' brains show shrinkage, synaptic loss and a lack of central neurotransmission in addition to the previously mentioned histological indicators [61] [62] [63]. According to the cholinergic theory Bartus and Emerich point out that abnormal or compromised cholinergic system functioning is capable of producing a memory loss in animal models that is

analogous to AD. This theory contends that the death of cholinergic neurons in the basal forebrain and the loss of central cholinergic transmission cause both cognitive and non-cognitive symptoms in Alzheimer's patients [64] [65] [66]. Other aspects of the cholinergic hypothesis include the death of cholinergic neurons in the Meynert basal nucleus and a significant drop in the amount of acetyltransferase the enzyme that creates acetylcholine [67] [68] [69] [70] [71].

## **PHARMACOLOGICAL TREATMENT**

### **Acetylcholinesterase Inhibitors**

To date cholinesterase inhibitors are the only medications that have proved to improve the cognitive process of Alzheimer's patients by enhancing cholinergic function in neuronal synapses hence reducing symptoms. These drugs function by preventing the cholinesterase enzymes from breaking down the neurotransmitter acetylcholine (ACh) in synapses following the transmission of a nerve impulse. The availability of these neurotransmitters in the synaptic cleft is increased by cholinesterase inhibitors which lowers Alzheimer's disease symptoms.

Many investigations have been undertaken in this field in order to find novel medications that operate on this pathogenic pathway. To date regulatory bodies have only approved tacrine, galantamine, rivastigmine, and donepezil as treatments for Alzheimer's disease [72]. The first medication recognised for the treatment of Alzheimer's disease was tacrine. It is a reversible, non-competitive, non-selective acetylcholinesterase (AChE) inhibitor with dose-dependent effectiveness a brief half-life and a high risk of liver damage. Before receiving a licence to treat Alzheimer's disease in 1996 the Japanese pharmaceutical industry developed, produced, and studied the drug donepezil which belongs to the Nbenzylpiperidine family. It is a noncompetitive, highly selective reversible AChE inhibitor that lessens Alzheimer's disease symptoms without having adverse side effects. However by utilising the cytochrome P450 system in its metabolism pharmacological interactions with other medicines can occur necessitating caution while using them together.

Rivastigmine is a pseudo-selective irreversible inhibitor developed from physostigmine. This medicine has good activity and tolerance in individuals with Alzheimer's disease and its metabolism does not involve the cytochrome P450 system lowering the risk of drug-drug interactions, increasing cognition and producing neuroprotective effects.

Galantamine is a tertiary alkaloid isolated from different Amaryllidaceae species that was discovered inadvertently in 1950. It is a selective, competitive and reversible inhibitor of AChE with nicotinic receptor modulation and mild hepatotoxicity. However because its metabolism is based on the cytochrome P450 pathway it must be used with caution when combined with other medicines. This medicine was just licenced for the treatment of Alzheimer's disease in 2001, but it had previously been used to treat a variety of neurological illnesses [73].

### NMDA Antagonist

Memantine is a noncompetitive NMDA receptor antagonist that is used to treat mild to severe stages of Alzheimer's disease. It has a half-life of less than 60 hours. Memantine prevents Abeta peptide-induced toxicity and inhibits excessive glutamatergic neurotransmission. It may also reduce Tau protein hyperphosphorylation. Kornhuber et al. found the receptor's blocking property when the MK-801 chemical was used as a selective NMDA receptor inhibitor. Memantine in vivo suppresses mitochondrial function lowers both cerebral blood flow and the harmful consequences of neuroinflammation and inhibits the synthesis of Abeta peptide as discovered by Parsons et al. in the 1990s. When compared to a placebo meta-analysis studies show that the medication reduces neuropsychiatric symptoms of Alzheimer's disease. Memantine does not significantly reduce agitation symptoms in those with moderate to severe Alzheimer's disease, according to research by Fox et al. [74].

### Glycogen Synthase Kinase Inhibitors

A serine/threonine kinase protein called glycogen synthase kinase-3 governs glycogen metabolism the cell cycle and proliferation and phosphorylates and inactivates glycogen synthase. There are two isoforms of GSK-3. GSK-3 activation produces hyperphosphorylation of Tau protein, which causes microtubule depolymerization resulting in the creation of neurofibrillary tangles and destabilisation of neuronal processes. Microtubules are cytoskeletal elements that help preserve the structure of neurons and promote the growth of axons and dendrites [75]. Thiazolidinones (TZD) were the first ATP-noncompetitive inhibitors with the potential to develop medications for Alzheimer's disease treatment.

### Stem Cell Therapy for Alzheimer's disease

One of the cutting-edge therapeutic modalities being investigated for the treatment of Alzheimer's is stem cell therapy. The proteins amyloid beta and tau which are affected by plaques and tangles in an Alzheimer's patient's brain. Neutrophin production is lower than in a normal brain because of the damage to the brain tissues. In order to regenerate new healthy brain cells stem cell therapies aim to replace the damaged cells with healthy stem cells that can proliferate on their own. Since the transplant is typically autologous there are fewer odds of immunological or tissue rejection.

Different types of stem cells are employed by scientists for these purposes:

- Mesenchymal stem cells (MSCs) and neural stem cells (NSCs)
- ESCs (embryonic stem cells)
- iPSCs (induced pluripotent stem cells) [76]

A type of stem cell known as mesenchymal stem cells (MSCs) has the capacity to differentiate into a variety of cell types including bone, cartilage and fat cells. They can be identified and grown in the lab for therapeutic purposes. They

are present in a variety of bodily tissues including bone marrow, adipose tissue and umbilical cord tissue.

### Benefits of stem cell therapy for Alzheimer's disease

There are various possible advantages of using mesenchymal stem cell (MSC) therapy for Alzheimer's disease, including:

1. Reduction of inflammation: MSCs have the ability to release chemicals that are anti-inflammatory which can help lessen neuroinflammation. Reducing inflammation can aid in slowing the progression of the disease because chronic inflammation is linked to the onset and development of Alzheimer's disease.
2. Stimulation of tissue repair: MSCs can differentiate into several cell types including neuron-like cells which can assist in the replacement of damaged or missing nerve cells in the brain. Potentially this procedure can aid in the recovery of cognitive function in those suffering from Alzheimer's disease.
3. Lessening the formation of amyloid plaque: Research has revealed that MSCs can lessen the deposition of amyloid beta protein which is a defining feature of Alzheimer's disease. This may decrease the disease's course and enhance mental capacity.
4. Minimal danger of immune rejection: MSCs have a low immunogenicity which makes it less probable that the immune system of the receiver will reject them. As a result MSC therapy may be a secure and effective choice for treating Alzheimer's disease.[77]

The researchers claim that by doing this they may be able to create a useful treatment model and testing environment for figuring out the best pharmacological regimen for AD patients while also examining the biology of the illness which would be advantageous for both patients and researchers. [78]

**Table 1.** Lists clinical trials of stem cell therapy for the treatment of AD [79]

Trial number	Cell source	Sponsor	Study phase	Route of administration	Criteria for Eligibility of Trial	Out come	Reference
<a href="#">NCT03172117</a>	h UBC-MSC	Medipost Co.Ltd.	Phase 1&2	Intraventricular	Diagnosis of probable Alzheimer type according to NINCDS-ADRDA criteria	Change from the baseline in ADAS-Cog	79
<a href="#">NCT01617577</a>	Filgrastim (G-CSF)	University of South Florida	Phase 1&2	Subcutaneous	People with probable AD (by NINCDS-ADRDA criteria	Cognitive measures including ADAS-Cog, selected CANTABS tests	79

### FUTURE DIRECTION

Since Alzheimer's was discovered, significant progress has been made in the diagnosis and treatment of the disease. Given the lengthy drug development process for Alzheimer's disease, critical elements have been ignored. However, when evaluating epidemiological statistics, variables such as population drift must be taken into account, as this will

change the status of malnutrition, obesity, and cardiovascular illnesses [80]. There is a need for more clinical indicators. Detect cognitive decline and behavioural changes blood proteins and other aspects. In addition, when treating an AD patient, the practitioner should consider the length of the condition for a more individualised treatment. Treatment in Alzheimer's disease using nutrition patients will surely be beneficial due to the minimal danger of infection. As additional antioxidants with specialised functions are discovered in botanicals and other natural foods, researchers are learning more about their roles in disease prevention and management [81]. A greater level of awareness is required. Spread information about the harmful by-products created as a result of cooking practises that are unhealthy. Because biomarkers are so crucial in diagnosis, their specificity for the treatment and prevention of various phases of Alzheimer's disease, as well as the distinction between sporadic and familial AD, would be extremely beneficial [82].

### CONCLUSION

Patients with AD won't be able to carry out even the most basic physical chores and they will be dependent on others for practically all of their daily activities. According to numerous studies, the causal metabolic pathways for AD's neurodegenerative nature include extracellular amyloid plaques, synaptic degeneration, and neuronal death. At any given age, genetics is responsible for around 70% of the risk of AD. Vitamin D deficient diet, whose active form appears to influence nerve growth factor in addition to the genetic and molecular aspects, appears to be another cause of AD. Therefore, in the future aspects stem cell therapy and biomarkers may be cutting-edge approaches to treating and detecting AD at an early stage.

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