

Editorial

Alzheimer's Disease – Research Progress and Achievements

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Introduction

Worldwide 57 million people living with dementia with nearly 10 million new cases diagnosed every year in which 60-70% are thought to have Alzheimer's disease. The most common form of dementia, Alzheimer is a brain disorder characterized by the slow erosion of a person's memory and thinking skills.

Alzheimer disease (AD) is the most prevalent type of dementia, accounting for at least two-thirds of cases in individuals aged 65 and older. AD is a neurodegenerative condition with insidious onset and progressive impairment of behavioral and cognitive functions. These functions include memory, comprehension, language, attention, reasoning, and judgment.

Scientists discover a major brain shift between ages 50 and 75, when many of the brain's original immune cells declined and were replaced by cells with more inflammatory characteristics. Researchers also found weakening of cells that help maintain the blood-brain barrier, along with widespread deterioration in the genome's three-dimensional organization.

According to CDC data, AD is ranked as the seventh leading cause of death in the United States in 2022, while COVID-19 ranked fourth. Before the COVID-19 pandemic, AD was the sixth leading cause of death following stroke¹.

The significant progress has been made in developing biomarkers for specific and early diagnosis of AD over the past decade. These biomarkers include neuroimaging markers obtained through amyloid and tau PET scans, cerebrospinal fluid (CSF), and plasma markers, such as amyloid, tau, and phospho-tau levels.² In recent years, there have been significant advancements in the development of medications that aim to moderate the progression of the disease, particularly with the discovery of new disease biomarkers.²

The symptoms of AD can vary depending on the stage of the disease. AD is classified into different stages based on the level of cognitive impairment and disability experienced by individuals. These stages include the preclinical or presymptomatic stage, mild cognitive impairment, and dementia stage. The dementia stage is further divided into mild, moderate, and severe stages. AD Stages from Preclinical to Severe Disease).³

The short-term memory loss is the initial and most common presenting symptom of typical AD. Individuals may have difficulty retaining new information while still recalling long-term memories.

Individuals may experience problem-solving, judgment, executive functioning, and organizational skills impairments following short-term memory loss.

They may struggle with tasks that require multitasking and abstract thinking. In the early stages of the disease, executive functioning impairments can range from subtle to significant. Instrumental activities of daily living such as driving, financial management, cooking, and detailed activity planning are affected relatively early in their dementia.

These early signs of cognitive decline are followed by language disorder and impaired visuospatial skills. Neuropsychiatric symptoms like apathy, social withdrawal, disinhibition, agitation, psychosis, and wandering are also common in the moderate to late stages. Difficulty performing learned motor tasks (dyspraxia), olfactory dysfunction, sleep disturbances, and extrapyramidal motor signs like dystonia, akathisia, and Parkinsonian symptoms occur late in the disease. Primitive reflexes, incontinence, and total dependence on caregivers follow this.⁴

Etiology

Alzheimer disease is characterized by gradual and progressive neurodegeneration caused by neuronal cell death. The neurodegenerative process typically begins in the entorhinal cortex within the hippocampus. Genetic factors have been identified to contribute to both early and late-onset AD.

AD is a multifactorial condition associated with many known risk factors. The most significant factor is age, with advancing age being the primary contributor. The prevalence of AD approximately doubles with every 5 years increase in age starting from age 65.

Cardiovascular diseases (CVD) are recognized as significant risk factors for AD. CVD is increasingly recognized as a modifiable risk factor for AD.⁵

Obesity and diabetes are also important modifiable risk factors for AD.⁶

Traumatic head injury, depression, smoking, family history of dementia is also included in the risk factors of AD.⁷

Epidemiology

The global prevalence of dementia was reported to be 20.3 million in 1990, and it significantly increased to 43.8 million in 2016, representing a remarkable rise of 116%. From 1990 to 2019, the incidence and prevalence of Alzheimer disease and other dementias rose by 147.95% and 160.84%, respectively. Projections indicate that the number of people affected

by dementia is expected to reach 150 million by 2050, representing a 4-fold increase.⁸

The incidence of Alzheimer's disease doubles every 5 years after age 65. Age-specific incidence rates significantly increase from less than 1% yearly before 65 to 6% per year after 85. Prevalence rates increase from 10% after the age of 65 to 40% after 85. Incidence rates of Alzheimer's disease are slightly higher for women, especially after 85.⁹

Pathophysiology

Alzheimer disease is characterized pathologically by an accumulation of abnormal neuritic plaques and neurofibrillary tangles in the brain. These pathological changes are accompanied by a loss of neurons, particularly cholinergic neurons in the basal forebrain and the neocortex.

Two prominent pathophysiological hypotheses have been proposed based on these pathological findings:¹⁰

1. **The Cholinergic Hypothesis** proposes that the reduced levels of acetylcholine (ACh) in the brain, resulting from neuronal loss in the Nucleus Basalis of Meynert, play a significant role in AD development.¹¹
2. **The Amyloid Hypothesis** is currently the most widely accepted pathophysiological mechanism for AD, especially in cases of inherited AD. The amyloid hypothesis suggests that amyloid beta (A β) peptide is derived from amyloid precursor protein (APP) through the actions of β - and γ -secretase enzymes.¹²

Brain Immune Cells Undergo a Major Midlife Shift. Between approximately ages 50 and 75, the researchers found a sharp decline in microglia that originate during embryonic development.

That result challenges a long-standing assumption that microglia established early in development remain in the brain for a person's entire life. The replacement microglia-like cells also showed stronger inflammatory signatures, raising the possibility that they could contribute to chronic inflammation in the aging brain.

"Microglia are critical for maintaining brain homeostasis,"

Alzheimer's damage may begin outside the brain. Immune cells in lymph nodes appear to kick-start inflammation. Destructive immune cells tied to Alzheimer's disease may get their marching orders from cells outside the brain rather than within it.

For years, researchers have gone all in on efforts to remove toxic tangles of proteins like amyloid and tau from the brain as a way of halting Alzheimer's, with limited success. But the immune system also plays an important role in neurodegeneration. What exactly that role is — protector or antagonist — has been unclear.

In 2023, neurologist David Holtzman and colleagues showed that immune system T cells accumulate around tau tangles — implying that they might cause damage. Halting these cells' entry into the brain reduced

inflammation, and also reduced neuronal damage, says Holtzman, of Washington University School of Medicine in St. Louis.

New study shows Alzheimer's disease can be reversed to achieve full neurological recovery—not just prevented or slowed—in animal models

For more than a century, people have considered Alzheimer's disease (AD) an irreversible illness.

In this study, the researchers used two of these mouse models: One carried multiple human mutations in amyloid processing; the other carried a human mutation in the tau protein.

Amyloid and tau pathology are two of the major early events in AD.

After finding that NAD⁺ levels in the brain declined precipitously in both human and mouse AD, the research team tested whether preventing loss of brain NAD⁺ balance before disease onset or restoring brain NAD⁺ balance after significant disease progression could prevent or reverse AD, respectively.

Histopathology

The typical histopathology of AD is characterized by the presence of 3 main elements:¹³

Neuritic Plaques: Neuritic plaques are spherical microscopic lesions featuring a core of extracellular amyloid beta-peptide (A β) surrounded by enlarged axonal endings.

Neurofibrillary Tangles: Neurofibrillary tangles are fibrillary intracytoplasmic structures that form inside neurons and are composed of a protein called tau.

Cortical Neuronal Degeneration: Among these degenerative changes, granulovacuolar degeneration of hippocampal pyramidal neurons is commonly observed.

Evaluation of Alzheimer disease

From a primary care provider standpoint, when evaluating a patient suspected to be suffering from AD, the tasks are essential like review and confirm the medical and family history, review the patient's medication list, perform a bedside cognitive assessment test and blood tests to rule out any reversible causes of dementia.

Routine laboratory tests do not reveal any specific abnormalities in AD. Complete blood count (CBC), complete metabolic panel (CMP), thyroid-stimulating hormone (TSH), and vitamin B12 levels are commonly conducted to exclude other potential causes of cognitive impairment.¹⁴

A brain computed tomography (CT) may reveal findings of cerebral atrophy and a widened third ventricle in individuals with AD.

More recently, volumetric MRI has emerged as a valuable tool for precisely measuring changes in brain volume. In AD, volumetric MRI can reveal shrinkage in the medial temporal lobe, particularly the hippocampus. This hippocampal atrophy is considered a characteristic feature of AD and is associated with memory decline.

Functional brain imaging techniques such as Positron Emission Tomography (PET), functional MRI (fMRI),

and Single-Photon Emission Computed Tomography (SPECT) are becoming increasingly valuable in mapping patterns of dysfunction in smaller brain areas of the medial temporal and parietal lobes.

Neuropsychological testing is the most reliable method for detecting mild cognitive impairment (MCI) in its early stages clinically.

Cerebrospinal fluid (CSF) analysis is a helpful diagnostic tool in the preclinical stage of AD. It serves as a biomarker for AD pathology and can detect changes well before the onset of overt clinical symptoms. However, it does not help determine the severity of AD.

Biomarkers for Alzheimer's disease

In the past year, blood tests for Alzheimer's have improved significantly, notably due to the incorporation of measurements of a specific phosphorylated form of the tau protein known as p-tau217.

The blood test results outperformed the accuracy of brain imaging and were comparable to results using the current standard test — spinal fluid biomarkers. Notably, the p-tau217 assay was highly accurate in identifying tau pathology in individuals with brain amyloid plaques. This suggests that this assay may help screen participants for anti-amyloid immunotherapies.

The ADHD link

What they found was that the ADHD adults had more iron in certain regions of their brain, along with higher levels of neurofilaments in their blood, both of which are markers for dementia and Alzheimer's. While it was a small case study, it nevertheless paves the way for further research to determine if a reduction of iron levels in the brain of a person with ADHD could reduce the likelihood of developing dementias like Alzheimer's down the line.

Treatment / Management of Alzheimer disease

Symptomatic Therapies of AD

Traditionally, there has been no cure for AD, and symptomatic treatment remains the primary approach in everyday clinical practice.¹⁵

Two categories of drugs are approved for treating AD: cholinesterase inhibitors and partial N-methyl D-aspartate (NMDA) antagonists.

Cholinesterase Inhibitors

Cholinesterase inhibitors function by increasing the levels of acetylcholine, a neurotransmitter that plays a role in nerve cell communication and is involved in learning, memory, and cognitive functions. Within this category, 3 drugs have received FDA approval for treating AD: **Donepezil**, **Rivastigmine**, and **Galantamine**.¹⁶

Partial N-Methyl D-Aspartate (NMDA) Memantine

Partial N-Methyl D-aspartate (NMDA) antagonist memantine blocks NMDA receptors, slowing down intracellular calcium accumulation.

Disease Modifying Therapies of AD

In the past, the treatment of AD has primarily focused on managing the symptoms. Now a days, new and

specific disease-modifying therapies are being developed and FDA has recently approved some drugs for example:

- **Aducanemab** received accelerated FDA approval in June 2020. It was shown to reduce amyloid-beta plaque in the brain. However, it missed the primary phase III trial endpoint of clinical improvement.¹⁷
- **Lecanemab** received accelerated FDA approval in January 2023. It reduced the amyloid-beta burden in the brain. The phase III trial showed a 27% slowing of disease progression.¹⁸
- **Donanemab** is expected to receive FDA approval in 2023. It reduced the amyloid-beta burden in the brain and slowed cognitive decline by 35%.¹⁹ About the above-said drugs Alzheimer's Society found that the drugs could slow down disease progress by 60% if given at early stage.

Other Management Strategies in AD

In managing AD, addressing accompanying symptoms such as anxiety, depression, and psychosis is essential, especially in the mid to late stages of the disease.

It is advisable to avoid tricyclic antidepressants because of their anticholinergic activity, which can worsen cognitive impairment. Antipsychotic medications should be used cautiously for acute agitation when other interventions have been exhausted and the patient's or caregiver's safety is at risk. Other medications are generally tried before consideration of antipsychotics. These generally include SSRI antidepressants such as **Citalopram** and **Anticholinesterase** such as **Donepezil**.

The general principle in using antipsychotics is to use the lowest dose that may help the patient's agitation. Benzodiazepines should not be used because they may worsen delirium and agitation in these patients.

Preventing and treating Alzheimer's disease and related dementias

In recent years, there has been significant progress for the treatment of early Alzheimer's, marked by the U.S. Food and Drug Administration's (FDA) approval of the use of specific antibodies against beta-amyloid (termed "anti-A β " or "anti-amyloid immunotherapies") to slow progression of the disease. While NIH did not fund the clinical trials that led to these approvals. Although the FDA approvals of these therapies for the treatment of early Alzheimer's represent a significant scientific milestone, further research is needed to develop additional interventions that are effective for treatment and prevention of disease for all who are at risk.

NIH is investing in a range of potential therapeutics to treat and prevent dementia.

NIH investments to develop new treatments for dementia explore a wide range of therapeutic approaches and support multiple stages of drug development research, from basic science to clinical trials.

For example, NIH has funded nearly a decade of research leading to the development of a small

molecule drug, called **CT1812**, that shows promise for treating multiple types of dementia. NIH-funded basic and preclinical research has shown that **CT1812** may help prevent neurotoxicity associated with dementia by displacing toxic protein aggregates at synapses, the spaces between brain cells that facilitate communication.

NIH also invests the drive research progress in drug development.

- Development status of drug candidates in clinical trials:
 - Phase I trials: 18
 - Phase II trials: 6
 - Phase III trials: 1 (**buntanetap**)

Buntanetap development and testing: A journey of public and private sector collaborative discovery

- Buntanetap (also known as posiphen) is an orally administered drug candidate that inhibits the production of key proteins involved in the pathogenesis of Alzheimer's, Parkinson's disease, and LBD.

Gene therapies

As a potentially innovative way to prevent or treat dementia, NIH is investing in research on gene therapy, an emerging technology that treats or reverses conditions by correcting problems with DNA.

Anti-amyloid immunotherapies

In parallel to trials testing a range of potential therapeutic options, NIH also seeks to better understand how to effectively and safely use the current FDA-approved anti-amyloid immunotherapies, i.e., lecanemab and donanemab. Efforts include studying the effects of these drugs at different stages of disease, in different populations, and in combination with other potential treatments.

New Blood Thinner Benefits for AD

These blood thinners may have an unexpected benefit for Alzheimer's patients. Newer blood thinners may do more than prevent strokes in people with Alzheimer's disease and atrial fibrillation. Researchers found that patients taking NOACs experienced a slower decline in cognitive function than those using warfarin or no blood thinners. The effect was modest each year but could add up over time.

People who have both atrial fibrillation and Alzheimer's disease may experience slower cognitive decline when treated with newer NOAC blood thinners, according to research from Karolinska Institutet published in the European Heart Journal.

Atrial fibrillation is a common heart rhythm condition in older adults and also affects many people living with Alzheimer's disease.

Behavioral, lifestyle, and other interventions

Multiple lines of research find that several forms of non-pharmacological interventions may also offer promise in reducing dementia risk factors and improving cognition and memory. Results from

randomized control trials indicate that interventions with blood pressure control, hearing aids, multivitamins, and personalized health coaching can reduce dementia risk in specific populations, but more research is needed.

NIH researchers are also continuing to build on past scientific discoveries on the link between diet and dementia risk. As one example, NIH-funded investigators found that individuals who consumed a modified Mediterranean ketogenic diet, composed of 5–10% carbohydrate, 60–65% fat, and 30% protein, for six weeks had significant changes in both blood and spinal fluid biomarkers associated with Alzheimer's risk. Specifically, individuals following this diet exhibited improvements in several risk factors, including increases in beneficial (high density lipoprotein, or HDL) cholesterol and reductions in body mass index and systemic inflammation. This study is the first exploration of diet-related metabolic changes in spinal fluid and provides evidence of the effects of diet on modifiable risk factors for Alzheimer's.

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