International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Evolution of Alzheimer Disease: History, Pathology and Epidemiological Trends

Shivaranjani Baskar

Student, Narayana e-techno school, Chennai, India

Abstract
Over the past decade, Alzheimer's has been one of the leading causes of death worldwide. A progressive neurodegenerative disease where you lose 90% of your memory and your capacity to perform daily tasks. Accounting 3 main stages (mild, moderate, severe) and eventually death, marks around the scratch arising from mood swings, depression, and aggression. A fatal, incurable disease that takes the life of women more than men. Alzheimer's initially affects the hippocampus and entorhinal cortex- regions that are responsible for memory formation. As neuron loss progresses, the pathology extends to other brain regions, leading to widespread neurodegeneration and cerebral shrinkage. In the advanced stages of this disease, damage becomes extensive, with marked shrinkage of brain tissue. Studies and research are still in the process of understanding the complex mechanisms in Alzheimer's disease, which is essential for developing effective prevention.

Keywords: Neurodegeneration, pathology, neurocognitive decline, amyloid protein plagues, tau protein, Neurofibrillary tangles, Plaque deposition.

Introduction

The Alzheimer journey begins with the person naming himself Alois Alzheimer and his patient Auguste Deter. No sooner than the 1890's deter started to develop this disease in many directions such as delusions, losing the ability to move, cook and believing Carl (her husband) was accusing her, she was dragging bedsheets outside and screaming for hours at night. She became extremely fearful of her neighbors and strangers, believing that someone was trying to harm or kill her. Over time, her jealousy became intense and irrational with her husband causing her to develop insomnia which became paranoid over her neighbours. On around 25 November 1901, Carl was forced to be taken to the Community Psychiatric Hospital at Frankfurt am Main, where she met Dr. Alois. Despite Carl's financial difficulties and his consideration of transferring her to another care facility, Alzheimer advised against such a move. The institution subsequently agreed to continue providing care at no cost, contingent upon formal consent for access to her medical records and the donation of her brain for postmortem research. Her emotions changed very quickly—she would shift from feeling anxious and suspicious to becoming withdrawn or overly complaining. Rushing out from her isolated room screaming, "I will not be cut. I do not cut myself.". The staff could not allow her to walk freely in the hospital because she would approach other patients inappropriately, which often led to those patients reacting aggressively toward her. When asked simple questions assessing basic orientation and knowledge, her responses were incoherent and unrelated to the questions posed. For example, when asked, *"Where are you right now?"* She replied, *"Here and everywhere, here and now; you must not think badly of me."* Although Alzheimer had seen patients whose mental abilities had completely broken down before, those cases were usually in people in their seventies, not someone so young.

After departing the institution in 1901 to take up a position in Munich, Alzheimer became head of the new institute's lab. On 8 April 1906, Alzheimer received formal notification of the death of Auguste Deter, an event that later enabled further pathological examination and retrospective analysis of her condition. Her brain was examined by Alois, and it was noted that her brain was enormously shrunken in certain areas, which led to Histopathological abnormalities in the brain, subsequently classified as amyloid plaques and neurofibrillary tangles. Further study led Alzheimer to conclude that, although a definitive pathological cause could not be established, senile plaques were closely associated with degeneration of the central nervous system and functioned as indicators of this form of dementia.

His observations refuted the notion that senile dementia was merely an outcome of normal aging, rather than identifying it as a disorder arising from distinct pathological processes. This shift in understanding paved the way for subsequent research and the development of clinical interventions aimed at mitigating the progression of dementia. Later, they re-examined her case using modern medical technologies, through which scientists from Giessen and Sydney identified a genetic cause for her disease, and their studies reported that a mutation in the PSEN1 gene that alters the function of γ-secretase, leading to the early formation of amyloid oligomers and resulting in a rapidly progressive degeneration of neurons.

On 3 November 1906, Alzheimer presented his observations on the pathological changes in the brain and their clinical expression in presenile dementia at the Tübingen meeting of the Southwest German Psychiatrists. Despite the significance of the findings, the presentation attracted little attention from those 88 attendees. As a result, Alzheimer’s talk ended without questions or commentary, and his account of a distinctive case of early-onset dementia passed largely unacknowledged. Disappointed by this response, Alzheimer later chose to formally publish his work, consolidating his research and earlier presentations into a written study. Although his initial presentation of these findings was met with little interest, Alzheimer persisted in studying similar cases. His move to Munich to work with Emil Kraepelin provided an environment that supported research, advanced laboratory facilities, and academic recognition.

Kraepelin ultimately acknowledged the significance of Alzheimer’s observations and introduced the term “Alzheimer’s disease” in 1910. This journey—from careful clinical observation to neuropathological correlation—established the foundation of modern Alzheimer’s disease research, even though its importance was fully recognized only decades later. In 1912, the University of Breslau appointed him as the chair of Psychiatry. His aspirations as a young assistant at the Frankfurt Hospital finally came to light; however, owing to his deteriorating health, he passed away on 19 December 1915.

Historical Examination

Alois Alzheimer’s Scientific Contributions of Auguste Deter’s brain revealed Histopathological abnormalities leading to severe shrinkage in the brain tissue, most prominently in regions essential for memory processing, which include the hippocampus and entorhinal cortex. Alzheimer found two principal pathogenic features in brain tissue: Extracellular Amyloid Plaques and Intracellular Neurofibrillary Tangles. Amyloid plaques, made up of amyloid-β that comes from aberrant APP processing(Amyloid precursor protein)(APP is cleaved by Beta secretase), are an early sign of disease that leads to neuron degeneration and ultimately leads to Alzheimer's.

By using a silver-based staining method developed by Max Bielschowsky, which provided a comprehensive image of these diseased structures, Alzheimer and Fischer made significant progress in their studies of plaques. Braak & Braak give a thorough account of the early evolution of silver staining techniques. Interestingly, in his 1907 publication, Alzheimer argued that the neurodegenerative disease should be understood through its clinical presentation and histological pathology. Alois was two steps ahead in neurology and closely aligned with contemporary efforts by attracting international groups to redefine Alzheimer's disease using biological markers rather than purely syndromic criteria.

Neurofibrillary tangles consist of hyperphosphorylated tau protein, which disrupts microtubules in the neuron and leads to its degeneration. Alzheimer identified the histological alterations, which were later known as Amyloid protein (Abeta) deposits and neurofibrillary tangles (NFTs), which result from excessive tau phosphorylation, which are now referred to as tau tangles. Apathy, sadness, anxiety, sleep difficulties, disinhibition, and wandering are only a few of the many symptoms. As the disease moves from early symptoms to mild cognitive impairment to severe dementia, the conditions and problems become increasingly severe. Neuropsychiatric symptoms are frequently seen as essential components of the illness rather than as aftereffects because they have a significant impact on patient behavior, caregiver stress, and long-term outcomes. All the early symptoms arise during the MCI stage—before the onset of dementia—and worsen progressively over time. In addition to this, the cognitive factors that have traditionally been highlighted in behavioral and psychological symptoms of dementia (BPSD) are also considered.

These symptoms are interconnected and have a common biological basis. BPSD is considered for patients suffering, caregiver burden, and diagnosis.

They cover a wide field of neuropsychiatric disturbances that may arise in emergency, inpatient, or outpatient settings, resulting in functional impairment and a reduced quality of life. Although there is no answer for severe emergencies, supportive, non-pharmacological, and pharmacological interventions can help to bring down symptoms.

However, no single solution has been discovered. Current evidence supports a biopsychosocial structure in which neuropsychiatric symptoms result from interactions between biological vulnerability, past experiences, and childhood trauma. In spite of this, individuals may display impaired judgment, reduced insight, and disinhibition, leading to inappropriate behaviors or poor decision-making. These changes reflect early contributions of the prefrontal cortex and orbitofrontal regions (which mainly deal with decision making), even before hippocampal-dependent memory systems are severely compromised.

Mild shifts in personality, like increasing rigidity, obsessiveness, or withdrawal from social events, can be early signs of neurodegeneration. Memory loss, communication disturbance, and paranoia are the signs of severe cases of dementia, a progressive neurodegenerative syndrome defined by cognitive decline in everyday activities. With the global aging of the population, dementia is expected to increase worldwide, emphasizing the need for a detailed characterization of its cognitive and neuropsychiatric manifestations. Memory impairment is a pivotal feature of dementia and spans a continuum from early episodic impairment to severe loss of autobiographical memory. The identification of rare autosomal dominant genetic mutations in familial Alzheimer's disease represented a significant step in elucidating disease pathogenesis. These discoveries established amyloid-β accumulation as an initiating scratch in neuronal injury, giving rise to the amyloid cascade hypothesis, which has remained a central framework in Alzheimer's disease research for nearly three decades. Importantly, these advances were enabled by the participation of families with inherited Alzheimer's disease in genetic research studies. The most prevalent dementia subtype, hippocampal and medial temporal lobe neurodegeneration, synaptic loss, neurofibrillary pathology, and disrupted calcium homeostasis, leads to impairment in new memory formation. Paranoia is a common neuropsychiatric symptom in dementia, reported in a substantial proportion of affected individuals.

Dementia-related psychosis, encompassing delusions and hallucinations, is strongly associated with negative outcomes, including increased rates of institutionalization, accelerated cognitive decline, and high caregiver burden. Delusional content often reflects interactions between environmental and personal factors and underlying cognitive impairments, particularly memory loss and spatial relationship problems; for example, misplacing objects may give rise to delusions of theft. The frequency and severity of paranoia and other behavioral disturbances increase with disease progression.

When such symptoms emerge in a 51-year-old individual, they are considered strange and warrant urgent clinical examination and consideration, as they deviate from expected age-related trajectories. The prevalence of Alzheimer's pathology rises sharply after 65 years of age; therefore, the appearance of cognitive and behavioral changes in midlife raises concern for alternative conditions that can replicate dementia.

Early-onset Alzheimer's disease (EOAD), defined by symptom onset before age 65, accounts for approximately 5–10% of all Alzheimer's disease cases. Rather late-onset AD, which often presents with non-amnestic features, including language impairment, visuospatial deficits, and personality changes. The presence of neuropsychiatric symptoms and signs in the early 50s may represent an earlier indicator of this slow-growing neurodegenerative disease.

Modern Understanding

The first scratch was from Dr.Alois Alzheimer, as we saw earlier. In 1906, amyloid-β (Aβ) was discovered, and later followed by the identification of tau protein as the core constituent of neurofibrillary tangles in 1985. Genetic insights emerged in 1987 when mutations in the APP gene, which was seen on chromosome 21, were shown to cause familial Alzheimer's disease, explaining the early and extensive plaque pathology observed in individuals with Down syndrome. In 1991, the Braak staging system provided a neuropathological framework correlating the progressive spread of tau tangles—from the entorhinal cortex to the hippocampus and neocortex—with worsening cognitive impairment. The genetic landscape expanded in 1993 with the discovery of the APOE ε4 allele as the strongest risk factor for late-onset Alzheimer's disease. Experimental advances followed in 1995 with the development of transgenic mouse models expressing mutant human APP, enabling in vivo study of amyloid deposition and neurodegeneration, and with the identification of presenilin (PSEN1 and PSEN2) mutations as the most common cause of early-onset familial disease through their role in γ-secretase–mediated Aβ production. Optimism grew in 1999 when immunization against Aβ successfully cleared plaques in mice, the same year that β-secretase (BACE1) was identified, completing the enzymatic pathway responsible for Aβ generation. Diagnostic capabilities advanced in 2004 with the introduction of Pittsburgh compound B for PET imaging, allowing non-invasive detection of amyloid pathology in living patients. Genetic examination in 2013 identified many genes interconnected to AD, showing that it is influenced by many genes. In 2020, a major step was taken in the confirmation of tau protein in blood, making disease monitoring easier. In the early 2020s, anti-amyloid antibody drugs began to be used in patients. One drug, aducanumab, was approved but later stopped because it was controversial. Newer drugs like lecanemab and donanemab worked a little better, but they showed a slight cognitive decline. AD was largely viewed as a consequence of aging. Clinicians commonly classified it as senile dementia, assuming progressive AD was a normal condition of old age. Researchers' interest was minimal because the cause was already found out by Alois Alzheimer, who was not directly connected to the elderly; this segregation later meant that AD was only diagnosed in younger patients, while in older patients, it was just due to age. Later, it was identified that accumulating neuropathological and clinical evidence challenged this view, developing Alzheimer's as age-related but not age-oriented.

By the late 20th century, AD became a major worldwide disease rather than a rare clinical disorder. Studies on epidemiological examination on a large scale revealed that AD significantly emerged in old age-related people, and it represented the majority of the cases in the US and other countries, overturning the fact that cognitive decline was a normal aspect. Similarly, in high-income countries, aging populations have led to a rapid expansion of the elderly demographic and economic impact of the disease. Standardized advancement in neuroimaging and improved awareness contributed to a significant rise in diagnosed cases, making AD one of the most common cases of restriction and dependency among senior citizens, stimulating increased investment in health care facilities, research resources, and insurance planning.

Pathogenesis and Histology

Amyloid beta

As we know, the two main pathological characteristics in Alzheimer's disease are amyloid-β plaques and tau proteins (neurofibrillary tangles). Firstly, the Aβ protein, commonly referred to as amyloid-β, forms plaques that are structurally heterogeneous. In so-called *classical* plaques, cellular elements such as dystrophic neuronal processes and activated glial cells are often observed, although these features are not consistently present in all plaques. Since their initial identification in the late nineteenth century, these deposits have been described using various terms, including senile plaques, amyloid plaques, and neuritic plaques. Over time, the term "Aβ plaques" has been adopted as a unifying label to encompass their diverse morphological features.

The amyloid cascade hypothesis proposes that the accumulation of amyloid-β (Aβ) represents one of the earliest and most critical events in the pathogenesis of Alzheimer's disease. Aβ is generated through the sequential proteolytic processing of the amyloid precursor protein (APP) by two enzymes. First, β-secretase (also known as BACE-1, beta-site APP-cleaving enzyme 1) cleaves APP, producing a soluble fragment (sAPPβ) and a membrane-associated fragment known as C99, which is 99 amino acids in length. This C99 fragment is subsequently cleaved by γ-secretase, leading to the release of Aβ peptides into the extracellular space. With time, these peptides can aggregate, ultimately giving rise to the plaques observed in the brains of individuals with Alzheimer's disease. Although β-secretase is not solely responsible for disease pathology and its inhibition alone does not fully resolve disease progression, under physiological conditions it plays important roles in neuronal development and myelination. The central issue is not random APP cleavage, but rather the preferential processing of APP by inappropriate enzymes or at incorrect sites, resulting in aggregation-prone Aβ species. These species can assemble into oligomers, which are particularly sticky and can further organize into structurally diverse plaques.

Amyloid formation begins with protein misfolding, followed by the self-assembly of misfolded species into filamentous aggregates. Misfolded protein conformations can act as templates, promoting the misfolding of normally folded molecules of the same protein. In addition, β-strands from adjacent protein molecules form extensive hydrogen-bonding interactions, giving rise to stable, elongated polymers in which β-sheets are oriented perpendicular to the fibril axis. Through this templated recruitment and stepwise assembly, misfolded monomers form protofilaments that later associate laterally to produce long, unbranched fibrils, typically measuring approximately 6–13 nm in diameter. Although these fibrils share a common cross-β structural backbone and appear similar under transmission electron microscopy, they exhibit considerable molecular-level polymorphism. Both axonal and dendritic processes contribute to plaque-associated neuritic elements. Several studies indicate that the majority of swollen neurites are axonal in origin; however, definitive determination of the relative axonal versus dendritic contribution requires rigorous quantitative analyses using process-specific markers in human tissue.

Tau proteins (Neurofibrillary tangles)

Neurofibrillary tangles (NFTs) are intracellular aggregates composed of misfolded, hyperphosphorylated tau protein and are widely recognized as a principal pathological hallmark of Alzheimer's disease (AD). Beyond AD, NFTs are also observed in a group of neurodegenerative disorders collectively termed tauopathies, covering a wider pathological relevance of tau dysfunction.

Structurally, NFTs are formed from atypical polymerized tau, a microtubule-associated protein that normally stabilizes neuronal cytoskeletal architecture. In disease states, hyperphosphorylated tau loses its affinity for microtubules and assembles into an insoluble filamentous form. There are two filamentous morphologies, paired helical filaments and straight filaments, both of which can exhibit structural variability across different tauopathies. These filaments aggregate to form NFTs & are localized within the neuronal cell body and later transmit from one neuron to another, thereby disrupting the entire neural network. But pathological tau accumulation is also observed in neuronal processes, including dendrites and axons, where it forms neuropil threads, as well as in dystrophic neurites surrounding neuritic amyloid-β plaques. Levels of total tau and phosphorylated tau serve as valuable biomarkers for the diagnosis and monitoring of neurodegenerative diseases. The phosphorylation state of tau plays a critical role in determining its intracellular localization and functional behavior. Phosphorylated tau has been detected within the neuronal soma of hippocampal neurons as well as in immortalized gonadotropin-releasing hormone (GnRH) neurons, leading to abnormalities in the redistribution of normal axons. The core problem is tau regulation, leading to a toxic gain-of-function. Under disease conditions, tau becomes abnormally hyperphosphorylated, spoiling the balance of neuronal enzymes. This excessive phosphorylation reduces tau's affinity for microtubules, causing microtubule destabilization and impairing axonal transport of essential transporters such as mitochondria and vesicles.

As a result, neurons gradually lose their shape and ability to transport materials inside the cell. At the same time, excessively phosphorylated tau is not broken down properly, folds abnormally, clumps together, and ultimately forms neurofibrillary tangles. These aggregates of tau and other proteins significantly exacerbate cellular breakdown. The improper clearance of tau protein, along with an imbalance in its isoforms and the formation of toxic clumps, transforms tau from a beneficial, soluble protein into a contributor to synaptic failure, neuronal death, and ultimately neurodegeneration.As we know, neurons are degenerative; in AD, there is a substantial loss of neurons with severe shrinkage of the brain, leading to cell death. Like a disease takes another step, neurodegeneration spreads to the association areas of the cerebral cortex that govern language, and social behavior. The disease spreads to the frontal cortex, especially the prefrontal area, and higher thinking abilities are affected. These brain regions control planning, judgment, attention, problem-solving, and self-control, and the degeneration of these regions can cause the opposite of their function. The temporal lobes involved in emotional regulation make personality changes. Thus, presentation is not random but directly related to the progressive involvement of specific brain regions. AD is a slow anatomical spread of pathology that disrupts the system and destroys the entire neural network, which renders individuals incapable of independent living and ultimately leads to death.

The Nun Study

A prolonged period of longitudinal study of the nun in 1986 by Dr. David Snowdon investigated about 678 Catholic nuns from the School Sisters of Notre Dame (USA) around the age of 75-102+. By documenting the sisters' autobiographical records, routine cognitive evaluations, and post-mortem brain analyses, researchers observed that strong linguistic skills, active social involvement, and an optimistic, purpose-oriented way of life can help mitigate the clinical expression of Alzheimer's disease. After the examination of their brains, it was found that they had Severe brain shrinkage & Amyloid plaques with neurofibrillary tangles, the presence of significant widening of sulci and narrowing of gyri in at least two lobes. Surprisingly, they had Normal memory, reasoning, and independent thinking. Evidence of the last stage of AD didn't match up with their minds. A strong reason was provided against this was cognitive reserve, the brain can compensate for damage, where alternate neurons can replace the damaged ones. Although it demonstrated a significant AD pathology, it highlighted the protective role of cognitive reserve built through education and lifelong mental engagement.

Current epidemiology and its Economy

The global dementia population is projected to reach 152 million by the middle of this century, with the most rapid growth expected in low- and middle-income countries. Based on 2020 estimates, the number of individuals affected by Alzheimer's disease (AD) in the United States may rise from 5.8 million to 13.8 million by 2050. Over recent decades, a notable increase in AD prevalence has also been reported in Japan and China.

It has been reported that the age-adjusted global prevalence of AD in women is approximately 1.17 times higher than in men. Mortality associated with AD increased by 146.2% between 2000 and 2018. According to 2023 census data, Alzheimer's disease is currently the sixth leading cause of death in the United States. As caregivers face increasing levels of strain, the family burden associated with caring for individuals with AD has become increasingly unsustainable, highlighting the important role of behavioral and environmental factors in AD pathogenesis. Many risk factors associated with Alzheimer's disease can also manifest as symptoms of the condition itself, indicating a potential reverse causal relationship. This overlap complicates accurate diagnosis, particularly in individuals with cognitive impairment. Although AD is commonly linked to amyloid-β (Aβ) and tau biomarkers, studies have shown that some cognitively healthy individuals with these biomarkers do not progress to Alzheimer's disease. This presents a major challenge, as identifying the disease at a truly pre-symptomatic stage remains difficult. Consequently, there is a clear need to develop diagnostic approaches and biomarkers that are less invasive, more sensitive, and suitable for early screening. At the same time, increasing evidence connecting modifiable risk factors to late-onset AD emphasizes the importance of prevention. Therefore, future research should focus not only on improving early and accurate diagnosis but also on establishing strong, evidence-based preventive strategies to reduce disease risk before irreversible cognitive decline occurs.

Covering over 10 million cases each year, with a new case every 3.2 seconds.

Financial strains of dementia are expected to increase in the upcoming years. In 2015, the global cost of dementia was estimated at approximately US$818 billion, equivalent to 1.09% of the world's gross domestic product. Since then, annual expenditures have risen sharply, now exceeding US$1.3 trillion, and are projected to reach US$2.8 trillion by 2030. These costs reflect a substantial economic burden distributed across multiple domains of care. Informal care and direct social care each account for nearly 40% of total expenditures, while direct medical care contributes about 20%, highlighting that the majority of dementia-related costs arise outside formal healthcare systems. Overall, the global cost for dementia would rank as the 14th largest economy worldwide. Japan ranks first with an estimated Alzheimer's rate of 3,079 cases per 100,000 people, largely due to having the highest proportion of elderly individuals in the world. In developing countries, AD diagnosis seems to be increasing due to the growing population, like North America, Western Europe, and Japan, due to their highest percentage of population. Second comes South Asia, where the fastest growth in cases is seen. China and India are projected to experience a sharp rise in Alzheimer's cases by 2050, driven by rapid population aging and the growing prevalence of mid-life risk factors such as diabetes and high blood pressure.

Genetic mutations and Familial cases

Alzheimer's disease (AD) is predominantly encountered in its late-onset sporadic form; however, it can also be categorized into familial and sporadic cases based on genetic inheritance. The hereditary variants are linked to mutations in three primary genes: the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). In contrast, sporadic AD may stem from a combination of polygenic influences and extrinsic factors, although the precise etiological mechanisms remain elusive.

Recent research has elucidated several molecular aspects of AD, highlighting its genetic complexity. Emerging evidence indicates that epigenetic factors significantly contribute to the pathogenesis of the disease. Notable milestones in AD research have identified promising methodologies aimed at better delineating genetic profiles that correlate with disease risk. The meticulous evaluation of clinical symptoms plays a vital role in early diagnosis, supported by insights from family and friends who may observe changes in the individual's daily activities.

Cognitive assessments are essential for diagnosing AD, complemented by neuroimaging techniques and blood tests to exclude alternative diagnoses and to detect proteins associated with AD pathology. Historically, definitive diagnosis was only feasible post-mortem through the identification of amyloid plaques and neurofibrillary tangles in brain tissue. However, contemporary advancements in medical science enable clinicians to diagnose AD with enhanced accuracy during a patient's lifetime. Biomarkers are crucial in this process, as they can signify the presence of amyloid and tau pathologies. These include specialized positron emission tomography (PET) scans and quantification of amyloid and tau proteins in blood or cerebrospinal fluid (CSF), which encases the brain and spinal cord.

Future directions

Suspected memory problems of a person can be examined by a step-by-step assessment to understand the cause of cognitive decline in order to find the causes that can be treated. This procedure takes a detailed medical history, performing physical and mental examinations, running basic laboratory tests, and obtaining brain imaging studies. Neuropsychological assessments and advanced brain imaging are used to evaluate better memory and thinking abilities. Doctors look for a specific type of neurocognitive disorder, for example, a history of multiple strokes may suggest vascular dementia, while a previous head injury may indicate traumatic encephalopathy. Alcoholics can be linked to alcohol related dementia.

Positron emission tomography (PET) and magnetic resonance imaging (MRI) usage have been explored in finding earlier and more definitive ways to diagnose AD, along with the identification of biomarkers in cerebrospinal fluid (CSF). The most accepted disease models are the amyloid cascade hypothesis, the tau hypothesis, the cholinergic hypothesis, and the excitotoxicity hypothesis in the pathology of AD, and several treatment mechanisms. Noncognitive symptoms of dementia (NCSD) are symptoms that give rise to AD and eventually long-term hospitalization. Early measures can be preventive, but leading symptoms and undetected attention may lead to severe cases. Wandering, aggression or agitation, delusions, and irritability are four key symptoms associated with greater disease severity. Although Pharmacological means are prescribed and are often considered more expedient, Nonpharmacological models are gaining ground first.

Preference. Their use is matched with undesirable outcomes, mortality rising with higher doses, and scarce evidence. Moreover, safety concerns are associated with Antipsychotic drugs, so the FDA has issued boxed (strong) warnings for both older and newer antipsychotics. None of these medicines is officially approved by the FDA to treat agitation or psychosis in dementia, so doctors use them off-label. The American Psychiatric Association (APA) says that antipsychotics should be used only when symptoms are severe, dangerous, or a life-or-death kind of distress to the patient. Doctors should start with the lowest effective dose, increase carefully if needed, and reduce or stop the drug once symptoms improve. There is no single antipsychotic that is both completely safe and highly effective. Hence, treatment must be personalized, weighing possible benefits against side effects for each patient. Global evidence indicates that institutional and real-world constraints continue to challenge effective surrogate decision-making in dementia care, even within well-regulated healthcare systems. In a nutshell, psychiatrists should prioritize helping patients retain autonomy and remain as actively involved as possible in decision-making, together with their families. Ethical care requires honest communication about the diagnosis, support for additional evaluations if the patient wishes, and discussion of advance directives with both the patient and family present. Patients should be fully included in decisions about their treatment and future care. As thinking and behavior gradually decline, being completely direct may not always be the kindest or most ethical approach. In the later stages, psychiatrists often need to focus more on reducing stress and emotional burden for both the patient and their caregivers, sometimes guiding families toward choices that keep everyone calmer and more comfortable. At this stage, ethical care is less about full independence and more about preserving dignity, comfort, and emotional well-being. What caregivers should do in these situations remains clinically and ethically debated. Some patients may cope better when caregivers remain fully honest, even if the truth causes emotional strain. Psychiatrists may reasonably adjust their guidance based on what they believe serves the individual patient's best interests, which often depends on the emotional responses and values of family members. As Alzheimer's disease (AD) progresses, psychiatrists should support caregivers who feel that withholding the full truth or using gentle untruths is necessary to protect the patient from emotional harm.

In the advanced stages of AD, when the illness is clearly progressing toward the end of life, psychiatrists should regularly help families weigh the benefits and burdens of ongoing interventions. If a patient is no longer able to eat enough to maintain weight without artificial nutrition, it may be appropriate to discuss with the family whether continued life-prolonging measures remain in the patient's best interests. This consideration becomes even more pressing if the patient later loses the ability to eat entirely. At the same time, psychiatrists must recognize that even in late-stage AD, patients may still have meaningful reasons to want to live, even if they can no longer express them verbally. Factors such as the absence of severe pain and the ability to experience close emotional connections with loved ones can continue to give life value. Ethical care, therefore, requires openness to both possibilities: allowing a natural death when burdens outweigh benefits, or supporting life-preserving measures when the patient's remaining experiences—such as comfort, relief from pain, and the presence of family—still hold meaning.

Conclution

Overall, Alzheimer's disease poses a burden on the elderly population.

From 1990 to 2021, there were an estimated 37.2 million total deaths from Alzheimer's disease and other dementias combined all over the world. While studies have uncovered fascinating insights from cognitive reserve to early biological changes, many questions remain unanswered. Synaptic dysfunction, neuronal loss, and widespread brain atrophy are driven primarily by amyloid-β accumulation, tau pathology, neuroinflammation, and metabolic dysregulation. The long preclinical phase highlights that pathological changes begin decades before symptoms appear, making early biological markers critically important. Although Early detection allows families to plan, access support, and implement strategies, investment in early diagnosis, preventive strategies, and cost-effective interventions is therefore not only a public health priority but also an economic imperative to reduce long-term societal and fiscal costs. Even as memories fade, the need for care, dignity, and love remains unchanged.

References

1. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. *JAMA.* 2019;322(16):1589–1599. doi:10.1001/jama.2019.4782
2. Safiri S, Ghaffari Jolfayi A, Fazlollahi A, Morsali S, Sarkesh A, Daei Sorkhabi A, Golabi B, Aletaha R, Motlagh Asghari K, Hamidi S, Mousavi SE, Jamalkhani S, Karamzad N, Shamekh A, Mohammadinasab R, Sullman MJM, Şahin F, Kolahi AA. Alzheimer's disease: a comprehensive review of epidemiology, risk factors, symptoms diagnosis, management, caregiving, advanced treatments and associated challenges. Front Med (Lausanne). 2024 Dec 16;11:1474043. doi: 10.3389/fmed.2024.1474043. PMID: 39736972; PMCID: PMC11682909.
3. Walker LC. Aβ Plaques. Free Neuropathol. 2020;1:31. doi: 10.17879/freeneuropathology-2020-3025. Epub 2020 Oct 30. PMID: 33345256; PMCID: PMC7745791.
4. Beach TG. A History of Senile Plaques: From Alzheimer to Amyloid Imaging. J Neuropathol Exp Neurol. 2022 May 20;81(6):387-413. doi: 10.1093/jnen/nlac030. PMID: 35595841; PMCID: PMC9122832.
5. Jain SK, Stevens CM, Margret JJ, Levine SN. Alzheimer's Disease: A Review of Pathology, Current Treatments, and the Potential Therapeutic Effect of Decreasing Oxidative Stress by Combined Vitamin D and l-Cysteine Supplementation. Antioxid Redox Signal. 2024 Apr;40(10-12):663-678. doi: 10.1089/ars.2023.0245. Epub 2023 Dec 8. PMID: 37756366; PMCID: PMC11001507.
6. Snowdon DA; Nun Study. Healthy aging and dementia: findings from the Nun Study. Ann Intern Med. 2003 Sep 2;139(5 Pt 2):450-4. doi: 10.7326/0003-4819-139-5_part_2-200309021-00014. PMID: 12965975.
7. Bondi MW, Edmonds EC, Salmon DP. Alzheimer's Disease: Past, Present, and Future. J Int Neuropsychol Soc. 2017 Oct;23(9-10):818-831. doi: 10.1017/S135561771700100X. PMID: 29198280; PMCID: PMC5830188.
8. Feng W, Zhang Y, Wang Z, Xu H, Wu T, Marshall C, Gao J, Xiao M. Microglia prevent beta-amyloid plaque formation in the early stage of an Alzheimer's disease mouse model with suppression of glymphatic clearance. Alzheimers Res Ther. 2020 Oct 2;12(1):125. doi: 10.1186/s13195-020-00688-

1. PMID: 33008458; PMCID: PMC7532614.
9. Khan S, Barve KH, Kumar MS. Recent Advancements in Pathogenesis, Diagnostics and Treatment of Alzheimer's Disease. Curr Neuropharmacol. 2020;18(11):1106-1125. doi: 10.2174/1570159X18666200528142429. PMID: 32484110; PMCID: PMC7709159.
10. Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. Lancet. 2016 Jul 30;388(10043):505-17. doi: 10.1016/S0140-6736(15)01124-1. Epub 2016 Feb 24. PMID: 26921134.
11. Petersen RC. New clinical criteria for the Alzheimer's disease spectrum. Minn Med. 2012 Jan;95(1):42-5. PMID: 22355912.
12. Feng W, Zhang Y, Wang Z, Xu H, Wu T, Marshall C, Gao J, Xiao M. Microglia prevent beta-amyloid plaque formation in the early stage of an Alzheimer's disease mouse model with suppression of glymphatic clearance. Alzheimers Res Ther. 2020 Oct 2;12(1):125. doi: 10.1186/s13195-020-00688-1. PMID: 33008458; PMCID: PMC7532614.
13. Hassan MN, Nabi F, Khan AN, Hussain M, Siddiqui WA, Uversky VN, Khan RH. The amyloid state of proteins: A boon or bane? Int J Biol Macromol. 2022 Mar 1;200:593-617. doi: 10.1016/j.ijbiomac.2022.01.115. Epub 2022 Jan 22. PMID: 35074333.
14. Passeri E, Elkhoury K, Morsink M, Broersen K, Linder M, Tamayol A, Malaplate C, Yen FT, Arab-Tehrany E. Alzheimer's Disease: Treatment Strategies and Their Limitations. Int J Mol Sci. 2022 Nov 12;23(22):13954. doi: 10.3390/ijms232213954. PMID: 36430432; PMCID: PMC9697769.
15. Jenkins MR, Peven JC, Kubic L, Handen BL, Krinsky-McHale SJ, Hom CL, Lee A, Tudorascu DL, McLachlan M, Zammit M, Minhas D, Luo W, Laymon C, Lee JH, Lott I, Cohen A, Ances BM, Rosas HD, Lai F, Zaman SH, Head E, Mapstone M, Christian BT, Hartley SL; Alzheimer Biomarker Consortium - Down syndrome. Behavioral and psychological symptoms of dementia and Alzheimer's disease progression in Down syndrome. J Neurodev Disord. 2025 Apr 11;17(1):19. doi: 10.1186/s11689-025-09604-w. PMID: 40217501; PMCID: PMC11987311.
16. Furukawa M, Tada H, Raju R, Wang J, Yokoi H, Yamada M, Shikama Y, Saito T, Saido TC, Matsushita K. Effects of tooth loss on behavioral and psychological symptoms of dementia in app knock-in mice. J Oral Biosci. 2024 Jun;66(2):329-338. doi: 10.1016/j.job.2024.03.005. Epub 2024 Mar 21. PMID: 38521152.
17. Goedert M, Sisodia SS, Price DL. Neurofibrillary tangles and beta-amyloid deposits in Alzheimer's disease. Curr Opin Neurobiol. 1991 Oct;1(3):441-7. doi: 10.1016/0959-4388(91)90067-h. PMID: 1821689.
18. Avila J, Lucas JJ, Perez M, Hernandez F. Role of tau protein in both physiological and pathological conditions. Physiol Rev. 2004 Apr;84(2):361-84. doi: 10.1152/physrev.00024.2003. PMID: 15044677.
19. Clarke, K., Etemadmoghadam, S., Danner, B., Corbett, C., Ghaseminejad-Bandpey, A., Dopler, M. B., … & Flanagan, M. E. (2025). The Nun Study: Insights from 30 years of aging and dementia research. Alzheimer's & Dementia, 21(2). https://doi.org/10.1002/alz.14626
20. Gustavsson A, Norton N, Fast T, Frölich L, Georges J, Holzapfel D, Kirabali T, Krolak-Salmon P, Rossini PM, Ferretti MT, Lanman L, Chadha AS, van der Flier WM. Global estimates on the number of persons across the Alzheimer's disease continuum. Alzheimers Dement. 2023 Feb;19(2):658-670. doi: 10.1002/alz.12694. Epub 2022 Jun 2. PMID: 35652476.
21. Piaceri I, Nacmias B, Sorbi S. Genetics of familial and sporadic Alzheimer's disease. Front Biosci

(Elite Ed). 2013 Jan 1;5(1):167-77. doi: 10.2741/e605. PMID: 23276979.

22. Geda YE, Schneider LS, Gitlin LN, Miller DS, Smith GS, Bell J, Evans J, Lee M, Porsteinsson A, Lanctôt KL, Rosenberg PB, Sultzer DL, Francis PT, Brodaty H, Padala PP, Onyike CU, Ortiz LA, Ancoli-Israel S, Bliwise DL, Martin JL, Vitiello MV, Yaffe K, Zee PC, Herrmann N, Sweet RA, Ballard C, Khin NA, Alfaro C, Murray PS, Schultz S, Lyketsos CG; Neuropsychiatric Syndromes Professional Interest Area of ISTAART. Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future. Alzheimers Dement. 2013 Sep;9(5):602-8. doi: 10.1016/j.jalz.2012.12.001. Epub 2013 Apr 3. PMID: 23562430; PMCID: PMC3766403.
23. Hampel H, Mitchell A, Blennow K, Frank RA, Brettschneider S, Weller L, Möller HJ. Core biological marker candidates of Alzheimer's disease - perspectives for diagnosis, prediction of outcome and reflection of biological activity. J Neural Transm (Vienna). 2004 Mar;111(3):247-72. doi: 10.1007/s00702-003-0065-z. Epub 2003 Dec 3. PMID: 14991453.
24. Gustavsson A, Norton N, Fast T, Frölich L, Georges J, Holzapfel D, Kirabali T, Krolak-Salmon P, Rossini PM, Ferretti MT, Lanman L, Chadha AS, van der Flier WM. Global estimates on the number of persons across the Alzheimer's disease continuum. Alzheimer's Dement. 2023 Feb;19(2):658-670. doi: 10.1002/alz.12694. Epub 2022 Jun 2. PMID: 35652476.
25. Aarsland, D., Sunde, A.L., Tovar-Rios, D.A. *et al.* Prevalence of Alzheimer’s disease pathology in the community. *Nature* (2025).
26. Tay LX, Ong SC, Tay LJ, Ng T, Parumasivam T. Economic Burden of Alzheimer's Disease: A Systematic Review. Value Health Reg Issues. 2024 Mar;40:1-12. doi: 10.1016/j.vhri.2023.09.008. Epub 2023 Nov 14. PMID: 37972428.