

## Alzheimer Disease

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### Abstract

Alzheimer's disease (AD) is typified by memory deficiencies that worsen with time, along with cognitive and behavioral abnormalities that eventually result in dementia. AD is one of the most difficult diseases to treat because of its prevalence, high cost of care, effects on patients and caregivers, and lack of mechanism-based therapies. The malfunction and loss of neurons in particular circuits and locations, especially in the populations of nerve cells supporting memory and cognition, causes the AD condition. The neuropathology of AD is characterized by intracellular and extracellular protein aggregation accumulations. In the neuronal perikarya and dystrophic neurites, abnormally phosphorylated tau forms paired helical filaments (PHFs) that combine to form neurofibrillary tangles (NFTs). The extracellular deposition of  $\beta$ -pleated assemblies of A $\beta$  peptide, which result in widespread and neuritic senile plaques, is the second pathogenic hallmark.

**Keywords:** Alzheimer disease; Etiology; Pathogenesis; Prevention

### 1. Introduction

The remarkable rise in life expectation during the twentieth century has made Alzheimer complaint (announcement) among the most common diseases of late life. An insidious loss of memory, cognition, logic, and behavioural stability leads inexorably to global madness and unseasonable death of the case. At necropsy, one finds myriad amyloid pillars and neurofibrillary befuddlements in the limbic and association cortices and regions that project to them. These lesions have served as the starting point for a ferocious biochemical and molecular inheritable attack on the complaint. In particular, progress in unravelling the genotype – phenotype connections of inherited forms of announcement has handed substantial support for the thesis that cerebral accumulation of the amyloid-  $\beta$  protein (A $\beta$ ) is an early, steady and necessary step in the development of the complaint. In view of enterprises about the amyloid — or A $\beta$  — thesis of announcement, it's useful to review the scientific underpinnings of this conception. At least eight kinds of substantiation support a central part for inordinate accumulation of A $\beta$  in the inauguration and progression of the complaint 1) Immunocytochemical studies on the smarts of subjects with Down pattern, Alzheimer complaint, or normal growing all suggest that unformed, nonfibrillar deposits of A $\beta$  — appertained to as verbose pillars — are the foremost sensible announcement- type lesion and antecede the development of other neuropathology features of the complaint. 2) Missense mutations incontinently girding the A $\beta$  region of the amyloid  $\beta$ - protein precursor (APP) gene are a specific cause of announcement, and each of these mutations has been shown to lead to redundant product of amyloid genic A $\beta$  peptides, particularly A $\beta$ 1 – 42. 3) Altered situations of A $\beta$ 1 – 42 peptide in the cerebrospinal fluid( CSF) can antecede the onset of announcement symptoms by numerous times or decades, as observed, for illustration, in individualities harbouring mutations in the presently( PS) 1 or 2 genes. 1, 2 4) Cortical situations of A $\beta$ 1 – 42 determined by enzyme-linked immunosorbent assay (ELISA) supplement tightly with both the presence and the degree of cognitive impairment. 3 5) Added up A $\beta$  peptides, including answerable oligomers insulated directly from announcement cortex,

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have been shown reproducibly to elicit cytotoxicity on neurons, enhance phosphorylated tau protein at announcement-specific epitopes, spark astrocytes and microglia in vitro and intrude with cognitive function in in vivo models.<sup>5, 6</sup> Transgenic overexpression of announcement-causing mutations in APP and/or PSI has yielded mouse models that, while not perfect, reproduce some of the characteristic neuritic and glial cytopathology of announcement and alter the creatures' gesture, supporting the conception that A $\beta$  accumulation can initiate neuritic dystrophy, gliosis, synaptic loss and indeed neurofibrillary distraction conformation.<sup>7, 8</sup> Treatments that lower cerebral A $\beta$ 1 – 42 situations in mouse models of announcement, for illustration, an A $\beta$  vaccine<sup>9 – 11</sup> or a modulator of the presently/  $\gamma$ - secretase enzyme that generates A $\beta$ , lead to lower neuropathology and bettered literacy geste in APP transgenic mice.<sup>8</sup> Some substantiation is arising that rectifiers solely directed against A $\beta$ (e.g., the A $\beta$  monoclonal antibody solanezumab) can decelerate the rate of cognitive decline in cases with mildAD.<sup>13</sup> This chapter reviews these and other recent molecular advances in the environment of the complex clinic pathological phenotype of the Alzheimer pattern. The influence of the known inheritable factors underpinning domestic forms of announcement on the development of A $\beta$  deposit and neuronal dysfunction is banded. A model of the complaint process that links A $\beta$  accumulation to numerous other features of the announcement phenotype, including neurofibrillary befuddlements, is presented, and arising points of remedial intervention are considered.

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## 2. Alzheimer disease and mild cognitive impairment

AD is named after Dr. Alois Alzheimer, who initially noticed signs of the disease in 1901 in a 51-year-old woman named Augusta D. One of the early symptoms was intense feelings of jealousy against her husband. She quickly began to exhibit quickly worsening memory problems; she was disoriented, moving items around her apartment and hiding them. She occasionally had the feeling that someone was trying to kill her and started to scream out. She passed away after 4.5 years of illness. A large concentration of NFTs and protein plaques was found in the brain during postmortem examination.

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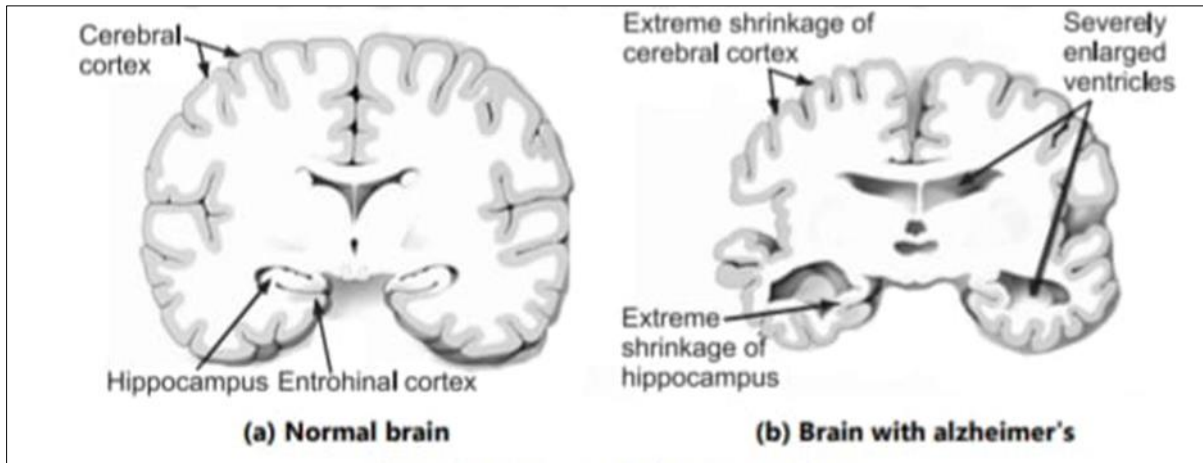
## 3. Clinical features and diagnosis

The remarkably sneaky beginning of the clinical presentation is a prominent feature. The patient's family is unable to determine when it all started. Family members go back and look for the first hint if they start to believe there is a problem. The spouse or kids will frequently see prior occurrences, whether significant or not, such as a sickness, accident, or emotional trauma, as the beginning point. However, taking into account the biology of the process reveals that the pathogenic and biochemical phenotype has been steadily developing for a very long time, most likely for a decade or more. As a result, the initial symptoms may be so mild and infrequent that they pass for normal behavior.

The popular press has published numerous articles about the challenges physicians face when diagnosing AD. A belief that obtaining an accurate diagnosis during life is difficult has arisen since, until recently, AD could only be definitively identified after postmortem examination. This no longer holds true for AD or for many other well identified systemic disorders, where a diagnosis can be made based on symptoms, signs, and laboratory results alone, but tissue examination—which is extremely uncommon in AD—is needed for conclusive evidence.

With a high degree of accuracy, skilled clinicians can differentiate AD from the majority of other dementias. The ability to confirm or refute a suspected clinical diagnosis of AD has been revolutionized with the introduction of positron emission tomography (PET) testing for amyloid deposition around 2004. According to autopsy series from dementia-focused clinics, a clinical diagnosis of AD can be made with greater than 95% accuracy. This number is probably a little lower in the wider medical community, maybe 70–80%.

Until recently, obtaining negative blood tests and a normal brain imaging study that helped rule out other causes of dementia were the main components of the diagnostic work-up for AD. Positive evidence for AD has now been found in imaging investigations, including functional magnetic resonance imaging (MRI) and fluorodeoxyglucose PET scans, as well as in the assessment of higher tau and decreased A $\beta$ 42 protein levels in the CSF.<sup>16</sup> Comprehensive psychometric evaluations can reliably confirm a medical diagnosis and precisely measure decline over time. A psychiatric consultation can assist in determining whether behavioral symptoms are caused by dementia and can also provide pharmaceutical treatments for them. Most excitingly, a US Food and Drug Administration (FDA)-approved amyloid ligand for PET is being widely employed in experimental clinical studies. Noninvasive imaging of the brain amyloid deposits by PET scanning has emerged as a diagnostic tool with enormous promise.



**Figure 1** Features of Alzheimer's diseasesa

### 3.1. Etiology

Alzheimer's affects the brain clearly, even if its causes are still unknown. Alzheimer's disease causes brain cell death and damage. Compared to a healthy brain, an Alzheimer's disease-affected brain has significantly fewer cells and less connections between the cells that remain. Alzheimer's causes a noticeable shrinking of the brain as more and more brain cells die.

### 3.2. Plaques

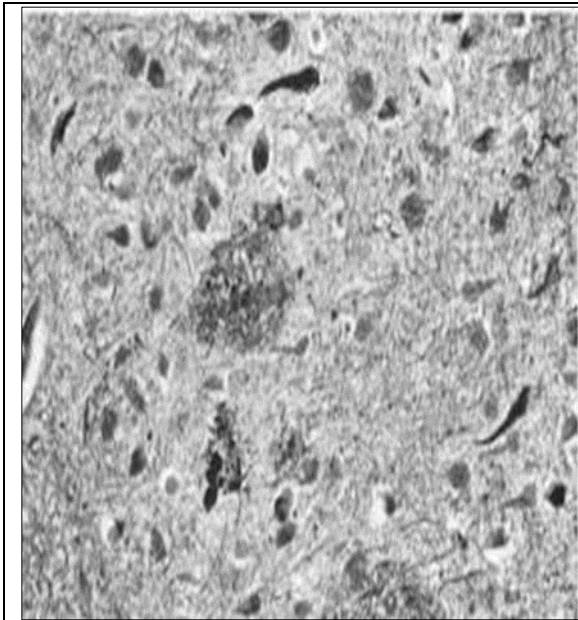
These aggregates of the protein  $\beta$ -amyloid have the potential to cause multiple harms and even the death of brain cells, one of which is interfering with the communication between cells. The accumulation of  $\beta$ -amyloid outside brain cells is a major suspicion, even though the exact etiology of Alzheimer's brain-cell loss is unknown.

- **Tangles:** Throughout their lengthy expansions, brain cells rely on an internal support and transport system to deliver nutrition and other necessary components. The tau protein's proper structure and functionality are essential to this system.
- **Loss of nerve cell connections:** Neurones lose their connectivity to one another and eventually die off as a result of the tangles and plaques. Brain tissue shrinks (atrophies) as neurons die. The transport mechanism fails as a result of tau protein strands twisting into aberrant tangles inside brain cells in Alzheimer's disease. Additionally, the deterioration and death of brain cells are closely linked to this failure.

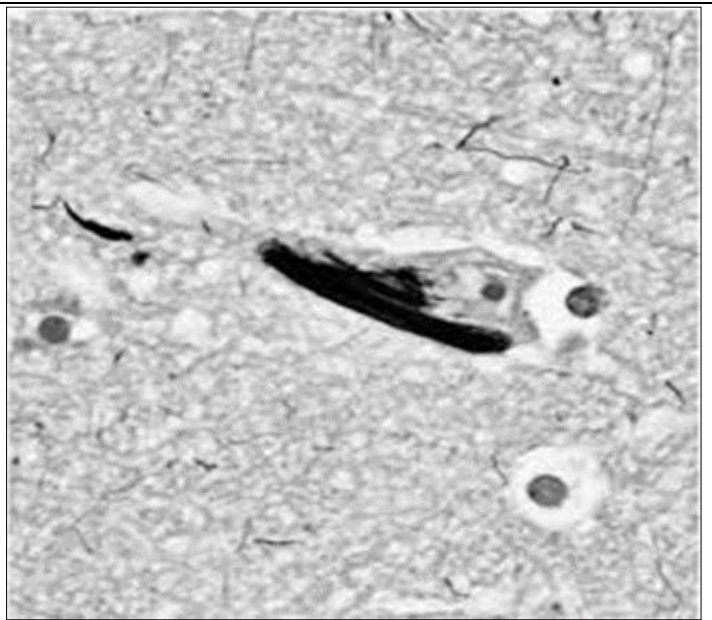
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## 4. Pathology

Generalized cortical atrophy, which is usually most noticeable in the medial temporal lobe and hippocampal regions, is one of the gross pathologies associated with AD.



**Figure 2** Bielschowsky silver staining reveal a typical Alzheimer's plaque (left of center) Several neurofibrillary tangles are also present



**Figure 3** Magnified view of a neurofibrillary tangle ( Bielschowsky stain )

Under a microscope, the afflicted brain regions show signs of inflammation, granulovacuolar degeneration, Hirano bodies, and the two typical inclusions: amyloid plaques and neurofibrillary tangles (NFTs). The distribution and density of NFTs, which are aggregates of tau protein and neurofilaments present in neuronal cell bodies (Figures 1 and 2), seem to be correlated with the clinical presentation. Neuritic plaques and neuropil threads are two more neurofibrillary abnormalities that arise in AD patients. Ab-protein clumps outside of neurons are known as amyloid plaques (Figure 1). Diffuse and neuritic plaques are the two types. Even though Ab makes up the majority of the neuritic plaques, there are also dystrophic neurites with tau in the amygdala and hippocampus (Braak Stages III/IV) and (4) tangles in the neocortex (Braak Stages V/VI).

The neuritic plaque score comes last and was adapted from the CERAD (Council to Establish a Registry for Alzheimer's Disease). The density of neuritic plaques in various neocortex regions is ranked by this score. Based on the combined amyloid, Braak, and CERAD (ABC) scores, a level of AD neuropathological change (none, low, intermediate, or high) is assigned. Comorbid conditions such as Lewy body disease, vascular brain damage, hippocampal sclerosis, argyrophilic grain disease, and TAR (trans-activator regulatory) DNAbinding protein-43 (TDP-43) inclusions are also given more weight in the revised neuropathological criteria.

## 5. Pathogenesis

The amyloid cascade theory is the predominant explanation for the etiology of AD. The primary component of amyloid plaques,  $\beta$ -amyloid protein, is a segment of APP that can be first cleaved by either  $\alpha$ - or  $\beta$ -secretase 1 (BACE1). G-secretase then cleaves the resulting peptide once more in either scenario. An Ab-polypeptide is produced if g-secretase cleaves APP first, followed by BACE. Depending on where g-secretase cleavage occurs, the majority of the amino acids in the Ab-polypeptide (Ab40 or Ab42) are either 40 or 42. While both versions tend to assemble, Ab42 aggregates more quickly due to the presence of two extra hydrophobic amino acids. Amyloid angiopathy, or vascular amyloid deposits, are primarily found to contain Ab40, whereas amyloid plaques primarily contain Ab42. NFTs, which are composed of hyperphosphorylated tau protein, are another component of the pathology linked to Alzheimer's disease. Depending on alternative splicing, the microtubule-binding protein tau has six isoforms. Tau is phosphorylated in a number of ways and acts as a substrate. Microtubules are destabilized by tau binding deficiency, but intracellular NFTs are produced when tau is hyperphosphorylated, causing microtubules to break apart and form neurotoxic filament tangles. The distribution and burden on NFTs and the symptomatology of AD are highly correlated.

The apolipoprotein E (ApoE) and other proteins accumulate further as a result of amyloid aggregation, as stated in the amyloid hypothesis. Plaque deposition is thought to set off a series of reactions that include inflammatory reactions, cytoskeletal damage, oxidative damage, and mitochondrial dysfunction. In vitro models of amyloid, the most neurotoxic

aggregate appears to be the oligomeric form, which is composed of soluble but aggregated Ab42. Both the soluble and fibrillar forms of amyloid have the potential to activate signaling pathways mediated by calcineurin and caspase, which in turn cause inflammation, dendritic remodeling, and loss of the neural spine.

Tau is cleaved by activated caspases, resulting in a shorter form of the protein that clumps together and causes more cellular damage. Ab might not be necessary for the ensuing cascade to continue. According to this revised theory, Ab by itself is not enough to result in extensive brain damage, but it is still a significant prospective therapeutic target, particularly when the disease is still in the presymptomatic stage. The aforementioned model responds to earlier objections leveled at the amyloid hypothesis, including the lack of a connection between the severity of dementia and the amount of amyloid present and the ineffectiveness of amyloid-targeting therapies for symptomatic AD. Still, the model is probably not complete. NFTs and other neuropathological alterations may occur before plaque deposition. Teenagers who passed away have abnormally phosphorylated tau in their lower brainstems. Nonetheless, as discussed in Section Genetics, every known autosomal dominant mutation causing familial AD directly contributes to the amyloid cascade and raises the generation of Ab42. While some disease symptoms (such as Ab aggregation, plaque formation, memory loss, and other behavioral abnormalities) are replicated when these mutations are expressed in transgenic mice, other features (such as NFTs and neuronal death) are not. On the other hand, autosomal-dominant FTD is caused by mutations in the microtubule-associated protein tau (MAPT) gene. The ApoE E4 genotype, which is the biggest genetic risk factor for sporadic AD, lowers Ab clearance and promotes Ab aggregation.

It's feasible that tau hyperphosphorylation and Ab accumulation are distinct processes with a harmful synergy that share a common origin. For instance, it's possible that aberrant amyloid species increase an early, but separately more benign, susceptibility to tau disease to neurotoxic levels. The failure of age-related defense systems against toxic or misfolded proteins, as well as exposure to hyperactive cellular activity, are additional typical etiologies of tau and amyloid pathology. Similar to other neurodegenerative illnesses, AD pathology usually propagates in a stereotyped and selective manner. The progression of NFTs from the brainstem to the paralimbic areas, entorhinal cortex, and association neocortex is correlated with the symptoms of AD. Usually, the primary cortices of the motor, sensory, auditory, and visual systems are spared. It has been suggested that misfolded proteins may migrate from neuron to neuron in the investigation into the origin of this pattern of dissemination. It has been demonstrated that tau and amyloid can cause proteins to misfold in a way that is similar to prions. Possibly due to the loss of inhibitory interneurons, AD is linked to aberrant electrical activity and network hypersynchrony in addition to alterations at the molecular and cellular levels. Magnetic resonance imaging (MRI) or electroencephalography (EEG) with functional connectivity can identify these modified neural network patterns. Enhanced hyperexcitability of networks could perhaps account for the elevated incidence of seizures observed in the AD population.

### 5.1. Genetics

It is well recognized that clinically typical AD can occasionally be inherited in an autosomal dominant manner and can cluster in families. The percentage of AD cases that are thought to be caused by hereditary factors has been estimated to range from as low as 5–10% to as high as 50% or higher. According to some researchers, most AD cases will eventually be found to have underlying genetic determinants, many of which may manifest as polymorphic alleles that predispose to the illness but do not always cause it.

It is challenging to ascertain the frequency with which hereditary variables cause a late-onset ailment like AD, especially one that was not identified and thoroughly investigated before the previous three decades. Furthermore, the discovery that the  $\epsilon 4$  allele of Apolipoprotein E predisposes people to develop typical AD in their 60s and 70s raises the possibility that other polymorphic genes with smaller effect sizes also predispose to the disorder. However, because these genes don't always cause the disease and won't show high penetrance, they might be harder to find in genetic epidemiologic studies.

### 5.2. The clinical Strategies Surface from Comprehending the Molecular Chain of Alzheimer's Disease

Out of all the theories put up to explain the origin of the condition, the  $A\beta$  hypothesis of AD has the most experimental evidence to support it. The Alzheimer disease model examined here suggests novel treatment approaches targeted at one or more crucial molecular stages of the illness's progression: 1) The proteases ( $\beta$ - and  $\gamma$ -secretases) that release  $A\beta$  from its precursor can be partially inhibited. A method for adjusting  $\gamma$ -secretase that has been tested on humans involves using nonsteroidal anti-inflammatory medication compounds, which decrease  $A\beta 42$  without disrupting Notch processing.

Nevertheless, it has not yet been demonstrated that these and other subsequent families of  $\gamma$ -secretase modulators are bioavailable and powerful enough in humans to result in clinical benefit. As of this writing, some BACE-1 (app75's  $\beta$ -

secretase) inhibitors are undergoing advanced clinical development. 2) Apart from secretase inhibition, there are several additional ways to reduce the formation and release of A $\beta$ . One such technique is to pharmacologically shift certain APP molecules from the amyloidogenic ( $\beta$ -secretase) to the nonamyloidogenic ( $\alpha$ -secretase) processing pathway. 3) One may try to stop the A $\beta$  monomer oligomerization process, which comes before fibrillogenesis. but blocking the monomer-to-dimer conversion alone would probably be necessary because blocking it afterward runs the danger of raising the concentrations of possibly synaptotoxic dimers.4) One may attempt to remove A $\beta$  peptides from the cortex, including monomers, oligomers, and fibrillar clumps. This seems to be one of the working mechanisms of passively administered anti-A $\beta$  antibodies and active A $\beta$  vaccines<sup>9</sup>, both of which have shown promise in AD mice models but have not yet been shown to be effective in human trials, despite encouraging results from at least one phase III trial.5) One may impede the actions of astrocytes and microglia that support the emergence of a long-term inflammatory response surrounding A $\beta$  deposits. 6) Although these molecules have not yet been fully identified and there are probably many of them, one could try to block the molecules (also known as "A $\beta$  receptors") on the surface of neurons (such as certain membrane lipids) or their numerous intracellular effectors that mediate the neurotoxic effects of A $\beta$  oligomers.

### 5.3. Diagnosis

An exact test to diagnose Alzheimer's disease does not exist. Only after death, upon microscopic inspection of the brain, can the disease's hallmark plaques and tangles be identified as Alzheimer's. These days, physicians usually depend on the following kinds of testing to help differentiate Alzheimer's disease from other causes of memory loss. Using the following steps, a qualified healthcare professional may frequently identify Alzheimer's disease: thorough physical examination The neurological examination, medical history, and symptoms—such as reflexes, muscular tone and strength, the capacity to stand up from a chair and move across a room, sense of hearing and sight, coordination, and balance—are all included. A quick mental status test to evaluate memory and other cognitive abilities is called a mental status assessment. When specific symptoms are present and alternative causes of dementia are ruled out, an Alzheimer's disease diagnosis is made. Exams can be performed to rule out further potential dementia causes, such as:

- Anemia,
- Brain tumor,
- Chronic infection,
- Intoxication from medication,
- Severe depression,
- Stroke,
- Thyroid disease,
- Vitamin deficiency.

Brain imagingThese days, the main purpose of brain imaging is to identify visual anomalies associated with diseases other than Alzheimer's, such strokes, tumors, or trauma, that may lead to cognitive impairment. Technologies for brain imaging consist of: A brain tumor or stroke are two further possible causes of dementia that can be checked for with brain imaging tests like computed tomography (CT) or magnetic resonance imaging (MRI). Brain scans may appear normal in the early stages of dementia. An MRI may reveal a reduction in the size of certain brain regions in later stages. Although the scans do not support the Alzheimer's disease diagnosis, they do rule out other possible causes of dementia (such as tumors and strokes). Only after death, upon microscopic inspection of the brain, can the disease's hallmark plaques and tangles be identified as Alzheimer's.

### 5.4. The brain tissue of individuals with Alzheimer's disease is more frequently altered by the following changes:

The term "neurofibrillary tangles" refers to twisted protein fragments that jam nerve cells. Abnormal clumps of dying and dead nerve cells, other brain cells, and protein are called "neuritic plaques". "Senile plaques" are regions where clumps of degenerating nerve cells have gathered around proteins.

### 5.5. Prevention

While there is currently no known way to prevent Alzheimer's disease, there are several measures that are worth implementing into daily life, especially if dementia runs in the family. Eat a low-fat diet, reduce your intake of linoleic acid from margarine, butter, and dairy products, increase antioxidants like carotenoids, vitamin E, and vitamin C by eating plenty of dark-colored fruits and vegetables, maintain normal blood pressure, and engage in mental and social activities throughout your life. Coldwater fish, such as tuna, salmon, and mackerel, are rich in  $\omega$ -3 fatty acids. Eat these foods at least twice or three times a week.

**Table 1** The U.S. Food and Drug Administration (FDA) approved medications for Alzheimer’s disease

Sr. No.	Drug name	Brand name	Approved for	FDA Approved
1.	donepezil	Aricept	All stages	1996
2.	galantamine	Razadyne	Mild to moderate	2001
3.	memantine	Namenda	Moderate to severe	2003
4.	rivastigmine	Exelon	All stages	2000
5.	donepezil	Namzaric	Moderate to severe	2014

## 6. Conclusions

Research suggests that problems connected to AD in the central nervous system may manifest in the bloodstream. A $\beta$  deposition can result from an increase in A $\beta$  concentration caused by abnormal APP metabolism. Both peripheral tissues and the central nervous system produce APP and A $\beta$ ; the reason why amyloid deposition is limited to the brain is yet unknown. This might be caused by APP metabolism via distinct preferred pathways, which would result in changed A $\beta$  concentrations, the existence of a component or factors that might speed up or stop A $\beta$  deposition, or a more efficient A $\beta$  clearance process from peripheral tissues. The data from peripheral and platelet investigations may be used to identify potential peripheral indicators for AD and aid in the development of a treatment plan for the condition. Thus far, research has indicated that APP isoform ratios may be helpful in both the diagnosis of AD and the tracking of the patient’s reaction to cholinesterase inhibitor therapy. Another possible diagnostic marker for AD patients may be their peripheral endothelial vascular responses. Human platelets emit amyloidogenic A $\beta$  peptide and create all types of APP. Therefore, platelets may be helpful in tracking how the body reacts to treatments that target APP metabolism, such as  $\gamma$ -secretase inhibitors and BACE, or how well an A $\beta$  vaccination is clearing amyloid.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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