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Original Article

Alzheimer's Disease: exploring the pathogenesis, progression, and strategies for management

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Abstract

Alzheimer's disease (AD) is a terrible neurological disease with many possible etiologies that have been explained and associated with spatial disorientation, memory loss and the gradual decline of intellectual capacity. Although current research on neurodegenerative illnesses has put certain candidate compounds through clinical trials. The progression of AD is marked by gradual cognitive decline, often leading to severe memory loss and functional impairment. Early diagnosis, coupled with a better understanding of biomarkers, is essential for managing patient outcomes and creating particular medications. Even though it was first recognized over a century ago, AD is still a life-threatening disease. The European Medicines Agency and the Food and Drug Administration accepted only four medications for the treatment of cognitive symptoms; these medications, however, cannot stop or slow the disease's progression, neurodegeneration, or memory loss.

Key words:

Alzheimer`s disease, cognitive decline, risk factors, progression and therapeutic targets.

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Introduction

1- Alzheimer`s disease history

Dementia is a general word for a particular group of symptoms, such as challenges with memory and thinking abilities that restrict the ability to do regular tasks. Dementia is defined as a decline in many cognitive functions including memory, visuospatial abilities, gnosis, praxis and language executive role, together with behavioral problems such as depression, anxiety, delusions, hallucinations and personality abnormalities. It explains a pattern of thinking and memory decline. Currently, AD is the most well-known form of dementia in advanced countries. Dementia has particular effects on each person, according to the degree of the disease and its pre-morbid characteristics. The difficulties related to dementia consist of three stages, early stage (first or two years), middle stage (second to fourth or five years) and late stage (fifth year or later) **(WHO, 2006).**

Alzheimer's disease (AD) is a terrible neurological disease with many possible etiologies that have been explained and associated with spatial disorientation, memory loss and the gradual decline of intellectual capacity. AD is characterized by several types of damaging, complicated and progressive processes that end in cell dysfunction and death **(Vermunt et al., 2019; Scheltens et al., 2021).**

While there is no effective therapy that delays its progression nowadays, Alzheimer's disease affects about 33 million people worldwide **(Alzheimer's, 2016; Kochanek et al., 2019; Association, 2019; Sheppard and Coleman, 2020).** The number of AD patients is expected to rise twice every 20 years, to reach 81 million by 2040 and this number is expected to overdo 152 million beside 2050 **(Ferri et al., 2005; Nichols et al., 2022).**

2-Symptoms of AD and its progression

Alzheimer's disease was first described by Alois Alzheimer in 1907 as a sporadic and chronic condition causing memory loss and confusion**.** The extra neuronal plaques and intraneuronal tangles are the most well-known neuropathological biomarkers. Acetylcholine and other neurotransmitters are decreased because of the loss of neuronal synapses and subsequent neuronal death **(Health et al., 2018; Lage, 2006).**

Alzheimer inspected his patient's postmortem brain and discovered a decrease in size of the brain in addition to strange accumulations known now as senile plaques and neurofibrillary tangles. This aberrant accumulation of malfunctioning proteins may be the primary cause of Alzheimer's disease. Now there are four well-recognized major alterations in AD patients' brains **(Health et al., 2018)**. Manifestation of extra-neuronal deposits made of the amyloid beta peptide is the first sign due to the inequality between production and clearance of Aβ, resulting in formation of monomers, oligomers and plaques to accumulate of Aβ **(Ricciarelli and Fedele, 2017).** The second hallmark was neurofibrillary tangles, an intraneuronal fibril consists of hyperphosphorylated tau protein **(Raskin et al., 2015).** Extra feature is neuroinflammation, which is thought to lead up to Aβ dysfunction **(Calsolaro and Edison, 2016).** It seems that

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microglia and astrocyte state changes and increasing levels of pro-inflammatory cytokines induce an extreme inflammatory response**.** At last, atrophy of the brain owing to cell death and structural failure, specifically in the hippocampus and cortex, is also noticeable in AD patients **(Fakhoury, 2018; Sun and Alkon, 2019).**

AD is categorized by memory loss, language difficulties, mood disturbance, agnosia, wandering, impaired spatial and temporal orientation, and other mental functions that impair the ability for performing daily life activities. These destructive effects happen owing to the degradation of the hippocampus and cortex neurons, specific regions responsible for cognitive activities **(Raskin et al., 2015; Alzheimer's, 2016; Sheppard and Coleman, 2020) (Fig. 1).**

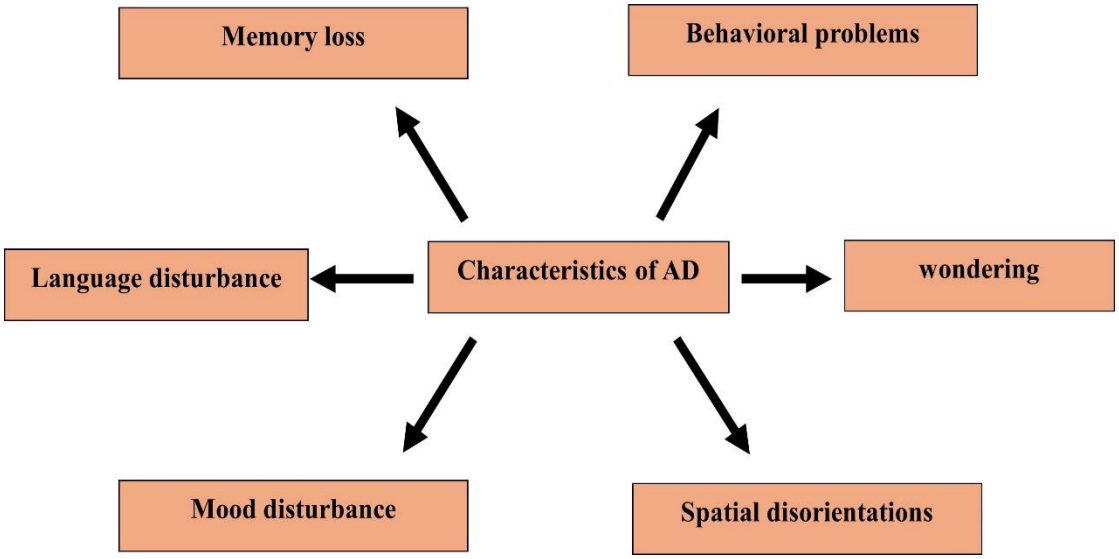

Fig. 1. The symptoms of AD.

AD progression promotes brain abnormalities, which include a decreased information transfer throughout synapses, which ends with death of neurons, thus contributive to the decline of functional and cognitive abilities **(Alzheimer's, 2016).** AD can appear in two distinct forms: the most common, sporadic late-onset type and the familial early-onset form, which accounts for about 1-5% of all cases. Researchers and academics have long been interested in identifying a modifiable precipitator for Alzheimer's disease. Late-onset cases account for around 95% of all cases, are less likely to be inherited and are more likely to have a random etiology including nonfamilial risk factors **(Chu, 2012).**

Although multiple potential risk loci for late-onset AD have been observed, it is unknown how they can affect the progression of progressive neurodegeneration. Early-onset Alzheimer's disease is frequently inherited and alterations in the amyloid precursor protein (APP), presenilin 1 and 2 genes, which have a role in the formation of the Aβ protein, have been related to the disease**.** In contrast, late-onset cases might need a "trigger" or specified biological

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conditions including inflammation, to initiate the amyloid plaque development and neuronal death **(Sevigny et al., 2016)**.

3-Risk factors of AD

Many reasons have been correlated with the increase in AD risk. Many conditions of hypertension, dyslipidemia, vascular risk factors, metabolic syndrome, hyperinsulinemia, diabetes, smoking and heart disease are possible risk aspects for AD. Apart from the rare cases of AD triggered by known hereditary mutations, specialists thought that Alzheimer's develops owing to multiple factors instead of a single cause **(Luchsinger, 2008; Mayeux and Stern, 2012; Alzheimer's, 2014)**.

3.1- Age and sex

Age increases the chance of AD. The sporadic late-onset type of Alzheimer's disease, which has been recorded in persons over the age of 65, is thought to develop up to two decades earlier to the first signs appearance **(Duthey, 2013)**. During the first few years, the brain has the ability to comply with changes that are caused by the disease, while there are no signs of Alzheimer's disease characteristic. Nonetheless, as the condition progresses, the brain lacks the ability to counteract its adverse effects, resulting in arising of symptoms**.** The prevalence of Alzheimer's disease is approximately one percent among individuals aged 65 to 70 years, rising to 6 to 8% for those over 85 years **(Alzheimer's, 2016)** and it is more prevalent in females than males. In men, high bioactive testosterone levels appeared to lower AD prevalence **(Chu et al. 2010).** Sixty-eight percent of those diagnosed with AD are women, while 32% are men **(Zhao et al., 2005).** Women are approximately two times more likely to have Alzheimer's disease than age-matched males and this disparity in gender has been connected to the lack of the female hormone estrogen later in life **(Morrison et al., 2006; Kalaria et al., 2008).**

3.2- Family history and genetics

An additional risk factor is familial history. In response, studies indicate that people who have a father, brother, or sister who have Alzheimer's are feasible to get the disease than those who don't have a first-degree family member with Alzheimer's. When more than one family member gets the illness, the risk rises**. Green et al. (2002)** found that having a first-degree relative, being female, or carrying the APOE ε4 allele increases the risk of dementia **(Green et al., 2002; Alzheimer's, 2013)**.

3.3- Mild cognitive impairment (MCI)

The MCI definition refers to older people suffering from cognitive impairment but fail to satisfy the criteria for dementia. People with MCI are most probable to suffer from dementia, particularly AD**.** MCI patients progressed to Alzheimer's disease at an annual rate of 10% to 15%, alongside 80% of these patients converting to AD after approximately 6 years of examination. Predictors of this progression included APOE ε4 allele carrier patients, brain atrophy, clinical severity, specific patterns of cerebrospinal fluid (CSF) markers and cerebral

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metabolism of glucose and Aβ deposition **(Petersen et al., 2009; Lopez, 2013; Weiner et al., 2013).**

3.4- Cardiovascular disease (CVD)

Growing data suggests that CVD and related risk factors are highly associated with the frequency of cognitive impairment and AD. The idea that CVD and dementia or cognitive decline may share a root cause which was first suggested over four decades ago**.** Numerous cardiovascular risk factors remain also risk factors for dementia, involving low and high LDL cholesterol especially diabetes and hypertension. Medium alcohol seems to be defending CVD and dementia **(Stampfer, 2006; Batty et al., 2014).**

3.5-Vascular and cerebrovascular disease

Cerebrovascular and stroke are correlated to a bigger risk of AD. Cerebrovascular changes like hemorrhagic cortical infarcts, white matter changes and vasculopathy all of them rise the risk of AD. Diabetes, hyperinsulinemia, adiposity and related vascular risk factors such as dyslipidemia and hypertension are correlated to a greater risk of cerebrovascular disease **(Luchsinger, 2008; Reitz et al., 2011).**

3.6-Type II diabetes

The incidence of type II diabetes (T2DM) is related to two-fold increased risk of AD**.** Findings to date indicate that T2DM and hyperinsulinemia rise the risk for AD, perhaps through their impacts on metabolism of amyloid beta and dysfunction of cerebrovascular, two early outcomes in preclinical pathology of AD**.** Insulin can penetrate the blood-brain barrier (BBB), stimulates amyloid beta excretion and prevents extracellular breakdown of Aβ by grappling with insulin-degrading enzyme (IDE), which is the main regulator of Aβ in both neurons and glial cells. Mice with IDE dysfunction have glucose intolerance, hyperinsulinemia and increased Aβ accumulation **(Farris et al., 2003; Luchsinger, 2008; Carlsson, 2010)**.

Hyperglycemia increases the glycation process, resulting in the development of advanced glycation end-products (AGEs) which are present because of the oxidation of glucose and fructose **(Takeuchi and Makita, 2001).** AGE receptors are found to be a special cell surface receptor for Aβ peptide, hence eliciting damage of neurons **(Yamagishi et al., 2005; Luchsinger, 2008).**

3.7- Education

Education may raise the ‘cognitive reserve’, which decreases the risk of late-onset dementia. The probability of having AD is highest among individuals with low or reduced degrees of education. Individuals with knowledgeably enriched lifestyles, like individuals with high educational or occupational ability, exhibit a decreased risk of stating AD pathology **(Mayeux and Stern, 2012).**

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3.8-Traumatic Brain Injury (TBI)

TBI is a critical global health problem featuring neurobehavioral implications leading to chronic disability. It results in brain edema, axonal damage and hypoxia; disrupts BBB activity; and promotes inflammatory responses, oxidative stress, neurodegeneration and cognitive decline. Epidemiological research showed that Aβ plaques are found in about thirty percent of patients who die acutely after TBI **(Johnson et al., 2010; Sivanandam and Thakur, 2012).** Thus, TBI appears as an essential epigenetic reason for AD **(Breunig et al., 2013)**.

3.9- Behavioral factors

Several behavioral factors were chosen, involving smoking and physical activity.

Smoking

Smoking has been considerably studied bothering a lot of brain disorders, mainly degenerative and vascular diseases. Nevertheless, the relation between smoking and neurological diseases has been disputable. Many epidemiological surveys found a direct effect of smoking on AD, but then the known relation between smoking and cerebrovascular disease was just partly considered **(Fratiglioni and Wang, 2000).** These agree with literature pointing to the role of smoking in oxidative stress and inflammation, both processes supposed to have a role in AD **(Uttara et al., 2009; Beydoun et al., 2014).**

Physical activity

Physical activity has several well-recognized benefits for inhibiting several chronic disorders **(Beydoun et al., 2014).** Aerobic exercise improves cerebral metabolic activity resulting in improvement in neuropsychological test scores. **Gomez-Pinilla et al. (1997)** revealed that exercise controls the expression of fibroblast growth factor-2 (FGF-2) and recommends that growth factors are likely moderators of the positive impacts of exercise on the brain. **Cotman and Engesser-Cesa. (2002) and Vaynman et al. (2004)** announced that physical activity shows an increase in brain-derived neurotrophic factors (BDNF) which increases neuronal survival, increases learning and protects against cognitive deterioration. In 2013**, Lin and Kuo** stated that regular physical activity has been shown to have curative benefits, like treating psychiatric diseases, encouraging brain injury retrieval and surviving neurodegenerative illnesses. These have been appropriate to increased capabilities of metabolism reserve and antioxidation. Moreover, regulations of viscerotropic factors secretion, inflammatory mediators and neurotransmitters are also implicated with exercise's effect on brain function.

3.10-Diet/ nutrition

Dieting is a crucial part of a healthy lifestyle and affects the risk of various diseases, in general the aging process. Assumed that free radicals and oxidative harm have been concerned with age-related brain disease **(Tamagno et al., 2012),** consumption of diet with high concentrations of complex phenols and other constituents with antioxidant properties

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(including vitamins E, vitamins C and carotenoids from fruit and vegetable), has been proposed to decrease the risk of dementia **(Hughes and Ganguli, 2009; Gu et al., 2010).**

4-Pathogenesis and Hypothesis of Alzheimer's Disease

Since its discovery, fatal neurodegenerative AD has been exploited to clarify its pathogenesis. Several complementary theories have been proposed to support its multifactorial characteristics **(Umar and Hoda, 2017**); till now, the exact cause of AD is still unknown. Cognitive profiles and common symptoms identify the clinical syndromes associated with Alzheimer's disease. Currently, researchers are focusing on understanding AD pathology through various mechanisms including cholinergic, β-amyloid, irregular tau protein metabolism, free radical damage and inflammatory response to discover curative treatments that could stop or modify the disease progression **(Umar et al., 2019a, b) (Fig. 2).**

4.1-Amyloid beta hypothesis

The amyloid cascade theory is the most widely accepted hypothesis, described for the first time in 1992 by **Hardy and Higgins,** they suggested that Aβ peptide buildup in the brain is the key factor responsible for AD development. Amyloid beta is a microscopic protein fragment in the brain composed of around 40 to 42 amino acid chains (sticky molecules). The generation and accumulation of Aβ is believed to act as the key factor of the initiation and progression of AD **(De Strooper and Annaert, 2000; Bolduc et al., 2016; Ricciarelli and Fedele, 2017).** Aβ is manufactured inside the cell in the endoplasmic reticulum (ER) and deposited inside the brain initiating AD **(Schreiner et al., 2015; Kim and Lim, 2021)**. The transmembrane protein amyloid precursor protein (APP) regulates axonal transport, neurite outgrowth and neuronal development**.** APP is proteolyzed by β- and γ-secretase to produce Aβ peptides **(Selkoe, 2001).**

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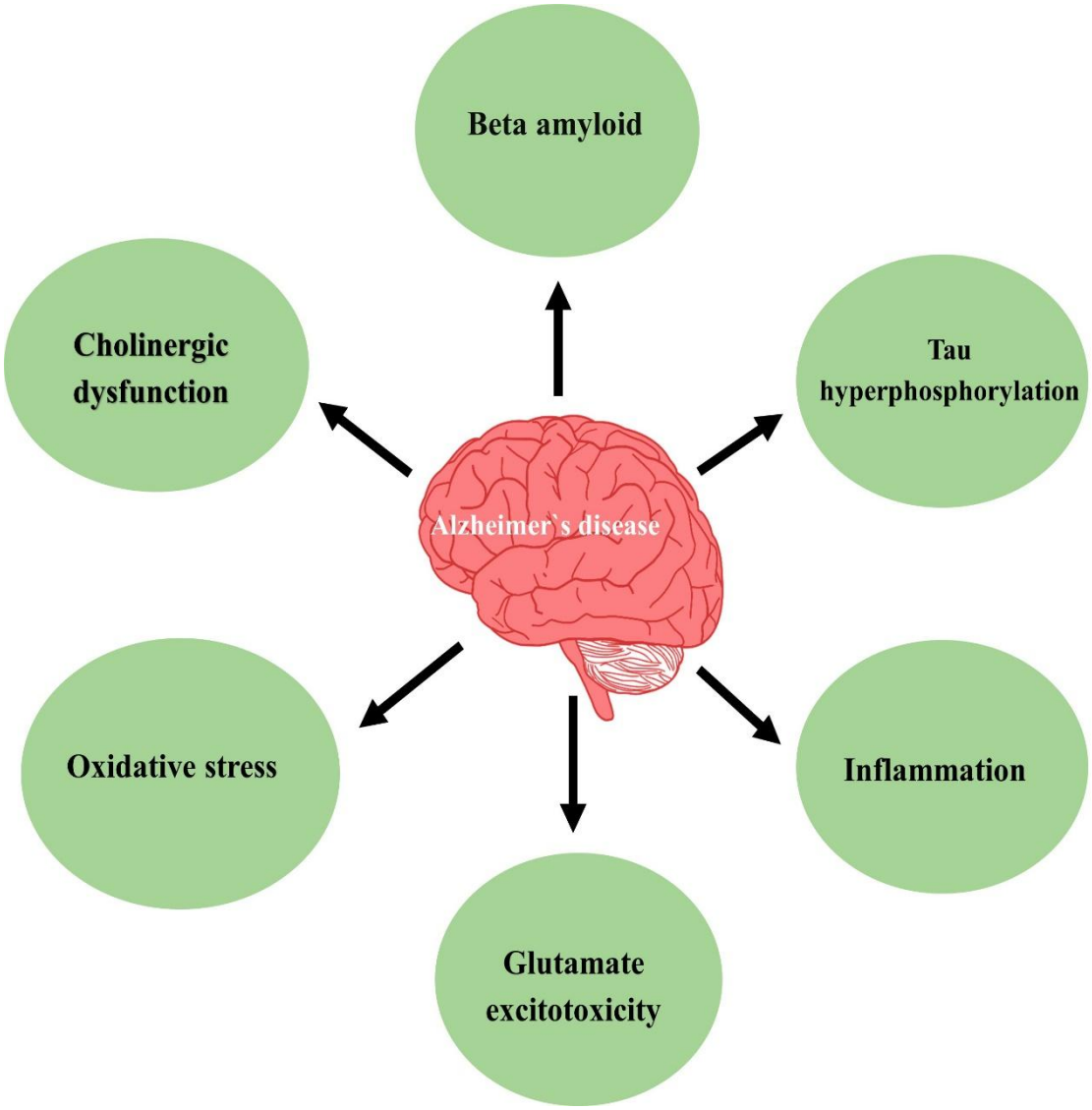

Fig. 2. The proposed hypothesis accepted for the pathology of Alzheimer`s disease.

The Aβ protein deposition in the brain produces a flow of events that could result in AD. In addition, inherited AD is triggered by mutations in the APP or PS1 or 2 genes **(Selkoe and Hardy, 2016; Weitz and Town, 2016).** The common distribution of senile plaques in certain elderly non-demented individuals was shown to be the same as in patients suffering from AD **(Fagan et al., 2009; Ch'etela et al., 2013).** These fragments initially form oligomers, and a series of these oligomers are known as fibrils. The fibrils subsequently cluster into β sheets, which clump into plaques and other sticky things. In Alzheimer's disease brains, plaque development begins with Aβ metabolism, with NFTs acting as secondary metabolites **(Hardy et al., 1998).**

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Several investigations have found that ApoE4 enhances Aβ40 deposition **(Donahue and Johanson, 2008).** APP is a single-pass transmembrane protein which has an extensive extracellular domain that corresponds to the amyloid precursor-like protein family. Despite this, only APP displays an internal Aβ site divergence that results in the formation of an amyloidogenic fragment**.** APP can be metabolized physiologically through two distinct pathways: non-amyloidogenic and amyloidogenic. In the non-amyloidogenic method, APP cleavage in the transmembrane region by γ -secretase, leading to the loss of the complete N-terminal ectodomain and the formation of the transmembrane -C-terminal fragment. Afterward, γ-secretase breaks down the -C-terminal segment around the transmembrane domain in order to produce the p3 (3kDa) peptide that is released to the extracellular milieu, as well as an intracellular C-terminal fragment **(Thinakaran and Koo, 2008; O'Brien and Wong, 2011).**

In contrast, the amyloidogenic method starts with β-secretase breakdown in the extracellular domain, which results in a β-terminal fragment instead of the α-C-terminal fragment generated by the non-amyloidogenic pathway. The β-terminal fragment is subsequently broken down within the transmembrane domain, releasing an undistinguishable intracellular C-terminal fragment and Aβ peptide to the extracellular milieu, which aggregates to form neurotoxic oligomers and fibrils of amyloid that later lead to formation of senile plaques **(O'Brien and Wong, 2011).** The primary toxic isoforms produced by alternative cleavage are Aβ40 and Aβ42/43**.** Aβ42, which is the most hydrophobic and hazardous isoform, is susceptible to forming oligomers, fibrils and amyloid plaques **(Raskin et al., 2015; Ricciarelli and Fedele, 2017).**

An additional explanation for the high concentrations of Aβ peptide is a failure in its clearance mechanism in the brain. Aβ could be cleaned up from the central nervous system (CNS) by different methods including capillary and artery drainage. Nevertheless, these drainage ways can be compromised in cerebral amyloid angiopathy, affecting Aβ removal **(Raskin et al., 2015).** Furthermore, other mechanisms are involved in Aβ clearance such as phagocytosis from microglia, or breakdown of enzymes by the insulin-degrading enzyme (IDE) and neprilysin (NEP) **(O'Brien and Wong, 2011).** If one of these processes is compromised, concentrations of Aβ will increase and cause Aβ monomers and oligomers to accumulate and production of senile plaques in the brain **(Raskin et al., 2015).**

4.2-The cholinergic hypothesis of AD

The nervous system's chemical messengers, neurotransmitters, are essential for maintaining the integrity of neuronal communication. Neurotransmitter system disruptions may cause a cascade of neurological deficits as seen in AD **(Yang et al., 2023).** Comprehending these disturbances is essential for both diagnosis and innovative therapy strategies **(Sharma et al., 2024).** Acetylcholine (ACh) is a vital neurotransmitter used by cholinergic neurons in many biological functions such as attention, stress, memory, wakefulness, sleep, learning and sensory information **(Sarter and Bruno, 1997).** The cholinergic theory of AD was the earliest theory to arise and the most extensively acceptable hypothesis. Given that the most prominent

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neurotransmitters is Ach in the hippocampus, this was first assumed that memory loss was caused by variations in the cholinergic system **(Gron et al., 2006).**

Consequently, the decline in cognitive function is related to the degeneration of cholinergic neurons in the forebrain and the reduction of acetylcholine in the cerebral cortex **(Francis et al., 1999).** For instance, one of the few medications available nowadays for relieving AD symptoms (namely agnosia) is the inhibition of acetylcholinesterase, AchE is responsible for metabolizing acetylcholine. **(Gron et al., 2006).** It was observed that choline acetyl transferase (ChAT) activity decreases in the patients' brains suffering from AD. The decreased activity of ChAT triggers a disruption in the cholinergic system and a decrease in the Ach concentration **(Bowen et al., 1976).** Therefore, it was suggested that increasing ACh concentration could help in AD treatment. Disturbance of cholinergic responses to the brain cortex can damage attention and utilization of instructional signals for decision-making. Insufficient Ach concentrations in the brain can be attributed to either a drop in production or rise in AChE enzymatic activity **(Terry and Buccafusco, 2003).**

The α7 Nicotinic Acetylcholine Receptors (α7 nAChRs) are a unique subtype of nicotinic receptors that have garnered significant attention in Alzheimer's Disease (AD) **(Fontana et al., 2023)**. Nicotinic Acetylcholine Receptors are ion channels that mediate fast synaptic transmission in the central and peripheral nervous systems. They are primarily found in the brain and their presence is particularly prominent in regions like the hippocampus, cortex, and basal ganglia—areas critically involved in cognition and memory **(Sinclair and Kabbani, 2023)**. Structurally, they are composed of five identical α7 subunits arranged symmetrically around a central pore. Each subunit has an extracellular N-terminal domain, four transmembrane domains (M1–M4), and a large intracellular loop between M3 and M4 **(Whiteaker and George, 2023)**. Functionally, their rapid activation and desensitization kinetics set them apart. When an agonist binds, the channel opens swiftly, allowing calcium to enter the cell. This unique behavior plays a crucial role in modulating synaptic plasticity and neuronal excitability **(Singh et al., 2024)**.

4.3-Glutamate excitotoxicity hypothesis

Another neurotransmitter is glutamate which is one of the major excitatory neurotransmitters found in the CNS. Glutamates have a significant role in learning, memory and synaptic plasticity. Excessive levels of glutamate in the brain could eventually result in excitotoxicity and cell death **(Esposito et al., 2013).** In AD patients, overactivation of glutaminergic neurons occurs and glutamate release increases leading to increased concentration of glutamate in the brain. Extra glutamate overstimulates NMDA receptors, triggering an excess of calcium ions to be released in the postsynaptic nerve cells. Elevated calcium ions concentrations may cause the activation of several enzymes leading to a disturbance in normal cellular function and cause cell death **(Kumar et al., 2022).**

Several protein receptors, such as insulin receptors, a7-nAchR, ephrin receptor and cellular prion protein, have been supposed to bind to Aβ peptides, provoking its toxic effects. The N-methyl-D-aspartate (NMDA) receptors have been getting a lot of attention due to their

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role in neurodegenerative mechanisms. The plasmalemma of neurons contains two classes of glutamate receptors: ionotropic and metabotropic receptors **(Selkoe, 2011)**.

After synapse activation, excess glutamate is taken up by glial cells, through their transporter's excitatory amino acids transporters (EAAT 1 and 2). Glutamate is converted into glutamine which is then transported back to presynaptic terminals where it is converted into glutamate by the glutaminase enzyme that restores in vesicles due to the activity of VGLUT1 and 2 vesicular transporters. Glutamate is necessary for forming new neural connections, memory and learning **(Esposito et al., 2013).**

The activation of the NMDA receptor has a crucial function in the management of long-term depression (LTD) and long-term potentiation (LTP) mechanisms. High-frequency motivation of the presynaptic location causes an increase in glutamate release in the synaptic cleft. The mGluRs and AMPA take part in the initial phase, but the NMDA receptors become active once the AMPA and mGluRs are continuously and synchronously activated. The synaptic NR2A containing NMDA receptors activation induces a high increase in calcium ion [Ca^{2+}] in postsynaptic sites, which activates additional events. All of these alterations contribute to the induction of LTP **(Esposito et al., 2013).**

In AD, several astrocytic processes such as glutamate clearance, calcium signaling, extracellular potassium buffering, and energetic metabolism are negotiated **(Acosta, et al., 2017; Rodríguez-Giraldo et al., 2022)**. Glutamate transporters have a critical role in maintaining levels of glutamate beneath the neurotoxic levels. Consequently, the glutamate clearance via these transporters is critical to resist excitotoxicity and neuronal death (**Manisha et al., 2020)**.

This metabolic linking amongst astrocytes and neurons, which is recognized as the glutamate-glutamine cycle, is essential to keep neurotransmission at excitatory synaptic terminals active**.** Simultaneously, this explains the regulation of extracellular glutamate concentration through astrocytes avoids the brain from the damaging effects of extreme glutamate. Extracellular glutamate is hurriedly removed by astrocytes through glutamate transporters, and when this process is interfered with, either by excessive glutamate production or by astrocyte failure, the result is excitotoxic neurotoxicity **(Horino-Shimizu et al., 2023)**.

4.4-Tau protein hypothesis

Tau protein is a microtubule-associated protein that is found in neurons, mainly found in axons. The described function for tau is as a neuronal microtubule-associated protein. Functional tau found as an extremely soluble and natively unfolded protein that binds with tubulin to assemble into microtubules and stabilize its internal structure, in addition to enhancing axonal transport and neurite outgrowth **(Iqbal et al., 2010; Sery et al., 2013).** Recent data suggests that tau has various additional functions. For instance, phosphorylation of tau prevents neurons from acute apoptosis by stabilizing ß-catenin. **(Li et al., 2007).** Additionally, tau regulates both kinesin's anterograde and dynein's retrograde transport to balance the microtubule-dependent axonal transport of biomolecules **(Stokin et al., 2005; Dixit et al., 2008).** The expected progress of therapies for AD and other associated disorders will

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greatly benefit from the mechanistic knowledge of the function of tau, particularly the challenging task of identifying the influences of phosphorylation at various places on tau.

The regulation of tau is done throughout regular homeostasis and stress-induced responses via posttranslational modifications which include glycosylation, glycation, ubiquitination, oxidation and nitration. Phosphorylation, one of the post-translational modifications, has been widely studied. Two to three residues of tau are phosphorylated in healthy brains. However, in other tauopathies and AD, the level of tau phosphorylation is higher, with around nine phosphates per molecule **(Iqbal et al., 1986; Kopke et al., 1993).** Tau hyperphosphorylation may result from a disturbance in the activity balance between tau kinases and tau phosphatases at several potential serine, threonine and tyrosine residues **(Iqbal et al., 2009).** Eventually, hyperphosphorylation of tau causes fibrillization and accumulation into neurofibrillary tangles (NFTs) **(Grundke-Iqbal et al., 1986; Alonso et al., 1996; Sengupta et al., 1998; Alonso et al., 2001; Alonso et al., 2004).**

Particularly, alterations in tau kinases and tau phosphatases expression and/or activation have been reported in AD and other associated diseases **(Liu et al., 2008; Pei et al., 2006; Zhou et al., 2008; Zhou et al., 2009).** When phosphate molecules are bound to tau, the charge balance between tau and microtubules is disrupted, resulting in p-tau monomers detaching from their microtubule host and pursuing aggregation **(Lim et al., 2014).** Once a significant amount of p-tau accumulates, these moieties coalesce to create oligomers, which eventually form PHFs. The formerly soluble AD p-tau becomes insoluble in the PHF and is harder to dissolve **(Alonso et al., 2018).** Normal tau remains present in the AD brain, although at a 60% lower level than in a healthy adult brain **(Alonso et al., 2018; Moore et al., 2023).**

Research studies in transgenic animal models of AD revealed that it is probable that some overlapping mechanisms such as Aß, inadequate brain glucose metabolism and inflammation, participate in the abnormal hyperphosphorylation of tau. One of the great interests in the discovery of therapeutic targets is to understand which of the cellular pathways could mediate posttranslational alterations of tau **(Oddo et al., 2004; Kitazawa et al., 2005; Caccamo et al., 2006; Gong et al., 2006; Liu et al., 2009; Fonseca et al., 2009).**

Furthermore, harmful effects of Aβ, another hallmark of AD, could lead to tau protein hyperphosphorylation, resulting in the formation of paired helictical filaments of neurofibrillary tangles inside neurons **(Raskin et al., 2015).** Even so, tau is also abnormally hyperphosphorylated in AD, which causes it to clump together into filamentous bundles. These filaments are unable to attach to tubulin, which disrupts the microtubules, impairs neurite growth and axonal transport and ultimately results in the death of neurons. As a result, the microtubule network becomes compromised, causing neurofibrillary degeneration **(Iqbal et al., 2010).**

Despite this, it seems that synaptic impairment is more connected with the severity of dementia in patients with AD rather than the amount of Aβ plaques **(Cubinkova et al., 2018; Sun and Alkon, 2019).** Supporting this, in the first 2 to 4 years of the beginning of the disease,

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biopsies of the brain reveal a reduced in synapses (44–55%) **(Sun and Alkon, 2019).** In addition, it appears that spine plasticity seems to be an essential factor of cognitive resilience that protects against dementia in people with AD pathogenesis **(Boros et al., 2017).** Accordingly, it suggests that enhancing synaptic network function is crucial for preventing dementia. The brain contains internal mechanisms for repairing the harm/injuries done to neurons, especially synapsis. These processes are involved in the upregulation of neurotrophins and growth-associated proteins, like the brain-derived neurotrophic factor (BDNF) and the nerve growth factor (NGF)**.**

4.5-Inflammation hypothesis

Neuroinflammation refers to a disorder where inflammation occurs in the central nervous system (CNS) and it might play an essential role in neurodegenerative disorders. Even though the inflammatory response is to defend the body, it can also influence the damage to tissue and disease pathology **(Lyman et al., 2014).** In the CNS, during neuroinflammation, astrocytes and microglial cells become activated **(Morales et al., 2014).** Several studies, in inflammatory mouse models, found that the activation of astrocytes and microglia promotes amyloid deposition **(Guo et al., 2002).** Pro-inflammatory cytokines like TNF-α and -γ, IL-1, -6 and -8 are crucial proteins in charge of triggering inflammatory reactions. These proteins have a protective purpose when they are functioning normally, but when present in excessive amounts, they may damage the brain tissues. (**Hu et al., 2012; Morales et al., 2014).**

The neuroinflammation hypothesis evolved from the idea that microglia and astrocytes play a significant part in the inflammatory stages of AD. Inflammation is beneficial under regular conditions, but excessive inflammation may also be harmful to the organism, involving the brain. Neuroinflammation is found in many neurological and neurodegenerative disorders. Additionally, *in vivo* research demonstrates that moderate cognitive impairment (MCI) patients exhibit neuroinflammation prior to the development of amyloid deposition **(Calsolaro and Edison, 2016).**

However, astrocytes and microglia, the main participants in the inflammatory response in the CNS, perform a double role in AD progression **(Fakhoury, 2018).** Microglial cells can be found in two separate phenotypes, the classically activated or M1 and the alternatively activated or M2. The M1 is activated by the interferon-gamma (IFNγ) or by the Toll-like receptors resulting in pro-inflammatory cytokines release [interleukin (IL) 1β, IL-12, tumor necrosis factor (TNF)-α and inducible nitric oxide synthetase (iNOS)] to destroy invading pathogens. In contrast, the M2 phenotype is motivated by IL-4 and IL-13 resulting in the anti-inflammatory cytokines release that support angiogenesis and tissue repair **(Calsolaro and Edison, 2016; Fakhoury, 2018).**

In fact, Aβ aggregates appear to exacerbate the M1 phenotypic activation causing the release of high amounts of pro-inflammatory cytokines that affect the homeostasis of the brain. However, moderate activation of microglia may help in the elimination of Aβ and result in the

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production of various neuroprotective substances, including BDNF, glial cell-derived neurotrophic factor and the NGF, that exert protective effects. Otherwise, astrocytes are also crucial for maintaining ionic homeostasis, controlling oxidative stress, transmitting neurotransmitters, remodeling synapses and modifying the permeability of the blood-brain barrier (BBB) **(Fakhoury, 2018).**

Additionally, astrocytes might also play a role in the Aβ clearance **(Minter et al., 2016; Fakhoury, 2018).** Nevertheless, AD severity has a strong correlation with astrogliosis within amyloid plaques, it is defined by elevated levels of astrocytes as well as modifications in their morphology and molecular expression **(Minter et al., 2016).** Certainly, despite being neuroprotective, astrocytes may form pro-inflammatory cytokines, like TNF-α and IL-1β**.** Additionally, astrocytes can interact with microglia, changing their state of activation (activating the M1 phenotype), decreasing their ability for phagocytosis and simultaneously increasing the release of pro-inflammatory cytokines **(Fakhoury, 2018).**

4.6-Oxidative stress hypothesis

Excessive formation of free radicals destroys the body's biological antioxidant defense system, causing oxidative stress that downregulates the endogenous defense system **(von Arnim et al., 2012; Anjum et al., 2020).** Neuronal cells are especially vulnerable to free radical damage because they contain a high concentration of unsaturated lipids that are easily oxidized, as well as a high concentration of redox-active transition metals which catalyze the generation of free radicals **(Urano et al., 2015).** Because of its high metabolic requirement and thus high oxygen consumption, the central nervous system is more likely to generate free radicals **(Magistretti and Allaman, 2015).** Also, neurotransmitter metabolism produces free radicals **(Siraki and O'Brien, 2002).**

Additionally, CNS exhibits significantly lower antioxidant defense, making it more susceptible to oxidative stress compared to other organs (such as the liver). **(Salim, 2017; Cobley et al., 2018).** In oxidative stress conditions, dysfunctional mitochondria are not capable of meeting the high energy needed by neuronal cells for their physiological and biochemical functions; thus, they become susceptible to prompt cell death **(Liguori et al., 2018).**

Free radicals/pro-oxidants are naturally molecules having unpaired electrons within their outermost orbit that may form when oxygen reacts with certain molecules **(Phaniendra et al., 2015).** Free radicals are not only unstable but also well reactive and they produce more free radicals when interacting with other molecules, starting a self-replicating chain reaction of the production of free radical. ROS and RNS are both components of free radicals. RNS has both nitrogen and oxygen atoms, whereas ROS are chemically active molecules that include oxygen (O). In addition, cells also produce reactive oxygen and nitrogen species which contain both free and non-free radical types such as hydrogen peroxide (H_2O_2), hydroxyl radical (OH), hypochlorous acid (HClO), nitric oxide (NO), nitrogen dioxide (NO_2), peroxynitrite (OONO), superoxide anion (O_2) and other species. In metal-catalyzed (free Fe and Cu) redox processes

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like the Fenton reaction, the OH radical is generated from H_2O_2 and is markedly unstable. It interacts quickly and unspecifically with a wide range of biological molecules **(Collin, 2019).**

5-Management of AD

Over the last two decades, the study of new pharmacological therapies that target the pathophysiological hallmarks of AD has been prompted by the burgeoning developments in the discipline of pathogenesis. The therapeutic goals in treating AD are to: (1) reduce cognitive symptoms, (2) decrease BPSD and (3) reduce the disease's progression. Currently pharmacotherapy only treats symptoms and mainly focuses on the dysfunction of cholinergic system and glutamatergic system. The advancement of disease-modifying medicines is currently ongoing.

Although AD was recognized a century ago it is still an incurable disease up to date. The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) approved only four medications for the treatment of cognitive symptoms; these medications, however, cannot stop or slow the disease's progression, neurodegeneration, or memory loss. Both the World Health Organization (WHO) and the Global Action Plan on the Public Health Response to Dementia 2017–2025, identified the unmet clinical need of finding a treatment for the disease in 2017. Globally, the total AD cases is currently estimated to be 46.8 million and by 2050 and expected to be 131.5 million in 2050 **(World Health Organization, 2017)** (Fig. 3).

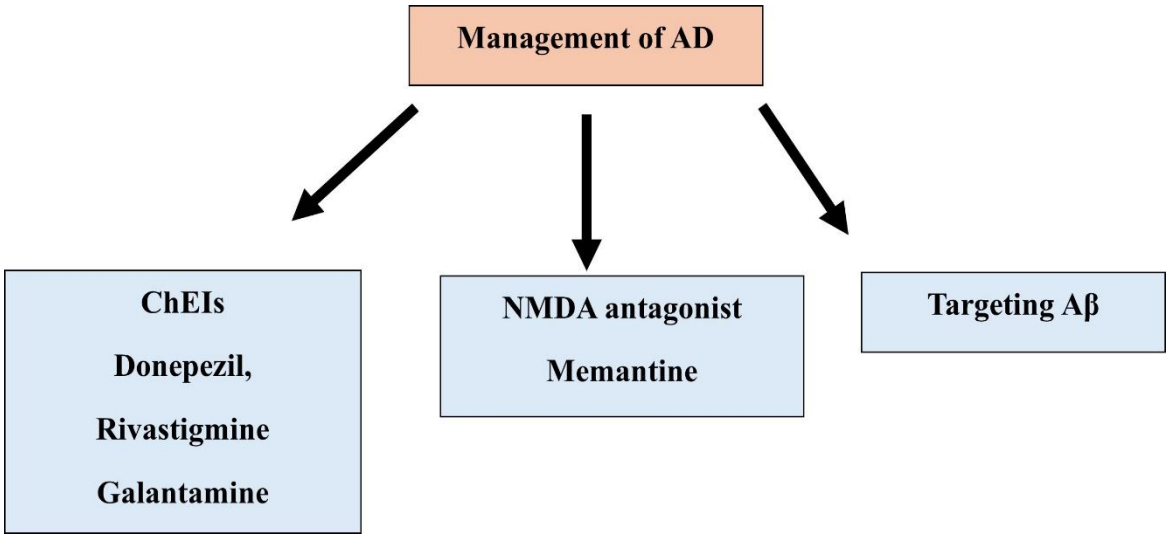

Fig. 3. The medications accepted by the EMA and FDA for the management of AD.

Neurotransmitter improvement therapy by cholinesterase inhibitors (ChEIs) is prescribed for patients having mild-to-moderate AD. Acetylcholinesterase is inhibited by cholinesterase inhibitors in the synaptic cleft, which is responsible for reduction of the hydrolysis of the acetylcholine released via presynaptic neurons and increases cholinergic synaptic transmission. These medications have a modest but discernible therapeutic effect. Tacrine was the first of

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them to be approved for therapeutic use, however it is no longer used due to its liver toxicity. Currently, the three accepted ChEIs for the treatment of mild-to-moderate AD symptoms are Donepezil, rivastigmine and galantamine. Currently, these treatments have also been used to patients with severe AD. Generally, studies on ChEIs were of good quality and exhibited that they can delay the decrease in cognitive function. These advantages are relevant to mild, moderate and severe AD patients **(Birks, 2006; Hansen et al., 2008; Qaseem et al., 2008).**

Targeting Aß in individuals with AD, even in those suffering milder stages of the disease, may not be enough due to the various pathways and subsequent damage induced by the buildup of Aß, even though it is still too early to know the results of these trials. The field will eventually advance to the point where clinical trials are conducted to examine multiple/combination medicines. Finding the most effective therapy combinations is a problem for ongoing preclinical investigations using animal models. For instance, aducanumab, a monoclonal antibody which targets Aβ, has been given preliminary approval by the Food and Drug Administration to treat AD. The decision has been the subject of discussion as it was only authorized due to its ability to lower Aβ levels, yet only a minor effect on clinical cognition measurements was seen for a subgroup of patients **(Høilund-Carlsen et al., 2020; Mullane and Williams, 2020; Mullard, 2021).**

Given its long-standing and important role in the molecular pathogenesis of AD, tau has received remarkably little attention as a therapeutic target, as seen by the clear distinction between clinical studies that target Aß vs. tau. The generation of animal models with tau disease has improved over the past ten years, which is helping to close this gap. **(Medeiros et al., 2011).**

Conclusion

Alzheimer's disease remains one of the most challenging neurodegenerative disorders, with a complex and multifactorial origin that continues to be the subject of intense research. Despite substantial progress in understanding its pathogenesis, including key factors such as amyloid-beta accumulation, tau protein aggregation, and neuroinflammation, the precise mechanisms underlying disease initiation and progression are still not fully elucidated. Several hypotheses, including those centered on genetic, environmental, and vascular factors, provide important insights, yet the search for a definitive cause remains ongoing.

Looking ahead, the future of Alzheimer's management lies in a multifaceted approach, combining advanced diagnostic tools, personalized therapeutic strategies, and more effective pharmacological agents. Further research into the molecular mechanisms of neurodegeneration, along with advancements in neuroimaging and biomarker development, will be key to unlocking new therapeutic targets. The continued progress in basic and clinical research offers hope for more effective treatments and, ultimately, a cure for this devastating disease.

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Conflict of interest statement

The authors declare that there are no competing interests.

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Author's contributions

Safinaz E. Elbaga conducted a literature search, wrote a rough draft and created figures. The study was conceptualized, planned, and conducted by the other authors. The final version of the manuscript has been reviewed and approved by all authors.

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