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Review Article

Review On the Complications and Management of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a disorder that causes degeneration of cells in the brain and is the leading cause of dementia, characterized by a decline in thinking and independence in personal daily activities. AD is considered a multifactorial disease: two main hypotheses have been proposed as the cause of AD, the cholinergic and the amyloid hypothesis. In addition, several risk factors such as increasing age, genetic factors, head injury, vascular disease, infection, and environmental factors play a role in the disease. Currently, there are only two classes of drugs approved for the treatment of AD, including cholinesterase enzyme inhibitors and Nmethyl D-aspartate (NMDA) antagonists, which are effective only in treating the symptoms of AD but do not cure or prevent the disease. Currently, research is focused on understanding the pathology of AD by targeting several mechanisms, such as abnormal tau protein metabolism, β-amyloid, inflammatory response, and cholinergic and free radical damage, in order to develop successful treatments that are able to stop or modify AD progress. This review discusses currently available drugs and future theories for the development of new AD therapies, such as disease-modifying therapeutics (DMTs), chaperones, and natural compounds.Alzheimer's disease (AD) is a disorder that causes degeneration of cells in the brain and is the leading cause of dementia, characterized by a decline in thinking and independence in personal daily activities. AD is considered a multifactorial disease: two main hypotheses have been proposed as the cause of AD, the cholinergic and the amyloid hypothesis. In addition, several risk factors such as increasing age, genetic factors, head injury, vascular disease, infection, and environmental factors play a role in the disease. Currently, there are only two classes of drugs approved for the treatment of AD, including cholinesterase enzyme inhibitors and Nmethyl D-aspartate (NMDA) antagonists, which are effective only in treating the symptoms of AD but do not cure or prevent the disease. Currently, research is focused on understanding the pathology of AD by targeting several mechanisms, such as abnormal tau protein metabolism, β-amyloid, inflammatory response, and cholinergic and free radical damage, in order to develop successful treatments that are able to stop or modify AD

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INTRODUCTION

Alzheimer's disease (AD) (named after the German psychiatrist Alois Alzheimer) is the most common type of dementia and can be defined as a slowly progressive neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles (Figure 1) due to amyloid-beta peptide. (Ap) accumulation in the most affected area of the brain, medial temporal lobe and neocortical structures [1]. Alois Alzheimer noticed the presence of amyloid plaques and massive loss of neurons when examining the brain of his first patient, who suffered from memory loss and personality change before his death, and described the condition as a severe disease of the cerebral cortex. Emil Kraepelin first named this medical condition in his 8th edition of the psychiatric manual [2,3]. Progressive cognitive loss can be caused by a cerebral disorder such as Alzheimer's disease (AD) or other factors such as intoxication, infection, abnormalities in the pulmonary and circulatory systems that cause reduced oxygen supply to the brain, nutritional deficiencies, vitamin B12 deficiency, tumors and more

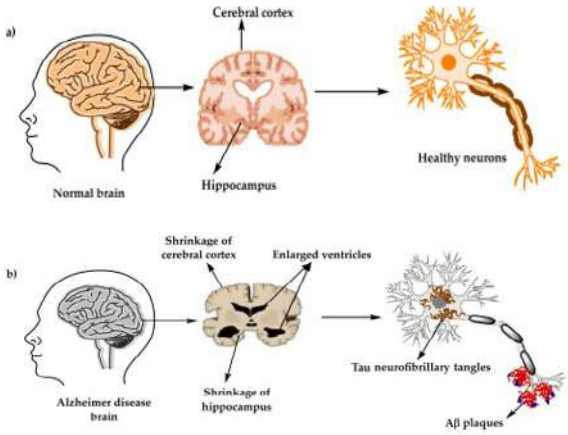

Figure 1. The physiological structure of the brain and neurons in (a) healthy brain and (b) Alzheimer's disease (AD) brain.

Alzheimer's Disease Diagnostic Criteria

A patient with suspected AD should undergo several tests in addition to medical and family history, including neurological examination, magnetic resonance imaging (MRI) for neurons, laboratory tests such as vitamin B12, and other tests [8]. According to some studies, vitamin (vit.) B12 deficiency has long been known to be associated with neurological problems and an increased risk of AD. Special fix vit. B12 deficiency is elevated homocysteine, which can cause brain damage through oxidative stress, increased calcium influx, and apoptosis. Diagnoses vit. B12 deficiency can be done by measuring serum vits. B12 level along with complete blood count and serum homocysteine tests [9,10]. In 1984, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) formed a task force (NINCDS-ADRDA) to establish clinical diagnostic criteria for Alzheimer's disease. These criteria include: (1) probable Alzheimer's disease that can be diagnosed as dementia that is confirmed by neuropsychological testing, progressive memory loss, impaired daily activities, and other symptoms such as aphasia (language disorder), apraxia (motor disorder), and agnosia (loss of perception). All these symptoms can begin at the age of 40-90 years, without any systemic or brain disease, (2) possibly Alzheimer's disease can be applied in the absence of neurological, psychiatric disorders and the presence of another disease such as a systemic or brain disease. however, they are not the primary cause of dementia and (3) definitive Alzheimer's disease as confirmed by histopathological confirmation obtained from biopsy or autopsy [11,12]. In 2011, the National Institute on Aging–Alzheimer's Association made several changes and updated the 1984 NINCDS-ADRDA criteria for greater

specificity and sensitivity in the diagnosis of Alzheimer's disease. The newly proposed criteria include probable and possible AD dementia for use in clinical settings and probable or possible AD dementia with pathophysiological evidence for research purposes, in addition to clinical biomarkers. There are two categories of Alzheimer's disease biomarkers: (a) brain amyloid markers such as positron emission tomography (PET) and cerebrospinal fluid (CSF) and (b) markers of neuronal damage such as cerebrospinal fluid tau, fluorodeoxyglucose (FDG) for metabolic activities, and magnetic resonance imaging (MRI) to measure atrophy

Alzheimer's Disease's Neuropathology

There are two types of neuropathological changes in AD that provide evidence of disease progression and symptoms and include: (1) positive lesions (due to accumulation), which are characterized by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil fibers, and other deposits found in brains of AD patients. In addition to (2) negative lesions (due to losses), which are characterized by extensive atrophy due to neural, neuropil and synaptic loss. In addition, other factors such as neuroinflammation, oxidative stress, and damage to cholinergic neurons can cause neurodegeneration [16–18].

3.1. senile plaques (SP)

Senile plaques are extracellular deposits of beta-amyloid protein (Aβ) with various morphologic forms, including neuritic, diffuse, dense, or classic and compact type plaques. Proteolytic cleavage enzymes such as β-secretase and γ-secretase are responsible for the biosynthesis of Aβ deposits from the transmembrane amyloid precursor protein (APP) [19–21]. These enzymes cleave APP into several amino acid fragments: 43, 45, 46, 48, 49 and 51 amino acids, which reach the final form Aβ40 and Aβ42. There are several types of Aβ monomers, including large and insoluble amyloid fibrils that can accumulate to form amyloid plaques and soluble oligomers that can spread throughout the brain. Aβ plays a major role in neurotoxicity and neural function, therefore the accumulation of denser plaques in the hippocampus, amygdala and cerebral cortex can cause stimulation of astrocytes and microglia, damage to axons, dendrites and loss of synapses in addition to cognitive impairment. [21–23].

3.2. Neurofibrillary tangle

(NFT) NFTs are abnormal filaments of hyperphosphorylated tau protein that can, at some stages, wrap around themselves to form a paired helical filament (PHF) and accumulate in the neuralperikaryal cytoplasm, axons, and dendrites, causing loss of cytoskeletal microtubules and tubulin-associated proteins. Hyperphosphorylated tau protein is a major component of NFTs in the brains of AD patients, and its development may reflect the morphological stages of NFTs, which include: (1) the pre-tangle phase, one type of NFT where phosphorylated tau proteins accumulate in the somatodendritic compartment without PHF formation, (2) mature NFTs, which are characterized by the aggregation of tau protein filaments with nuclear relocation to the peripheral part of the soma and (3) extracellular tangles or Ghost stage NFT, which results from neuronal loss due to large amounts of fibrillar tau protein with partial resistance to proteolysis [24,25].

3.3. Synaptic loss Synaptic damage

in the neocortex and limbic system causes memory impairment and is generally observed in the early stages of AD. Mechanisms of synaptic loss include defects in axonal transport, mitochondrial damage, oxidative stress, and other processes that may contribute to small fractions such as Aβ and tau accumulation at synaptic sites. These processes ultimately lead to the loss of dendritic spines, presynaptic terminals, and axonal dystrophy [26]. Synaptic proteins serve as

biomarkers to detect synapse loss and severity, such as neurogranin, postsynaptic neuronal protein, visinin-like protein-1 (VILIP-1), and synaptotagmin

Stages of Alzheimer's disease

The clinical stages of Alzheimer's disease can be divided into (1) the preclinical or presymptomatic stage, which can last several years or longer. This stage is characterized by mild memory loss and early pathological changes in the cortex and hippocampus, without functional impairment in daily activities and the absence of clinical signs and symptoms of AD [1,29,30]. (2) Mild or early stage AD, when patients begin to show several symptoms, such as difficulties in the patient's daily life with loss of concentration and memory, disorientation of place and time, mood changes and the development of depression [30,31]. (3) Mid-stage AD, when the disease spreads to cortical areas, resulting in increased memory loss with problems recognizing family and friends, loss of impulse control, and difficulties in reading, writing, and speaking [30]. (4) Severe or late-stage AD, which involves spread of the disease throughout the cerebral cortex with severe accumulation of neuritic plaques and neurofibrillary tangles, leading to progressive functional and cognitive impairment where patients do not recognize their family at all. and may be bedridden with difficulty in swallowing and urination and may ultimately lead to the patient's death from these complications [1,32]

5. Causes and risk factors of Alzheimer's disease

AD has been considered a multifactorial disease associated with several risk factors (Figure 2), such as increasing age, genetic factors, head injury, vascular disease, infection, and environmental factors (heavy metals, trace metals, and others). The underlying cause of the pathological changes in Alzheimer's disease (Aβ, NFT and synaptic loss) is still unknown. Several hypotheses have been proposed as the cause of AD, but two of them are considered to be the main cause: some believe that impairment of cholinergic function is a critical risk factor for AD, while others suggest that alteration of amyloid β-protein production and processing is the main initiating factor. However, there is currently no accepted theory to explain the pathogenesis of AD

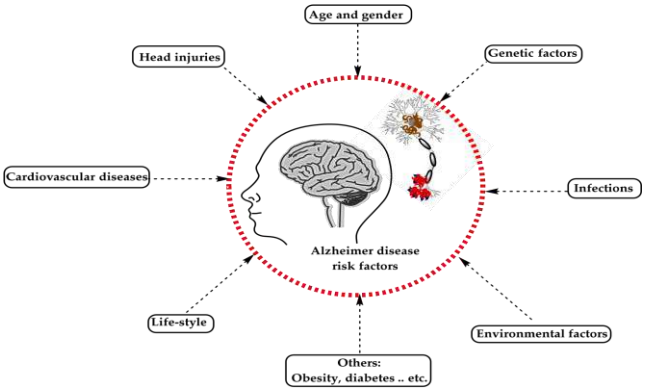

Figure 2. The risk factors for Alzheimer's disease.

Hypotheses of Alzheimer's disease

1. Cholinergic hypothesis In the 1970s, neocortical and presynaptic

cholinergic deficits related to the enzyme choline acetyltransferase (ChAT), which is responsible for the synthesis of acetylcholine (ACh), were reported. Due to the essential role of ACh in cognitive functions, the cholinergic hypothesis of AD has been proposed. ACh is synthesized in the cytoplasm of cholinergic neurons from choline and acetyl coenzyme A by the enzyme ChAT and transported to synaptic vesicles by the vesicular acetylcholine transporter (VAChT) (Figure 3). In the brain, ACh is involved in several physiological processes such as memory, attention, sensory information, learning and other critical functions. Cholinergic neurons have been found to degenerate in AD, causing alternating cognitive function and memory loss. B-amyloid is thought to affect cholinergic neurotransmission and cause a decrease in choline uptake and ACh release. Studies have shown that cholinergic synaptic loss and amyloid fibril formation are

related to the neurotoxicity of Aβ oligomers and the interaction between AChE and Aβ peptide. Other factors contribute to the progression of AD, such as the reduction of nicotinic and muscarinic (M2) Ach receptors, located on presynaptic cholinergic terminals, and deficits in excitatory amino acid (EAA) neurotransmission, where glutamate concentrations and daspartate uptake are significantly reduced in many cortical areas in brain A.D. This is in addition to the use of cholinergic receptor antagonists such as scopolamine, which has been found to induce amnesia. This effect can be reversed by using compounds that activate the formation of acetylcholine [35–37]. Consequently, the cholinergic hypothesis is based on three concepts: decreased presynaptic cholinergic markers in the cerebral cortex, severe neurodegeneration of the nucleus basalis of Meynert (NBM) in the basal forebrain, which is the source of cortical cholinergic innervation, and the role of cholinergic antagonists Memory decreases compared to agonists that have the opposite effect

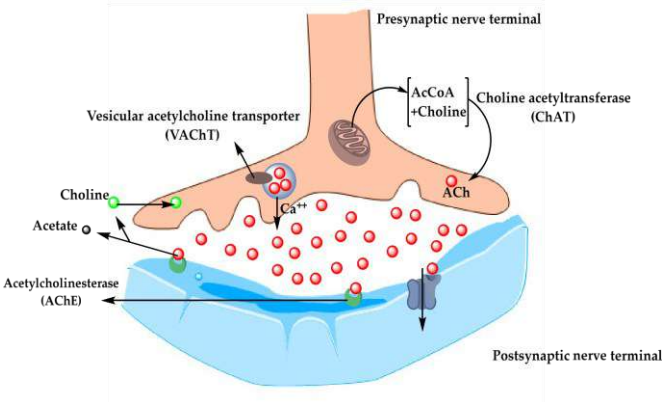

Figure 3. The pathway for the synthesis and transportation of acetylcholine between presynaptic and postsynaptic nerve terminals.

The amyloid hypothesis For decades, abnormal β-sheet deposition in the central nervous system has been found to be strongly correlated with dementia, leading to the concept of the amyloid hypothesis. However, amyloid plaques (AP) have also been found to be deposited in normal healthy brains with aging, raising the question of whether AP deposition is responsible for the onset of AD or not? Therefore, alternative hypotheses for the non-inherited form of AD (NIAD) have been proposed in recent years, but currently the amyloid hypothesis remains the most accepted pathological mechanism for hereditary AD (IAD). The amyloid hypothesis suggests that the degradation of Aβ, derived from APP by β- and γ-secretase, is reduced by age or pathological conditions, leading to the accumulation of Aβ peptides (Aβ40 and Aβ42). An increase in the Aβ42/Aβ40 ratio induces the formation of Aβ amyloid fibrils, which leads to neurotoxicity and the induction of tau pathology, and subsequently leads to neuronal cell death and neurodegeneration. AD risk factors and mutations of several genes such as APP, PSEN1, and PSEN2 have been found to affect Aβ catabolism and anabolism, rapidly causing Aβ accumulation and rapid progression of neurodegeneration [39–41]. Risk factors for Alzheimer's disease. Aging The most important risk factor for AD is aging. Younger individuals rarely have the disease, and most cases of AD have a late onset, starting after age 65 [42]. Aging is a complex and irreversible process that occurs through multiple organs and cellular systems with reduction in brain volume and weight, loss of synapses, and ventricular enlargement in specific regions accompanied by SP and NFT deposition. In addition, several conditions such as glucose hypometabolism, cholesterol dyshomeostasis, mitochondrial dysfunction, depression, and cognitive decline can occur during aging. These changes also occur during normal aging, making it difficult to distinguish cases in early AD [43,44]. AD can be divided based on age of onset into early-onset AD (EOAD), a rare form with approximately 1–6% of cases, most of which are familial AD characterized by having more than one member in more than one generation. with AD and ranges from 30-60 or 65 years. The second type is late

onset AD (LOAD), which is more common with age of onset over 65 years. Both types can occur in individuals with a positive family history of AD and families with late onset of the disease [45]. Genetics Genetic factors have been discovered over the years and have been found to play a major role in the development of AD. 70% of AD cases have been linked to genetic factors: most cases of EOAD are inherited in an autosomal dominant pattern and mutations in dominant genes such as amyloid precursor protein (APP), presenilin-1 (PSEN-1), presenilin-2 (PSEN-2) and apolipoprotein E (ApoE) are associated with AD [46,47]. Here we discuss the strong genetic risk factors for AD. • Amyloid precursor protein (APP) APP is a type I transmembrane protein cleaved by α-, β-, and γ-secretase to release Aβ and other proteins and is encoded by the APP gene on chromosome 21. Thirty mutations have been found in the APP gene, twenty-five of which are associated with AD and cause accumulation of Aβ with an increased amount. Meanwhile, there is one protective mutation, A673T, which protects against AD by reducing the secretion of Aβ, Aβ40 and Aβ42 [48,49]. All mutations surround the secretase cleavage site, for example, the KM670/671NL mutation in mouse models showed increased levels of amyloid plaques in the hippocampus and cortex without NFTs. Mutations A673V, D678H, D678N, E682K and K687N showed cortical atrophy, while E682K showed hippocampal atrophy. Neuropathological reports for the A673V mutation demonstrated the presence of NFTs and Aβ, activation of microglia and astrocytes, and neuronal loss compared to the rest of the aforementioned mutations, which according to neuropathological reports show no change in intracellular Aβ [48,50]. Other mutations such as T714I, V715A, V715M, V717I, V717L, L723P, K724N and I716V affect the γ-secretase cleavage site and cause an increase in the Aβ42/Aβ40 ratio, while E692G and E69ec cleave the E6ec mutation of D69av and cause polymorphic aggregates with the ability disrupt the integrity of the bilayer. E693delta is also a deletion mutation that increases the generation of synaptotoxic Aβ [51,52].

Risk factors for Alzheimer's disease

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(ApoE) are associated with AD [46,47]. Here we discuss the strong genetic risk factors for AD. • Amyloid precursor protein (APP) APP is a type I transmembrane protein cleaved by α-, β-, and γ-secretase to release Aβ and other proteins and is encoded by the APP gene on chromosome 21. Thirty mutations have been found in the APP gene, twenty-five of which are associated with AD and cause accumulation of Aβ with an increased amount. Meanwhile, there is one protective mutation, A673T, which protects against AD by reducing the secretion of Aβ, Aβ40 and Aβ42 [48,49]. All mutations surround the secretase cleavage site, for example, the KM670/671NL mutation in mouse models showed increased levels of amyloid plaques in the hippocampus and cortex without NFTs. Mutations A673V, D678H, D678N, E682K and K687N showed cortical atrophy, while E682K showed hippocampal atrophy. Neuropathological reports for the A673V mutation demonstrated the presence of NFTs and Aβ, activation of microglia and astrocytes, and neuronal loss compared to the rest of the aforementioned mutations, which according to neuropathological reports show no change in intracellular Aβ [48,50]. Other mutations, such as T714I, V715A, V715M, V717I, V717L, L723P, K724N, and I716V affect the γ-secretase cleavage site and cause an increase in the Aβ42/Aβ40 ratio, while E692G and rettation of E6ec cleavage mutation D69av and cause polymorphic aggregates with the ability disrupt the integrity of the bilayer. E693delta is also a deletion mutation that increases the generation of synaptotoxic Aβ [51,52]. • Presenilin-1 (PSEN-1) and Presenilin-2 (PSEN-2) The PSEN1 and PSEN2 genes are also an autosomal dominant form of EOAD located on chromosomes 14 and 1, respectively. PSEN-2 and PSEN-1 are homologous, with 67% similarity, with a difference in the N-terminus and hydrophilic region. A mutation in the PSEN1 gene with more than 200 mutations is more common, while a rare form with less than 40 mutations has been identified in the PSEN2 gene [53,54]. PSEN1 is a core protein that activates the γ-secretase complex and plays an important role in the production of Aβ from APP. Knockout studies of PSEN1 have shown synaptic dysfunction and memory impairment in mice, indicating its essential role in memory and neuronal maintenance [51]. PSEN1 mutations are simple, involving a single amino acid substitution, and a severe mutation can result from two amino acid substitutions [55]. Mutations in the PSEN1 gene increase the Aβ42/Aβ40 ratio by reducing Aβ40 levels. The results obtained by Sun et al. study demonstrated that C410Y or L435F mutations in PSEN1 knock-in mice increased the Aβ42/Aβ40 ratio due to greater Aβ40 reduction [56]. In contrast, PSEN-2 mutations are rare and play a minor role in Aβ production. Any mutation in PSEN-2 can have a severe effect on the Aβ 42/40 ratio and cause familial AD in the presence of normal PSEN-1 alleles. Some of the PSEN-2 mutations cause a significant increase in γ-secretase activity with an increase in Aβ-42 and Aβ 42/40 ratio levels, such as N141I, T122P, M239V, and M239I, while others are rare polymorphisms and have no effect on Aβ ratio levels. 42, -40 and Aβ 42/40 and are not considered to be pathogenic mutations [53,57]. • Apolipoprotein E (ApoE) ApoE protein is a glycoprotein highly expressed in liver and brain astrocytes and some microglia and serves as a receptor-mediated endocytosis ligand for lipoprotein particles such as cholesterol, which is essential for myelin production and normal brain function. The ApoE gene located on chromosome 19 has three isoforms, ApoE2, ApoE3 and ApoE4, due to single nucleotide polymorphisms (SNPs) that cause changes in the coding sequence. The ApoEε4 allele is a strong risk factor for both

EOAD and LOAD compared to the ApoEε2 and ApoEε3 alleles, which are associated with a lower risk and a protective effect, respectively [58]. ApoEε4 plays an important role in the deposition of Aβ as a senile plaque and causes cerebral amyloid angiopathy (CAA), which is known as a marker of AD [59]. ApoEε4 has also been shown to be associated with vascular damage in the brain, leading to the pathogenesis of AD [60]. • ATP Binding Cassette Transporter A1 (ABCA1) Adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1) is part of a large family of ABC transporters that regulate cholesterol efflux in the circulation, such as apolipoprotein-AI (ApoAI), and into the brain, such as ApoE. In addition, ABCA1 maintains the stability of ApoE lipidation and serves as a mediator of high-density lipoprotein (HDL) formation, reflecting its role in atherosclerosis and cardiovascular disease. Studies in a mouse model of AD have shown that ABCA1 deficiency increases amyloid plaques and eliminates ApoE lipidation [61]. In humans, mutation in ABCA1 results in Tangier disease, which is characterized by low plasma levels of high-density lipoprotein (HDL) and ApoAI, tissue cholesterol accumulation, and AD pathogenesis. [62]. • Clusterin gene (CLU) and bridging integrator 1 (BIN1) Unlike PSEN1, PSEN2, and APP mutations, which result in familial or EOAD, clusterin (CLU) and bridging integrator 1 (BIN1) genes are novel risk factors for LOAD. In 2009, Genome-Wide Association Studies (GWAS) identified the CLU gene located on a chromosome.

• **Other genes** Other gene polymorphisms associated with an increased risk of AD include the vitamin D receptor (VDR) gene polymorphism, which affects the affinity of vitamin D to its receptor and can cause neurodegenerative disease and neuronal damage [73]. Additionally, epigenetic factors such as DNA methylation, histone and chromatin modifications have been shown to be involved in AD

. Environmental factors Aging and genetic risk factors cannot explain all cases of AD. Environmental risk factors including air pollution, diet, metals, infections, and many others can induce oxidative stress and inflammation and increase the risk of developing AD. Here we present the most important environmental factors and their relationship to AD [75,76].

• **Air pollution** Air pollution is characterized by changing the nature of the atmosphere by introducing chemical, physical or biological pollutants. It is associated with respiratory and cardiovascular diseases and has recently been documented to be associated with AD. Six air pollutants have been defined by the National Air Quality Standards (NAAQS) in the US as a threat to human health, including ozone (O3), nitrogen oxides (NOx), carbon monoxide (CO), particulate matter (PM), sulfur. . oxide (SO2) and lead. Studies in animal and cell models have shown that exposure to high levels of air pollution can lead to damage to the olfactory mucosa and bulb, in addition to the frontal cortex, similar to AD. In individuals exposed to air pollutants, there is an association between oxidative stress, neuroinflammation and neurodegeneration with the presence of hyperphosphorylated tau and Aβ plaques in the frontal cortex. Air pollution can cause an increase in Aβ42 formation, accumulation and cognitive impairment [77,78].

• **Diet** In recent years, the number of studies on the role of nutrition in AD has increased. Several dietary supplements, such as antioxidants, vitamins, polyphenols, and fish, have been reported to reduce the risk of AD, while saturated fatty acids and high caloric intake have been associated with an increased risk of AD [79]. Food processing causes the degradation of heat-

sensitive micronutrients (e.g. vitamin C and folates), the loss of large amounts of water, and the formation of toxic secondary products (advanced glycation end products, AGEs) from the non-enzymatic glycation of free amino groups. in proteins, lipids and nucleic acids. The toxic effect of AGEs is characterized by their ability to induce oxidative stress and inflammation by modifying the structure and function of cell surface receptors and body proteins. Various studies have shown that elevated serum AGEs are associated with cognitive decline and AD progression. The AGE receptor (RAGE) is found in various locations in the body, including microglia and astrocytes, and has been found to be overexpressed in the brain of AD patients and serves as a transporter and cell surface receptor for Aβ [80]. Malnutrition is another risk factor for AD. Deficiencies in nutrients such as folate, vitamin B12, and vitamin D can cause cognitive decline, in addition to AD patients having problems with eating and swallowing, which may increase the risk of malnutrition [81].

Medical factors Several risk factors are associated with the onset of Alzheimer's disease. In addition to this list, older people with AD usually have health problems such as cardiovascular disease (CVD), obesity, diabetes, and more. All of these conditions are associated with an increased risk of AD [88,89].

• **Cardiovascular disease** (CVD) CVDs are recognized as an important risk factor for AD, such as stroke, which is associated with an increased risk of dementia due to loss of neural tissue, increases the degenerative effect, and affects amyloid and tau pathology. Atrial fibrillation also causes embolism, which leads to stroke and decreased memory and cognitive function. In addition, heart failure affects the pumping function of the heart and results in insufficient blood flow to the body and hypoperfusion of the brain, leading to hypoxia and nerve damage. The ischemic heart disease hypothesis suggests that atherosclerosis, peripheral artery disease, hypoperfusion, and embolism are all associated with an increased risk of AD. Hypertension is associated with vessel wall thickening and lumen narrowing, which reduces cerebral blood flow and, in chronic cases, can cause cerebral edema, all of which are considered risk factors for AD and CVD. CVD is a modifiable risk factor and focusing on its relationship with AD may lead to prevention and delay of the disease [89,90].

• **Obesity and diabetes** Obesity is the term used for having too much body fat in individuals as a result of consuming more calories than they burn and can be calculated using the body mass index (BMI). Increased body fat is associated with reduced blood flow to the brain, which promotes cerebral ischemia, memory loss, and vascular dementia. Obesity, unhealthy diet and other factors can cause impaired glucose tolerance (IGT) or diabetes, which is characterized by hyperglycemia affecting peripheral tissues and blood vessels. Chronic hyperglycemia can induce cognitive impairment due to increasing amyloid-beta accumulation, oxidative stress, mitochondrial dysfunction, and neuroinflammation. Obesity is characterized by increased secretion of pro-inflammatory cytokines from adipose tissue, which stimulate macrophages and lymphocytes and ultimately lead to local and systemic inflammation. This inflammation promotes insulin resistance, hyperinsulinemia and subsequently hyperglycemia. Obesity is a well-known risk factor for type 2 diabetes, CVD, and cancer, which are identified as risk factors for dementia and AD. Brain inflammation causes an increase in microglia and results in reduced synaptic plasticity and impaired neurogenesis. Microglia can affect insulin receptor substrate 1 (IRS-1) and

block intracellular insulin signaling, which has an important role in neural health. Alteration of insulin action may therefore lead to Aβ accumulation and reduce tau protein degradation associated with AD [91–94] . Treatment There are currently approximately 24 million cases of Alzheimer's disease reported worldwide, and by 2050, the total number of people with dementia is expected to increase fourfold. Although AD is a public health concern, there are currently only two classes of drugs approved for the treatment of AD, including cholinesterase enzyme inhibitors (naturally derived, synthetic, and hybrid analogs) and N-methyl D-aspartate (NMDA) antagonists.). Several physiological processes in AD destroy ah-producing cells that reduce cholinergic transmission through the brain. Classified as reversible, irreversible and pseudoreversible, acetylcholinesterase inhibitors (AChEIs) work by blocking the cholinesterase enzymes (AChE and butyrylcholinesterase (BChE)) from breaking down ACh, leading to an increase in ACh levels in the synaptic cleft [95–97] . On the other hand, excessive NMDAR activation leads to increased levels of Ca2+ influx, which promotes cell death and synaptic dysfunction. An NMDAR antagonist prevents excessive activation of the NMDAR glutamate receptor and thereby Ca2+ influx and restores its normal activity. Despite the therapeutic effect of these two classes, they are effective only in treating the symptoms of AD, but do not cure or prevent the disease [98,99]. Unfortunately, only a few clinical trials with AD have been initiated in the last decade and have resulted in major failures. Several mechanisms have been proposed to understand AD pathology in order to modify its pathway and develop successful treatments, which include abnormal tau protein metabolism, β-amyloid, inflammatory response, and cholinergic and free radical damage [30,100]. On the other hand, most modifiable risk factors for AD, such as cardiovascular habits or lifestyle, can be prevented without medical intervention. Studies have shown that physical activity can improve brain health and reduce AD by activating brain vascularization, plasticity, neurogenesis, and reducing inflammation by reducing Aβ production, all of which lead to improved cognitive function in the elderly. In addition, a Mediterranean diet (MD), intellectual activity, and higher education may reduce AD progression and memory loss and increase brain capacity and cognitive function. Several studies have revealed that a multidomain intervention that includes lifestyle (diet, exercise, and cognitive training), depression of AD symptoms, and control of cardiovascular risk factors can increase or maintain cognitive function and prevent new cases of AD in the elderly [101]. Here, we summarize currently available drugs and theories for the development of new AD therapies.

Treatment

There are currently approximately 24 million cases of Alzheimer's disease reported worldwide, and by 2050, the total number of people with dementia is expected to increase fourfold. Although AD is a public health concern, there are currently only two classes of drugs approved for the treatment of AD, including cholinesterase enzyme inhibitors (naturally derived, synthetic, and hybrid analogs) and N-methyl D-aspartate (NMDA) antagonists.). Several physiological processes in AD destroy ah-producing cells that reduce cholinergic transmission through the brain. Classified as reversible, irreversible and pseudoreversible, acetylcholinesterase inhibitors (AChEIs) act by blocking the cholinesterase enzymes (AChE and butyrylcholinesterase (BChE)) from breaking down ACh, leading to an increase in ACh levels in the synaptic cleft [95–97] . On the other hand, excessive NMDAR activation leads to increased levels of Ca2+ influx, which promotes cell death and synaptic

dysfunction. An NMDAR antagonist prevents excessive activation of the NMDAR glutamate receptor and thereby Ca2+ influx and restores its normal activity. Despite the therapeutic effect of these two classes, they are effective only in treating the symptoms of AD, but do not cure or prevent the disease [98,99]. Unfortunately, only a few clinical trials with AD have been initiated in the last decade and have resulted in major failures. Several mechanisms have been proposed to understand AD pathology in order to modify its pathway and develop successful treatments, which include abnormal tau protein metabolism, β-amyloid, inflammatory response, and cholinergic and free radical damage [30,100]. On the other hand, most modifiable risk factors for AD, such as cardiovascular habits or lifestyle, can be prevented without medical intervention. Studies have shown that physical activity can improve brain health and reduce AD by activating brain vascularization, plasticity, neurogenesis, and reducing inflammation by reducing Aβ production, all of which lead to improved cognitive function in the elderly. In addition, a Mediterranean diet (MD), intellectual activity, and higher education may reduce AD progression and memory loss and increase brain capacity and cognitive function. Several studies have revealed that a multidomain intervention that includes lifestyle (diet, exercise, and cognitive training), depression of AD symptoms, and control of cardiovascular risk factors can increase or maintain cognitive function and prevent new cases of AD in the elderly [101]. Here, we summarize currently available drugs and theories for the development of new AD therapies.

Symptomatic treatment

AD Cholinesterase inhibitors According to the cholinergic hypothesis, AD is caused by a decrease in the biosynthesis of acetylcholine (ACh). Increasing cholinergic levels by inhibiting acetylcholinesterase (AChE) is believed to be one treatment strategy that improves cognitive function and nerve cell function. AChEIs are used to inhibit the degradation of acetylcholine at synapses, leading to continuous accumulation of ACh and activation of cholinergic receptors. Tacrine (tetrahydroaminoacridine) (1, Figure 4) was the first cholinesterase inhibitor drug approved by the FDA for the treatment of AD, which works by increasing ACh in muscarinic neurons, but it was withdrawn from the market immediately after its launch. to the high incidence of side effects such as hepatotoxicity and the lack of benefit observed in several studies. Later, several AChEIs such as donepezil (2, Figure 4), rivastigmine were introduced and are currently used for the symptomatic treatment of AD [34,97,102,103]. Another strategy that may help in the treatment of AD is to increase choline reuptake and, as a result, increase acetylcholine synthesis at presynaptic terminals. This can be achieved by targeting the choline transporter (CHT1), which is responsible for supplying choline for ACh synthesis. The development of drugs that are able to increase CHT1 at the plasma membrane may become a future therapy for AD [36]. • Donepezil Donepezil (2, Figure 4) is an indanone benzylpiperidine derivative and a second-generation AChEI and is considered a major drug in the treatment of AD. Donepezil binds reversibly to acetylcholinesterase and inhibits the hydrolysis of acetylcholine, leading to a higher concentration of ACh at the synapses. The drug is well tolerated with mild and transient cholinergic side effects that are related to the gastrointestinal and nervous systems. Of note, donepezil has been used to treat AD symptoms such as improving cognition and behavior without altering AD progression [104–106]. • Rivastigmine Rivastigmine (3, Figure 4) is a pseudo-irreversible inhibitor of AChE and butyrylcholinesterase (BuChE) that acts by

binding to the two active sites of AChE (anionic and ester sites), resulting in the prevention of ACh metabolism. BuChE is found mostly in glial cells with only 10% of AChE activity in normal brain, while in AD brain its activity is increased to 40–90% while ACh activity is simultaneously decreased, suggesting that BuChE action may indicate moderate to severe dementia.

Rivastigmine dissociates more slowly than AChE, therefore it is called pseudo-irreversible and undergoes metabolism at the AChE and BuChE synapse. The drug is used in mild to moderate cases of AD. It improves cognitive functions and daily life activities. Oral administration of the drug is associated with adverse effects such as nausea, vomiting, dyspepsia, asthenia, anorexia and weight loss. These side effects are in many cases the main reason for stopping the use of the drug, but they can be compensated for over time and the drug is then easier to take. Rivastigmine can be administered by transdermal patches for controlled and continuous delivery of the drug through the skin with increased tolerability and caregiver satisfaction. Patches can also provide a lower dose compared to pills, resulting in fewer side effects. Most AD patients suffer from memory loss and swallowing problems that affect their adherence to oral medications at regular intervals. Therefore, the use of transdermal patches is the most suitable method for drug delivery in AD patients [107–110].

• **Galantamine** (GAL) Galantamine (4, Figure 4) is considered a standard first-line drug in mild to moderate AD. GAL is a selective tertiary isoquinoline alkaloid with a dual mechanism of action in which it acts as a competitive inhibitor of AChE and can allosterically bind to and activate the α-subunit of nicotinic acetylcholine receptors. GAL can improve behavioral symptoms, daily activities, and cognitive performance with good efficacy and tolerability, similar to other AChE inhibitors. Several delivery systems have been developed to improve drug delivery to the brain: Wahba et al. attached GAL to cerium-containing hydroxyapatite particles for selective drug delivery to affected areas in the brain. Misra et al. and Fornaguera et al. used solid lipid nanoparticles and nanoemulsification approaches to deliver GAL hydrobromide. The results of these studies have shown a promising strategy for safe drug delivery. Hanafy et al. developed GAL hydrobromide/chitosan nasal complex nanoparticles that showed good pharmacological efficacy, while Woo et al. used a patch system as a carrier for a controlled release drug formulation [111–114]. 6.1.2. N-methyl D-aspartate (NMDA) antagonists. NMDAR is thought to have a dominant role in the pathophysiology of AD. NMDAR stimulation leads to Ca2+ influx, which activates signal transduction and subsequently triggers gene transcription necessary for the formation of long-term potentiation (LTP), which is important for synaptic neurotransmission, plasticity and memory formation. Excessive NMDAR activation causes abnormal levels of Ca 2+ signaling and excessive stimulation of glutamate, the primary excitatory amino acid in the CNS, resulting in excitotoxicity, synaptic dysfunction, neuronal cell death, and cognitive decline. Several noncompetitive NMDAR antagonists have been developed and entered clinical trials, but most have failed due to low efficacy and side effects. Memantine (5, Figure 4) is the only approved drug in this category for the treatment of moderate to severe AD; in addition, other noncompetitive NMDAR antagonist compounds are in development, such as RL-208 (3,4,8,9-tetramethyltetracyclo[4.4.0.03,9.04,8]dec-1-yl)methylamine hydrochloride), a polycyclic amine compound that can have a promising therapeutic effect in age-related cognitive problems and AD [115–117]

CONCLUSIONS

Alzheimer's disease is now considered a global health problem; subsequently, the National Institute on Aging–Alzheimer's Association reclassified and updated the 1984 NINCDS-ADRDA criteria for greater specificity, sensitivity, and early identification of patients at risk of developing AD. Several criteria have been proposed for a more accurate diagnosis of AD, including clinical biomarkers, body fluids, and imaging studies. Despite this, the treatment of AD remains symptomatic without changing the prognosis of the disease. Cholinesterase enzyme inhibitors such as galantamine, donepezil, and rivastigmine and NMDA antagonists such as memantine improve memory and alertness but do not prevent progression. Several studies have shown that modifying lifestyle habits, such as diet and exercise, can improve brain health and reduce AD without medical intervention and is considered the first-line intervention for all AD patients. Recently, research has focused on the pathological features of AD such as Aβ and p-tau. Future therapies, such as disease-modifying therapies, may alter AD progression by targeting the Aβ pathway, and many drugs have entered clinical trials, such as AN-1792, solanezumab, bapineuzumab, semagacestat, avagacestat, and tarenflurbil, but have not demonstrated efficacy in late clinical stages. Other DMTs are still under investigation, such as those targeting Aβ and tau pathology, such as aducanumab, gantenerumab, crenezumab, tideglusib, lithium, and others. Other promising compounds called chaperones, such as heat shock proteins and vacuolar sorting protein 35 (VPS35), work by helping other proteins to function normally and arrive safely at their destination in the cell, and therefore may be used as treatments for neurodegenerative diseases. In addition, natural extracts used in traditional Chinese medicine have shown great potential in the treatment of AD by acting on several mechanisms. In conclusion, it can be said that the success of AD treatment depends on its early administration and monitoring of the patient's disease progression using biomarker diagnostics. Future therapies that target tau pathology and the use of combination therapy may have the potential to slow the progression of AD pathology. There is an urgent need to design a potent, selective and effective drug to treat AD patients and those at risk of developing the disease. Author contributions: Literary research and writing of the first draft was carried out by Z.B. and the final draft, including revisions, was prepared by R.K. All authors have read and agree to the published version of the manuscript. Funding: This research received no external funding. Conflict of interest.

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