

## A Comprehensive Review on Alzheimer's Disease its Pathogenesis, Epidemiology, Diagnostics and Treatment

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### ABSTRACT

The global impact of Alzheimer's disease (AD) is significant. The current prevalence of Major Neurocognitive Disorder is estimated to affect approximately 44 million individuals. Presently, the United States harbors a population of approximately 6.2 million individuals who are afflicted by Alzheimer's disease (AD) dementia. It is of significance to highlight that mortality associated with Alzheimer's disease (AD) exceeds the combined mortality rates of both breast cancer and prostate cancer. Based on the findings of the National Institute on Aging, the frequency of Alzheimer's disease (AD) exhibits a twofold rise every five years subsequent to attaining the age of 65. Furthermore, with the ongoing process of population aging, an increasingly substantial portion of the population is affected by this particular condition. Based on forecasts, it is anticipated that the United States will experience a financial impact of \$355 billion in 2021 as a result of Alzheimer's disease (AD).

Furthermore, same projections indicate that this amount is expected to increase significantly to over \$1.5 trillion by the year 2050. As a result, this would place a significant financial strain on the country. Alzheimer's disease (AD) is a neurodegenerative condition that is distinguished by the existence of extracellular amyloid  $\beta$  ( $A\beta$ ) plaques and intracellular neurofibrillary tangles consisting of hyperphosphorylated  $\tau$ -protein. The aforementioned abnormal characteristics primarily present themselves inside the cortical and limbic regions of the human brain. The aforementioned ailment is characterized by the presence of memory impairment and a progressive deterioration of neurocognitive abilities. The atypical division of amyloid precursor protein (APP) by  $\beta$ -secretases and  $\gamma$ -secretases leads to the production of  $A\beta_{40}$  and  $A\beta_{42}$  individual molecules, which then undergo the process of oligomerization and aggregation, finally culminating in the formation of senile plaques. The aforementioned disease is additionally aggravated by pathogenic microorganisms, including the human immunodeficiency virus (HIV).

Moreover, within the framework of disease pathophysiology, the presence of heightened amounts of  $A\beta$  peptides within the central nervous system induces the infiltration of microglial cells. Presently, there exists a notable focus within the realm of scientific inquiry on gaining a comprehensive understanding of the pathological nature of Alzheimer's disease (AD) by means of exploring diverse pathways.

These mechanisms include the abnormal metabolism of tau proteins, the presence of  $\beta$ -amyloid, the inflammatory response, as well as the damage caused by cholinergic dysfunction and free radicals. The ultimate objective of this research is to develop efficacious treatments that can effectively halt or alter the progression of AD. The present study provides an analysis of the pathophysiological mechanisms underlying Alzheimer's disease, as well as an examination of the diagnostic methods employed in its identification. Furthermore, the review explores the many therapy modalities now utilized in managing this neurodegenerative disorder.

**Keywords-** Alzheimer disease, Diagnosis, Pathogenesis, Therapeutic effect.

## I. INTRODUCTION

The most common type of dementia is Alzheimer's disease (AD), which was given that name in honor of the German psychiatrist Alois Alzheimer. The medial temporal lobe and neocortical areas of the brain accumulate amyloid-beta peptide (A), which is characterized by a progressive deterioration in cognitive function[1]. Neuritic plaques and neurofibrillary tangles are features of this neurodegenerative disease. When Alois Alzheimer examined the brain of his first patient, who had signs of memory loss and personality changes prior to passing away, he found amyloid plaques and considerable neuronal damage[2]. In his description of the condition, the cerebral cortex was severely affected (see Figure 1). Brain diseases like Alzheimer's disease (AD) and other conditions like intoxications, infections, abnormalities in the pulmonary and circulatory systems that reduce the amount of oxygen reaching the brain, nutritional deficiencies, vitamin B12 deficiency, tumors, and other etiologies are all responsible for the progressive decline in cognitive abilities[3].

Alzheimer's disease (AD) is a neurodegenerative condition marked by aberrant soluble protein processing and polymerization, which alters protein structure. When soluble neuronal proteins are misfolded, which can happen as a result of genetic mutations, environmental factors, or the aging process naturally, they go through structural changes[4].

The proteins gather as a result of these altered conformations, which leads to abnormal neural functioning and subsequent neuronal death. Alois Alzheimer, a German doctor who examined Auguste Deter, a 51-year-old woman, is credited with discovering Alzheimer's disease (AD) as a neurodegenerative disorder. Aside from hallucinations, Auguste Deter also experienced memory loss, language difficulties, and dizziness. He came to the conclusion that her illness went beyond what is typically considered dementia after looking at the results of her postmortem examination, which showed the presence of plaques and tangles in the cerebral cortex[5]. His discovery was followed by tests that revealed neuritic  $\beta$  amyloid ( $\beta$ A) plaques were present among dementia patients.

The PS1 genetic mutation, which is a rare but significant factor, is thought to be responsible for the disease's early development. Neurodegenerative illnesses with aberrant protein conformations include Parkinson's disease, Creutzfeldt-Jakob disease, Huntington's disease, and Machado-Joseph disease. Specific proteins namely,  $\beta$ -synuclein, Cellular Prion Protein (PrPc), Scrapie Prion Protein (PrPSc), Htt, and Ataxin3 proteins—are thought to be abnormal in these illnesses. Once a thorough grasp of the illness's fundamental elements and pathogenesis mechanism has been gained, it is imperative to address a number of issues, including the causes, pathogenesis, and

diagnostics of Alzheimer's disease (AD). In order to fight this disease, it is also crucial to investigate the creation of novel therapeutic strategies.

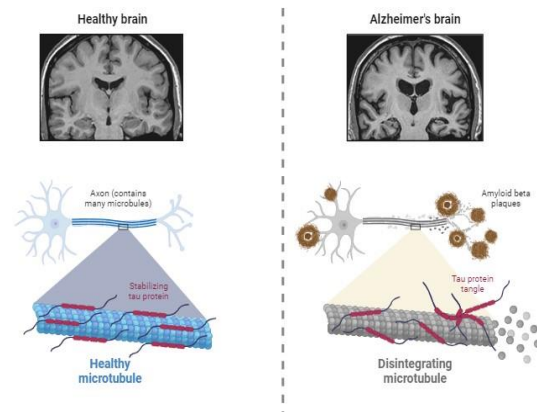


Fig 1: Healthy brain vs Alzheimer's brain

### Pathogenesis

Understanding the pathogenesis of Alzheimer's disease and creating efficient therapeutic strategies fall within a broad area of research. Alzheimer's disease (AD) is a neurodegenerative condition distinguished by its complex makeup and unrelenting progression. The user supplied a number, which is 8. It is commonly acknowledged that this phenomena has a significant role in the occurrence of dementia cases on a global level. An estimated 5.3 million people live in the United States and have Alzheimer's disease (AD). Among this group, 5.1 million people are 65 years of age or older, while 200,000 people have been identified as having younger-onset AD. The figure nine. Extracellular A plaques and intracellular neurofibrillary tangles (NFTs) are two histological characteristics frequently seen in Alzheimer's disease (AD). The NFTs are made up of hyperphosphorylated microtubule-associated proteins, whereas these plaques are made up of aggregated  $A\beta$  protein[6]. During the earliest stages, the basal, temporal, and orbitofrontal neocortex regions of the brain are where A plaques are most frequently formed. These plaques then spread to the neocortex, hippocampus, amygdala, diencephalon, and basal ganglia, among other areas.  $A\beta$  is seen to be present in a number of areas, including the mesencephalon, lower brain stem, and cerebellar cortex, in cases of high relevance. The locus coeruleus, along with the transentorhinal and entorhinal areas, have all shown signs of  $\tau$ -tangle development as a result of A buildup in the brain. The virus spreads to the neocortex and hippocampal regions at the crucial stage.

### Epidemiology

Alzheimer's disease (AD) can be classified into two main types: familial and sporadic. Additionally, it can be further categorized based on the age of onset, distinguishing between early-onset AD (occurring in individuals younger than 65 years) and late-onset AD

(manifesting in individuals older than 65 years). The prevalence of Alzheimer's disease (AD) in the general population during a period of six months ranges from 5.5% to 9%. The incidence of the disease exhibits a twofold increase per decade. Alzheimer's disease (AD) currently affects approximately 50% of individuals aged 85 years and above[7].

Individuals who exhibit cognitive impairment but do not satisfy the commonly acknowledged clinical criteria for Alzheimer's disease (AD), nevertheless display a discernible decline in cognitive functioning compared to their previous levels, particularly in the domain of new learning, may be diagnosed with moderate cognitive impairment (MCI). According to recent research findings, it has been shown that a significant proportion of persons, specifically 40%, are prone to developing Alzheimer's disease (AD) within a span of three years[8].

The timely identification of Alzheimer's disease (AD) holds significant importance in various aspects, such as the administration of cholinesterase inhibitors for treatment, alleviation of caregiver stress, provision of community assistance, postponement of institutionalization, formulation of lifestyle plans, and addressing legal concerns.

## II. DIAGNOSIS OF ALZHEIMER'S DISEASE

Extensive research efforts have been dedicated to the exploration of more timely and conclusive diagnostic methods for Alzheimer's disease (AD). Notably, advancements in testing techniques, such as the increased utilization of positron emission tomography (PET) and magnetic resonance imaging (MRI), have emerged over the past decade[9]. Additionally, the identification of biomarkers in cerebrospinal fluid (CSF) and, more recently, serum, has contributed to the progress in this field. Although there are certain diagnostic improvements accessible to the general population, their availability is often restricted and comes with a significant cost. Below, you will find a comprehensive review of developing diagnostic techniques[10].

### *i. Volumetric Data*

In simpler terms, changes in the volume of specific brain regions can be used as a predictor of the likelihood that moderate cognitive impairment (MCI) would progress to Alzheimer's disease (AD). Radiologists can perform volume assessments, or you can use software tools for MRI volumetric data that have been FDA-approved, such as Neuroquant and Neuroreader[11]. It is well known that a key biomarker for Alzheimer's disease is a change in hippocampus volume. Magnetic resonance imaging (MRI) examinations are regarded as a supplemental part of the diagnostic process rather than being independently sufficient for making a diagnosis due to the limited

sensitivity of this metric in the detection of Alzheimer's disease (AD)[12].

### *ii. Diffusion Tensor Imaging*

Diffusion Tensor Imaging (DTI) is a sophisticated neuroimaging methodology that leverages the diffusion characteristics of water molecules to produce magnetic resonance pictures that are indicative of alterations in the overall arrangement of axons at a macroscopic level[13]. The utilization of this methodology enables the assessment of the arrangement of vertical cellular micro-circuits, sometimes referred to as "minicolumns." Prior research has established that minicolumns exhibit discernible and gradual changes throughout the aging process, as well as in individuals with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Moreover, there is a correlation between alterations in the cortical columnar architecture, an accumulation of plaques, and a loss in cognitive function[14]. Neurodegeneration can be assessed and utilized as an indicator through the utilization of proprietary software for measuring Diffusion Tensor Imaging (DTI).

### *iii. PET Scan*

Individuals diagnosed with Alzheimer's disease (AD) demonstrate the presence of pathological forms of two proteins, specifically amyloid- $\beta$  ( $A\beta$ ) and hyperphosphorylated tau, in their brain tissue. Positron emission tomography (PET) scans possess the capacity to assess the presence of proteins and serve as a reliable biomarker[15]. The occurrence of amyloid deposition occurs prior to the emergence of clinically severe cognitive deficits, whereas the accumulation of tau protein correlates with the progression of cognitive decline. This discovery underscores the potential efficacy of positron emission tomography (PET) scans in the diagnosis and surveillance of illness progression.

### *iv. CSF and Blood Tests*

Cerebrospinal fluid (CSF), which can be obtained through lumbar puncture, surrounds the brain. The levels of  $A\beta$  and tau proteins in the cerebrospinal fluid (CSF) experience changes several years before the onset of clinically significant symptoms of Alzheimer's disease (AD). Over the course of recent decades, a number of tests have been created to analyze cerebrospinal fluid (CSF). Among these tests, two have gained significant recognition: the CSF  $A\beta_{42}:A\beta_{40}$  ratio and the measurement of CSF tau phosphorylated at threonine 181 (P-tau181). The assessment of cerebrospinal fluid (CSF) P-tau217 levels in the peripheral circulation exhibits considerable potential as a biomarker, demonstrating a notable level of sensitivity and specificity[16].

C2N Diagnostics, a company based in St. Louis, Missouri, has successfully created and introduced a blood test known as Precivity AD. This test, which is readily accessible in a majority of locations within the United States and the European Union, has been designed as an alternative to cerebrospinal fluid (CSF)

analysis due to the greater convenience of blood sample collection[17]. The examination use mass spectrometry as a means of identifying particular strains of beta-amyloid present in serum, which exhibit decreased levels in individuals with Alzheimer's disease. Currently, the test is not included in insurance coverage, which incurs a substantial expense. However, eligible persons have the opportunity to alleviate this cost through participation in a financial assistance program. The test should not be considered as an independent diagnostic instrument; instead, its results provide a likelihood score and should be interpreted in conjunction with other testing methods. Furthermore, investigations pertaining to the plasma A $\beta$ 42:A $\beta$ 40 ratio and P-tau181 have indicated possible significance.

### III. TREATMENT FOR ALZHEIMER'S DISEASE

The primary objectives of treatment encompass the attainment of enhanced cognitive functioning and the mitigation of behavioral disruptions, including but not limited to depression, psychosis, agitation, and sleeplessness.

#### *i. Psychosocial treatment for Alzheimer's disease (AD)*

Enhancing environmental manipulation, providing family support, and implementing preventive measures for various medical comorbidities have the potential to enhance the overall functioning of individuals with Alzheimer's disease. In the pursuit of prolonging the duration in which people with Alzheimer's disease (AD) can reside in their own homes, it is crucial to make certain modifications to the patient's surroundings[18]. The utilization of written daily reminders has been found to be beneficial in facilitating the execution of daily tasks and responsibilities. Clocks, calendars, and windows of significant prominence hold considerable importance. It is recommended that modifications to patient activities be kept to a minimum. It is crucial to prioritize the maintenance of sufficient hydration, proper nutrition, regular exercise, and personal cleanliness[19]. The presence of family support is of utmost importance as it plays a crucial role in mitigating the susceptibility of individuals to experiencing depression, anxiety syndromes, and sleeplessness.

#### *ii. Pharmacotherapy for Alzheimer's disease (AD)*

The current pharmaceutical options accessible to healthcare professionals for the management of Alzheimer's disease (AD) encompass cognitive enhancers to address cognitive impairment, as well as mood stabilizers, antipsychotics, antidepressants, and hypnotics to address behavioral disturbances[20].

#### *iii. Treatment of cognitive disturbance, Cholinesterase inhibitors for Alzheimer's disease (AD)*

The utilization of cholinesterase inhibitors in Alzheimer's disease (AD) is predicated upon the identification of cholinergic insufficiency as a characteristic feature of the pathology[21]. Clinically

relevant responses have been observed exclusively in patients with Alzheimer's disease (AD) who have been treated with cholinesterase inhibitors. The utilization of these chemicals leads to an elevation in the concentration of acetylcholine that is accessible for synaptic transmission through the inhibition of enzymes accountable for its hydrolysis, such as acetylcholinesterase[22]. These pharmaceutical substances demonstrate utility across the entire spectrum of the disease, with a special emphasis on their efficacy during the intermediate stage[23].

The cholinesterase inhibitors now approved for clinical use on a global scale encompass donepezil, tacrine, galantamine, and rivastigmine. Physicians and families may not observe a significant immediate amelioration in symptoms; nonetheless, patients undergoing pharmaceutical treatment will exhibit a relatively diminished decline in cognitive function as compared to control groups[24].

#### *iv. Treatment of behavioral disturbance*

The majority of individuals with Alzheimer's disease (AD) experience a diverse array of behavioral disorders that are associated with dementia. Among these disturbances, depression and psychosis have received significant attention in terms of therapy research. Aggressive treatment of depression in those diagnosed with Alzheimer's disease (AD) is recommended, along by diligent surveillance of cognitive abilities[25]. Given the scarcity of clinical trial data, the management of depression in Alzheimer's disease (AD) remains primarily empirical. This approach involves initiating treatment with an antidepressant at a conservative dosage and gradually titrating it upwards[26]. Adequate dosage and duration of treatment are necessary to achieve a clinical response in people with depression who do not have dementia. The older population experiencing depression may require a duration of up to six weeks to exhibit a response to antidepressant medication. Similarly, individuals diagnosed with Alzheimer's disease should also anticipate a comparable timeframe for therapeutic effects to manifest[27].

Reversible monoamine oxidase inhibitors, such as brofaromine and moclobemide, have demonstrated efficacy in treating depression and dementia in patients. Unlike the classic monoamine oxidase inhibitors (phenelzine, tranylcypromine), these reversible inhibitors offer comparable effectiveness without the presence of significant possible side effects[28].

The utilization of tricyclic antidepressants is restricted to nortriptyline and desipramine due to their lower anticholinergic effects in comparison to their precursor molecules, amitriptyline and imipramine. The numerical value provided is 58. Both interventions were examined in double-blind, placebo-controlled trials and demonstrated efficacy in the treatment of depression among individuals with Alzheimer's disease[29].

Various newer antidepressants, such as fluoxetine, sertraline, paroxetine, fluvoxamine,

citalopram, nefazodone, bupropion, mirtazapine, and venlafaxine, have demonstrated potential benefits in treating depression in individuals with Alzheimer's disease (AD)[30]. However, it is important to note that only fluoxetine, paroxetine, and fluvoxamine have been subjected to rigorous evaluation through double-blind, placebo-controlled trials[31-34]. Currently, the usual treatment for depression in individuals with Alzheimer's disease (AD) consists of selective serotonin reuptake inhibitors (SSRIs). Psychosis and behavioral problems frequently aggravate depression in these patients, and might manifest as distinct features of the disorder[35]. The prevalence of psychosis among individuals diagnosed with Alzheimer's disease (AD) ranges from 25% to 50%. Numerous therapeutic interventions have been suggested; however, the scarcity of controlled experimental studies remains a significant limitation[36]. The management of psychosis in individuals with Alzheimer's disease (AD) should primarily involve the utilization of atypical antipsychotic medications, such as risperidone and olanzapine[37-39]. These particular medications have been extensively studied in rigorous scientific investigations employing the double-blind placebo-controlled trial design[40].

#### IV. CONCLUSION

Alzheimer's disease (AD) is a widely widespread neurological ailment that affects persons on a worldwide level. This disorder is characterized by the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs), resulting in eventual impairment of neuronal function, as observed from a clinical standpoint. The process of amyloid aggregation arises from the sequential breakdown of amyloid precursor protein (APP) by  $\beta$ -secretase and  $\gamma$ -secretase enzymes. The process of cleavage results in the generation of extracellular peptides known as A $\beta$  40 and A $\beta$  42. Alzheimer's disease (AD) is further characterized by the presence of neurofibrillary tangles (NFTs). The occurrence of these tangles can be ascribed to the hyperphosphorylation of the microtubule-associated protein  $\tau$ . Glycogen synthase kinase 3 (GSK3) and cyclin-dependent kinase 5 (CDK5) are the primary kinases responsible for the phosphorylation of the tau protein. The aggregation of microglia at the location, together with the accumulation of plaques and tangles, plays a vital role in triggering innate immunoresponses against aggregation. The presence of an uncommon genetic mutation impedes the regular functioning of microglial surface receptors, hence intensifying the advancement of Alzheimer's disease. The present urgency necessitates the understanding of these diverse components and subsequently devising pharmaceutical interventions that particularly target them. There exists a potential for the advent of a novel era in the realm of diagnosing and treating Alzheimer's disease (AD), a development that will have significant implications for

the field of public health. If the possibility of early diagnosis becomes feasible, the individuals who are diagnosed early will impose additional demands on an already strained healthcare system due to their newly identified care requirements. It may be necessary to allocate resources towards enhancing public knowledge of the health ramifications associated with dementia. There is a need for the dissemination of information pertaining to the efficacy of treatments, with efforts aimed at eradicating the societal stigma around mental health illnesses and seeking treatment for them. Moreover, there is a pressing need for enhancing the overall accessibility of mental health care.

#### REFERENCES

- [1] De-Paula V.J., Radanovic M., Diniz B.S., Forlenza O.V. Alzheimer's disease. *Sub-Cell. Biochem.* 2012;65:329–352. doi: 10.1007/978-94-007-5416-4\_14.
- [2] Cipriani G., Dolciotti C., Picchi L., Bonuccelli U. Alzheimer and his disease: A brief history. *Neurol. Sci. Off. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol.* 2011;32:275–279. doi: 10.1007/s10072-010-0454-7.
- [3] Blass J.P. Alzheimer's disease. *Dis. A Mon. Dm.* 1985;31:1–69. doi: 10.1016/0011-5029(85)90025-2.
- [4] Terry R.D., Davies P. Dementia of the Alzheimer type. *Annu. Rev. Neurosci.* 1980;3:77–95. doi: 10.1146/annurev.ne.03.030180.000453.
- [5] Rathmann K.L., Conner C.S. Alzheimer's disease: Clinical features, pathogenesis, and treatment. *Drug Intell. Clin. Pharm.* 1984;18:684–691. doi: 10.1177/106002808401800902.
- [6] Henry W, Querfurth H, LaFerla F. Mechanisms of disease Alzheimer's disease. *New Engl J Med.* 2010;362:329–344. doi: 10.1056/NEJMr0909142
- [7] Alzheimer's A. 2015 Alzheimer's disease facts and figures. *Alzheimer'S Dementia.* 2015;11(3):332. doi: 10.1016/j.jalz.2015.02.003
- [8] Goedert M. Alzheimer's and Parkinson's diseases: the prion concept in relation to assembled A $\beta$ , tau, and  $\alpha$ -synuclein. *Science.* 2015;349(6248):1255555. doi: 10.1126/science.1255555
- [9] Lombardi, G., Crescioli, G., Cavedo, E., Lucenteforte, E., Casazza, G., Bellatorre, A.-G., et al. Filippini, G. (2020, March 2). Structural magnetic resonance imaging for the early diagnosis of dementia due to Alzheimer's disease in people with mild cognitive impairment. *Cochrane Database Syst Rev*, 3(3), CD009628. 10.1002/14651858.CD009628.pub2
- [10] Chance, S. A., Clover, L., Cousijn, H., Currah, L., Pettingill, R., & Esiri, M. M. (2011, August). Microanatomical correlates of cognitive ability and decline: Normal ageing, MCI, and Alzheimer's disease. *Cereb Cortex*, 21(8), 1870–1878. 10.1093/cercor/bhq264

- [11] van Veluw, S. J., Sawyer, E. K., Clover, L., Cousijn, H., De Jager, C., Esiri, M. M., & Chance, S. A. (2012, October). Prefrontal cortex cytoarchitecture in normal aging and Alzheimer's disease: A relationship with IQ. *Brain Structure & Function*, 217(4), 797–808. 10.1007/s00429-012-0381-x
- [12] Hanseeuw, B. J., Betensky, R. A., Jacobs, H. I. L., Schultz, A. P., Sepulcre, J., Becker, J. A., et al. Johnson, K. (2019, August 1). Association of amyloid and tau with cognition in preclinical Alzheimer disease: A longitudinal study. *JAMA Neurology*, 76(8), 915–924. 10.1001/jamaneurol.2019.1424
- [13] Jansen, W. J., Ossenkoppele, R., Knol, D. L., Tijms, B. M., Scheltens, P., Verhey, F. R. J., . . . Zetterberg, H., & the Amyloid Biomarker Study Group. (2015, May 19). Prevalence of cerebral amyloid pathology in persons without dementia: A meta-analysis. *JAMA*, 313(19), 1924–1938.
- [14] Palmqvist, S., Janelidze, S., Quiroz, Y. T., Zetterberg, H., Lopera, F., Stomrud, E., et al. Hansson, O. (2020, August 25). Discriminative accuracy of plasma phospho-tau217 for Alzheimer Disease vs other neurodegenerative disorders. *JAMA*, 324(8), 772–781. 10.1001/jama.2020.12134
- [15] Landhuis, E. (2021). Detecting Alzheimer's gets easier with a simple blood test. *Scientific American*, 3(1). Retrieved from <https://www.scientificamerican.com/article/detecting-alzheimers-gets-easier-with-a-simple-blood-test/>
- [16] Fandos, N., Pérez-Grijalba, V., Pesini, P., Olmos, S., Bossa, M., Villemagne, V. L., . . . Sarasa, M., & the AIBL Research Group. (2017, September 12). Plasma amyloid  $\beta$  42/40 ratios as biomarkers for amyloid  $\beta$  cerebral deposition in cognitively normal individuals. *Alzheimers Dement (Amst)*, 8, 179–187.
- [17] Janelidze, S., Mattsson, N., Palmqvist, S., Smith, R., Beach, T. G., Serrano, G. E., et al. Hansson, O. (2020, March). Plasma P-tau181 in Alzheimer's disease: Relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nature Medicine*, 26(3), 379–386. 10.1038/s41591-020-0755-1
- [18] American Psychiatric Association. Practice Guidelines for the treatment of patients with Alzheimer's Disease and other dementias of late life. *Am J Psychiatry*. 1997;154(suppl 5):1–39.
- [19] Mittleman MS., Feris SH., Shulman E., et al. A family intervention to delay nursing home placement of patients with Alzheimer's disease: a randomized controlled trial. *JAMA*. 1996;276:1725–1731.
- [20] Stern Y., Tang MX., Albert M., et al. Predicting time to nursing home care and death in individuals with Alzheimer's disease. *JAMA*. 1997;277:806–812.
- [21] Schachter AS., Davis KL. Alzheimer's disease. *Curr Treat Options Neurol*. 2000;2:51–60.
- [22] Schachter AS., Davis KL. Guidelines for the appropriate use of cholinesterase inhibitors in patients with Alzheimer's disease. *CNS Drugs*. 1999;11:281–288.
- [23] Rogers SL., Doody RS., Mohs RC., Friedhoff LZT. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. *Arch Intern Med*. 1998;158:1021–1031.
- [24] Shintani EY., Uchida KM. Donepezil: an anticholinesterase inhibitor for Alzheimer's disease. *Am J Health Syst Pharm*. 1998;54:2805–2810.
- [25] Rogers SL., Farlow MR., Doody RS., et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology*. 1998;50:136–145.
- [26] Rogers SL., Friedhoff LT. Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: an interim analysis of the results of a US multicenter open label extension study. *Eur Neuropsychopharmacol*. 1998;8:67–75.
- [27] Burns A., Rossor M., Hecker J., Gautier S., et al. The effects of donepezil in Alzheimer's disease: results from a multinational trial. *Dement Geriatr Cogn Disord*. 1999;10:237–244.
- [28] Samuels SC., Davis KL. A risk-benefit assessment of tacrine in the treatment of Alzheimer's disease. *Drug Saf*. 1997;16:66–77.
- [29] Davis KL., Thai LJ., Gamzu ER., et al. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. The Tacrine Collaborative Study Group. *N Engl J Med*. 1992;327:1253–1259.
- [30] Gracon SI., Knapp MJ., Berghoff WG., et al. Safety of tacrine: clinical trials, treatment IND, and postmarketing experience. *Alzheimer Dis Assoc Disord*. 1998;12:93–101.
- [31] Knapp MJ., Knopman DS., Solomon PR., Pendlebury WW., Davis CS., Gracon SI. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. *JAMA*. 1994;271:985–991.
- [32] Thomsen T., Bickel U., Fischer JP., et al. Galanthamine hydrobromide is a long-term treatment of Alzheimer's disease: selectivity toward human brain acetylcholinesterase compared with butyrylcholinesterase. *J Pharmacol Exp Ther*. 1995;274:767–770.
- [33] Parys W., Pontecorvo M J. Treatment of Alzheimer's disease with galanthamine, a compound with a dual mechanism of action. *Janssen Research Foundation*. 1998 Data on file
- [34] Bores GM., Huger FP., Petko W., et al. Pharmacological evaluation of novel Alzheimer's disease therapeutics: acetylcholinesterase inhibitors related to galanthamine. *J Pharmacol Exp Ther*. 1998;277:728–738.
- [35] Sramek JJ., Anand R., Wardle TS., et al. Safety/tolerability trial of SDZ ENA713 in patients with probable Alzheimer's disease. *Life Sci*. 1996;58:1201–1207.

[36] Nair NP., Amin M., Holm P., et al. Moclobemide and nortriptyline in elderly depressed patients. A randomized, multicentre trial against placebo. *J Affect Disord.* 1995;33:1–9.

[37] Schweitzer E., Rickels K., Hassman H., et al. Buspirone and imipramine for the treatment of major depression in the elderly. *J Clin Psychiatry.* 1998;59:175–183.

[38] Taragano FE., Lyketsos CG., Mangone CA., Allegri RF., Comesana-Diaz E. A double-blind, randomized, fixed-dose trial of fluoxetine vs amitriptyline in the treatment of major depression

complicating Alzheimer's disease. *Psychosomatics.* 1997;38:246–252.

[39] Katona CL., Hunter BN., Bray J. A double-blind comparison of the efficacy and safety of paroxetine and imipramine in the treatment of depression with dementia. *Int J Geriatr Psychiatry.* 1998;13:100–108.

[40] Olafsson K., Jorgensen S., Jensen HV., Bille A., Arup P., Andersen J. Fluvoxamine in the treatment of demented elderly patients: a double-blind, placebo-controlled study. *Acta Psychiatr Scand.* 1992;85:453–456.