JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

# Review of Alzheimer's disease and its current treatment strategies

***Jeya sheely J, Thiruppathi M, Natarajan P, Keerthana N**

Department of pharmacology

Sankaralingam Bhuvaneswari College of pharmacy, Anaikuttam, Sivakasi, Tamil nadu, India.

Pin code: 626130

**Abstract:** Alzheimer disease is a progressive neurodegenerative disorder in other words is a metabolic disorder; mainly suffer in older people, which severely affected in the patient's life. In the current years, the number of people affected has seen a rapidly enhance. It is predicted that up to 107 million subjects will be suffering by 2050 worldwide. In this area research has uncovered a large amount about the biological and environmental underpinnings of Alzheimer, mainly it's correlated with β-Amyloid and Tau based mechanism; however, the exact molecular events and biological pathways behind the disease to be discovered. Biochemical studies and neuropathological studies of brains since individuals with Alzheimer disease provide clear proof for an activation of inflammatory pathways, and prolong use of anti-inflammatory drugs is linked with lessen risk to develop the disease.The etiology of Alzheimer disease was unclear, but it is likely both genetic and environmental factors are involved . Imaging has played different roles in the study of Alzheimer disease exceeding the past four decades. First, computed tomography and magnetic resonance imaging were used diagnostically in dementia. In this review, we are discussing about in especially, briefly describe the pathophysiology, epidemiology and related risk factors potentially associated with the disease. We will describe the current treatments strategies and their complications with the current treatment, and suggestions for future in research and treatment.

**Keywords**: Alzheimer disease, Anti-inflammatory, Biological pathways, Computed tomography, Current treatment Immune system, Magnetic resonance imaging.

## 1. Introduction:

Alzheimer disease (AD) is a neurodegenerative disorder that progresses over time and is characterized by behavioral changes, a gradual decline in cognitive ability, and tau and amyloid deposits in the hippocampus region of the brain. The most typical short-term memory, executive function, praxis, and visuospatial dysfunction symptoms of Alzheimer's disease. There are a number of uncommon forms of Alzheimer's disease that have been identified. Although recent developments in amyloid imaging and genetics show great promise for making possible early and presymptomatic diagnosis of Alzheimer disease and its discrimination since clinical assessment, involved in cognitive testing, remains serious for the diagnosis and staging of the disease, other neurodegenerative disorders in United States [1].Despite growing evidence that Alzheimer disease pathology begins to accumulate in the brain, the first clinical symptoms typically appear after the age of 65[2, 3]. A significant body of clinic pathologic associated (CPC) scholarship on Alzheimer disease (AD) has been developed over many years of international research [4-6]. The number of people with Alzheimer's disease is predicted to rise from 26.6 million in 2006 to 107 million by 2050, with 16.5 of those people living in Europe [7, 8]. 68% of the global increase is concentrated in low- and middle-income nations [9]. The disease is

presented in three main stages, each with unique difficulties and symptoms. Physicians can forecast future symptoms and potential treatment options by estimating the disease's stage at the moment. The symptoms of Alzheimer's disease vary in severity and are specific to each individual case. Both familial and sporadic cases of Alzheimer disease can result from the inheritance of specific genes. The more prevalent form of Alzheimer disease, known as sporadic Alzheimer disease, has been linked to the apolipoprotein 4 (APOE4) allele, with homozygotic conditions carrying a higher risk [10, 11]. Alzheimer's disease develops as a result of environmental, vascular, and psychological factors. As of late, there are no medications that can stop the progression of neurodegeneration in Alzheimer's disease; instead, symptomatic care is the mainstay of treatment [12].In mild to moderate cases of Alzheimer's disease, for instance, cholinesterase inhibitors (CIs) that support cholinergic neurotransmission are used. In moderate to severe cases, memantine, an antagonist of the N-methyl-D-aspartate (NMDA) receptor, is used to prevent excitotoxicity, and antipsychotics and antidepressants are used to treat neuropsychiatric symptoms [13,14]. Neuritic plaques (NPs) and neurofibrillary tangles (NFTs), which have the potential to delay neurodegeneration, are the targets for Alzheimer's disease treatment in the future [15].

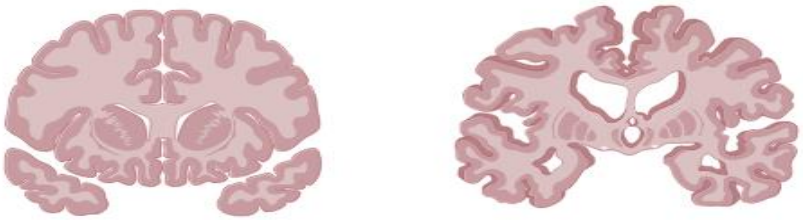
**2.Disease pathology of Alzheimer's**

Amyloid is thought to produce too much and be cleared too slowly in Alzheimer's disease. Tau hyperphosphorylation and neuronal toxicity are subsequent events. Brain atrophy from localized neuronal and synaptic loss, extracellular β-amyloid deposition in the form of neuritic plaques, and intraneuronal tau protein deposition in the form of intraneuronal neurofibrillary tangles are the main pathologic characteristics of Alzheimer disease (AD).β - Amyloid also builds up in the blood vessels of the brain. The severity of cerebral amyloid angiopathy varies from minor deposits of amyloid to significant deposits that alter the architecture of the arteries and result in cortical microinfarcts, microaneurysms, and cerebral microhemorrhages. Or large bleeding it is believed that amyloid deposition starts 20 years before the onset of clinical symptoms [2]. Neuritic plaques are microscopic, spheroid-shaped lesions that contain an extracellular amyloid peptide (A) core and abnormal axonal endings on all sides. Amyloid precursor protein (APP), a sizable protein, is the source of A. The actions of the enzymes α-,β -, and γ-secretase can cleave APP. APP is first cleaved by α secretase in healthy individuals before being further cleaved by γ secretase [16, 17]. The risk of the formation of a peptide is eliminated by the activity of secretase. Instead of secretase, the β-secretase enzyme acts to cleave the APP molecule in the neurons of patients with Alzheimer disease, causing the cell to release the resulting sAPP [18]. It's interesting to note that recent data point to the necessity of cholesterol for the final step in the formation of αβ, the γ-secretase cleavage of amyloid precursor protein [19].Current longitudinal studies of cognitively healthy individuals who test positive for amyloid have as their main goal determining the likelihood that these individuals will develop dementia in the future. In addition to AD, neurofibrillary tangles are also present in prion disease, dementia pugilistica, chronic traumatic encephalopathy, and healthy aging. There is a strong correlation between the burden of neurofibrillary tangles and neuronal loss and global cognitive impairment [20, 2 1].

.

**Figure: 1**Difference between the Normal and Alzheimer brain

**Normal brain** **Alzheimer brain**



### 3. Epidemiology

Based on epidemiological data gathered over the previous few years, Alzheimer Disease International commissioned an international group of experts in 2005 to come to a consensus on the prevalence and estimation of dementia in 14 World Health Organization regions. According to the findings, there were 24.2 million dementia sufferers worldwide at the time, and 4.6 million new cases were reported annually [22].The highest prevalence of dementia is found in North America and Western Europe at age 60 (6.4 and 5.4% of the population, respectively), followed by Latin America (4.9%) and China and its developing western-Pacific neighbours (4.0%). The frequency rates per year (per 1000) for these nations were estimated to be 10.5 for North America, 8.8 for Western Europe, 9.2 for Latin America, and 8.0 for China and its developing neighbours in the western Pacific. In all of these nations, the rate of mortality increased exponentially with age, especially in the seventh and eighth decades of life. Additionally, the prevalence rates for AD rise exponentially with advancing years, sharply rising after age 65. Between the ages of 60 and 85, the prevalence of dementia most commonly Alzheimer disease increases by almost 15 times [23]. In this cohort, AD dementia accounted for 70% of all dementia cases across the age spectrum [24]. The ADAMS investigators reported that an additional 22% (or 5.4 million Americans) in a later publication. In the absence of overt dementia, people aged 71 or older have cognitive impairment [25]. There are racial differences in AD prevalence that have been documented. While other genetic and societal factors are likely at play, older African Americans and Hispanics have a higher prevalence of AD compared to older Caucasians, in part because of lower educational attainment and a higher prevalence of cardiovascular co-morbidities [26–28].

### 4. Factors at Risk for Alzheimer's disease

There are many variables that have been linked to an increased risk of AD, but among them, cerebrovascular disease and its precursors have been reported most frequently (Table 1). Risk has been found to rise in the presence of a history of diabetes, hypertension, smoking, obesity, and dyslipidemia. It's interesting to note that dementia is preceded by cerebrovascular disease, which includes large cortical infarcts, single strategically placed infarcts, multiple small infarcts, and cerebral hemorrhage, cortical changes brought on by hypoperfusion, white matter changes, and vasculopathies [29-52].

**Table 1: Risk of Alzheimer's disease**

| Antecedent | Direction | Possible mechanisms |
|---|---|---|
| **Cardiovascular disease** | enhanced | Strategic location parenchyma destruction and ↑αβ-deposition |
| **Smoking** | enhanced | Oxidative Stress Effects on the Brain |
| **Hypertension** | Enhanced &reduced | microvascular condition |
| **Type II diabetes** | enhanced | Cerebrovascular Effect αβ and insulin compete for clearance |
| **Obesity** | enhanced | Improve the risk of type II diabetes inflammatory |
| **Traumatic head injury** | enhanced | Deposition of ↑αβ amyloid precursor proteins. |
| **Education** | reduced | Provides cognitive reserve |
| **Leisure activity** | reduced | lipid metabolism and brain activity |
| **Mediterranean diet** | reduced | anti-inflammatory, Antioxidant |
| **Physical activity** | reduced | stimulates brain vascularization and brain plasticity |

## 5. Defensive elements for Alzheimer disease

### 5.1Mental Reserve

Additionally, studies of "normal aging" have shown that people with higher educational attainment experience slower cognitive and functional decline as they age [53], providing evidence that education plays a role in age-related cognitive decline. These studies suggest that the same education-related factors that postpone the onset of dementia of the AD type also help people deal with the normal cognitive changes brought on by aging more skilfully. Increased literacy was also linked to a slower decline in memory, executive function, and language skills in an ethnically diverse cohort of elderly people without dementia in New York City [54]. Many others around the world have noted a lower risk of dementia in subjects with higher education [55-61]. Cohort studies on the influences of premorbid IQ, education, occupation, and mental activities on dementia risk were examined in a meta-analysis [62]. In this study, increased cognitive activity was also linked to slower rates of memory deterioration.

### 5.2 Diet

Dietary fats can raise cholesterol levels, which can raise the risk of brain vascular disease. The risk of AD may also rise as a result of this sequence [63]. Intake of saturated fats in the highest quintile of dietary fats the fifth was linked to a doubling of the risk of developing Alzheimer's disease. The highest intake of n-6 polyunsaturated fats and monounsaturated fats decreased the risk of developing AD, whereas trans-unsaturated fats were linked to a 3-times-higher risk [65] . Higher intakes of total and saturated fat have also been linked to an increased risk of AD, but there is no

proof that this association holds true for polyunsaturated fat [64]. Omega-3 fatty acids are crucial dietary elements for the early stages of brain development. Consuming fish or omega-3 fatty acids has been linked in numerous studies to a lower risk of AD [65-67]. According to two studies [68, 69], people who consume more vitamin D in their diet have a lower risk of developing Alzheimer's disease. In a third study, this association was not found, possibly as a result of the lower vitamin D intake[70].

*5.3 Factor of Physical Activity*

Exercise can enhance learning in both young and aged animals [71] activate brain plasticity mechanisms, remodel neuronal circuitry in the brain [72], promote brain vascularisation [73], and stimulate neurogenesis [71]. It may also increase neuronal survival and resistance to brain insults [74]. Increase levels of brain derived neurotrophic factor, mobilize gene expression profiles that would be predicted to benefit brain plasticity [72], and reduce levels of C-reactive protein and interleukin-6, two inflammatory markers [75, 76]. A Cochrane review [77] found that eight of 11 random, controlled trials of exercise in older people without known cognitive impairment reported that aerobic exercise interventions were associated with improvements in cognitive function.

5.4 Strengthening of Cognitive

The potential impact of cognitive engagement on the risk of AD has specifically been examined in a number of studies [78–81]. The studies relied on participants' self-reports of how frequently they engaged in particular activities that might have a cognitive component.

**6. Diagnosis**

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is currently the gold standard for dementia diagnosis [82].Major neurocognitive impairment and mild neurocognitive impairment are the two cognitive syndromes recognized by DSM-5. Major Neurocognitive impairment must be diagnosed when there is objective cognitive decline that interferes with daily activities and is not brought on by delirium or another neurologic, medical, or psychiatric disorder. Not brought on by delirium or another neurologic, medical, or psychiatric disorder, and does not interfere with daily activities. The National Institute on Aging (NIA) and the Alzheimer's Association1 have most recently developed a new set of diagnostic criteria that cover all three major stages of AD (i.e., the preclinical, the prodromal, and the overt dementia stages)[83-85].

6.1 Alzheimer Disease and Biomarkers

Biomarkers have historically been crucial in the evaluation of dementia patients in addition to supporting clinical diagnosis. Every patient with objective cognitive decline must undergo a structural imaging scan, per the American Academy of Neurology (AAN) guidelines for the diagnostic evaluation of dementia [86]. This advice was given in response to a review of the data from a Class II study that revealed that 5% of all patients with cognitive complaints had a causative non-degenerative lesion, such as a subdural hematoma or normal pressure hydrocephalus that was growing slowly [87]. A brain CT or MRI scan can reveal ischemic changes in addition to a potentially treatable lesion, which would require additional testing and possibly the start of therapy to lower vascular risk factors or introduce behavioral changes. Compared to CT, MRI's improved resolution enables better quantification of the cerebral structures and better differentiation between AD patients who are mildly affected and those who are not. Mesial temporal atrophy is one of the findings that may point to the pathology of AD[88-90]. And global brain atrophy with pronounced ventricular enlargement in more advanced stages [91,92]. Recent research has shown that perfusion abnormalities can be detected using arterial spin-labeling MRI sequences[93]. Due to the high sensitivity but relatively low specificity of SPECT and PET validation studies, the risk of false-positive diagnoses has increased [94, 95]. Currently, Medicare only pays for the

use of FDG-PET and SPECT to distinguish AD from front temporal dementia. The method for making a clinical diagnosis of AD may change as a result of the recent development and validation of amyloid PET imaging.

6.2 PET**:** Positron emission tomography, or PET, produces a three-dimensional, color image of the human body using radiation signals [96]. The patient receives an injection of a radiotracer, which consists of a radioactive drug attached to a naturally occurring taking place chemically. Glucose is typically and widely used in the study of Alzheimer's disease. The radiotracer makes its way to the organs that utilize that particular molecule as energy. Positron emissions occur during the compound's metabolism. The PET scan picks up the energy from these positrons and transforms it into an image that appears on the output screen. By demonstrating how efficiently the radio tracer is destroyed, this image illustrates how the patient's body works. The range of colors and intensities produced by the positron energy reflect the level of brain activity. The process of using a PET scan to find changes in glucose metabolism in the brain of an Alzheimer's patient was described in a study that was published in the Journal of Clinical Psychiatry in 1996. Patients whose disease was more advanced and had spread to more parts of the brain experienced a further decline in rate [97].

6.3 CT: During a computed tomography (CT) scan, the body is captured in a series of cross-sectional images [98]. The various scans are combined and incorporated into one complete image with the aid of a computer. The CT scan gives the doctor information about the tissue densities throughout the body and in different regions of the brain. A contrast dye may be injected to provide a distinction for better clarity. In order to distinguish between similar tissues and improve visual clarity, a contrast dye may be injected [99].

6.4 MRI: Magnetic resonance imaging (MRI) methods produce two or three dimensional images of the body that can be used to diagnose injury and illness. MRI techniques were first used in 1977. The super conducting magnet, which creates a strong and stable magnetic field, is a crucial part of the MRI system [100]. Smaller gradient magnets produce weaker magneto-electric fields. These magnets make it possible to scan various body parts. There are billions of atoms in each cell of the human body. However, the electromagnetic field affects the hydrogen atoms. Then, the device emits a hydrogen-specific radio frequency pulse, which changes the direction that these protons spin in. The protons release energy when the spinning stops, which the system interprets. Each type of tissue reacts differently to a contrast dye and appears as a different shade of gray when the image is produced [96]. The ability of an MRI to accurately identify the structural alterations and cellular degeneration present in an Alzheimer's patient's brain is being tested by researchers. Even before any overt clinical symptoms of Alzheimer's disease manifest, the hippocampus frequently exhibits atrophy [101]. A more recent investigation into the use of sodium magnetic resonance imaging in the diagnosis of Alzheimer's disease was carried out in 2009 by the Departments of Radiology and Neurology at the University of Pennsylvania. Similar to the above-discussed principle, this imaging method is used. However, this method uses sodium (23Na), which is naturally abundant, to measure the atoms of hydrogen. Because sodium in the brain can identify tumors and monitor cell death, this ion was chosen [102]. Five elderly adults in good health and five others with a possible diagnosis of Alzheimer's disease made up the participants. The intracellular space is reduced when neuronal death takes place. As a result, there is a higher concentration of sodium in the extracellular space, which results in patients' MRI signals being stronger. Who suffer from Alzheimer's [103] .

**7. Modern therapeutic strategies**

AD is currently being managed today; attempts are made to manage AD multifactorially and specifically based on the following elements:

1. Honest and effective communication between the doctor, the caregiver, and the patient will enable timely symptom identification, accurate assessment and diagnosis, and appropriate direction.

[2] Behavioral strategies

- Routines that is established, consistent, and simple;
- Communicative strategies like calm interactions, providing enjoyable activities, using simple language, and only "saying no" when safety is at risk;
- Timely planning for legal and medical needs and decisions; and Exercise therapy, light therapy, and music therapy are all forms of cognitive behavioral therapy (CBT) [105, 106].

[3] Support for caregivers:

- Scheduled brief periods of rest for the caregiver;
- Psychoeducation, which includes preparing for dementia's effects on cognition, function, and behaviors, expectations, and avoiding circumstances that might exacerbate symptoms or pose a greater risk to safety and wellbeing.
- Promoting the establishment of caregiver support networks [104].

**7.1Current Treatment Landscape Research for AD**

The state of AD treatment research at the moment since 2003, the FDA has not approved a new drug for AD, and despite numerous time-consuming and expensive trials, there are no approved DMTs for AD [107,108]. In actuality, over 200 research projects failed or were abandoned in the last ten years[104]. Agents with mechanisms of action (MOA) that either target disease modification or symptoms are still abundant in the AD drug pipeline [109,104]. Semagacestat [110], bapineuzumab [111], solanezumab [112], and bapineuzumab were some of the most recent anti-amyloid agents to fail in phase 3 clinical trials in patients with early-stage, mild-stage, or mild-to-moderate stage AD. Lanabecestat [113], verubecestat [114], and atabecestat [115] also failed in trials of β -secretase inhibitors (BACE). The most common and widely accepted explanations for the numerous failures of clinical trials of DMT agents for AD include starting therapies too late in the course of the disease, using the wrong drug doses, treating the wrong primary target, and primarily having a poor understanding of the pathophysiology of AD [116]. The clinical endpoint of the chosen trials may be extremely premature, according to a novel approach to the issue, which also contends that the variability in diagnostic markers and end points may lead to an incorrect diagnosis of patients' disease states and is, at long last, a certain source of errors [108]. The suggested solution appears to be the use of clinical trial simulators [108] given the fact that longer trial durations increase the probability of detecting a significant effect but at the same time increase the costs tremendously. These simulators can forecast whether a trial's strategy and clinical end point selection are appropriate or not before the trial even starts [117]. They are built using mathematical, computational, and statistical tools. They can also aid in the refinement of the study's design, increasing the likelihood that anticipated new drugs will be successful or sparing incredibly valuable time and resources by foreshadowing the impending failure of any inappropriate therapy[118]. Despite the fact that clinical trial simulators are used is not common in current research, [119] this practice shouldn't be abandoned, especially when considering potential treatments for long-lasting diseases with slow progression, like AD [118].

8. Authentic immunization**.**

Immunogens include A, phosphorylated tau (ptau) peptides, or particular synthetic peptides like polymerized British amyloidosis (ABri)-related peptide (pBri)[120]. A highly amyloidogenic protein with a distinctive carboxyl terminus that is unrelated to any other human protein is produced as a result of the mutation that causes the rare hereditary amyloidosis known as ABri. This terminus is matched by the pBri peptide, which triggers an immune response that recognizes A and ptau. B cells receive the immunogens from antigen-presenting cells. Antibodies to Ab or ptau epitopes will be produced when Ab or ptau peptides are used, respectively. Antibodies to both A and pta epitopes will be produced when pBri is used [121].

8.1 Immunization passive.

Systemically and sufficiently for BBB penetration, monoclonal Absto Ab, ptau, or b sheet epitopes are infused. In order to clear, degrade, or alternatively disaggregate or neutralize their targets, antibodies act as they cross the BBB [121]. By encouraging macrophage and microglia function, innate immunity is stimulated either actively or passively to treat disease pathology [121]. Overall, A-targeted treatment approaches are currently being tested in preclinical AD because they appear effective when applied very early in the course of the disease, before the appearance of any symptoms. Although promising, strategies that aim to treat tau pathology currently run the risk of being toxic. However, it is hypothesized that ptau and pathologies may have evolved via different pathways that can have synergistic effects on one another in sporadic late-onset AD [122]. Therefore, it's possible that the two ptau and pathologies must be simultaneously targeted for effective AD immunotherapies [121]. With poor outcomes up to this point, immunotherapeutic approaches have dominated in the last 15 years. However, the research being done now to develop immunotherapies for AD has changed as a result of the lessons learned from these failures [121].

8.2 Immunotherapy in action:

AD is being tested in a phase 2 clinical study for mild to moderate AD (NCT02579252) [109, 104, 123] and contains a synthetic tau peptide.

Immunity that is passive. A humanized anti-tau MAb called ABBV-8E12 was evaluated in a phase 2 clinical trial in people with early Alzheimer's disease (NCT02880956)[124]. A patient with familial AD provided stem cells for the creation of the humanized IgG4 MAb against tau fragments known as BIIB092[125]. Participants in a phase 2 clinical trial with AD MCI and mild AD are evaluated for the agent's efficacy and safety[4].An anti-tau MAb called RO7105705 (MTAU9937 A) is being evaluated in a phase 2 study in people with prodromal and mild AD (NCT03289143)[123,126]. Phase 1 clinical trials for three additional anti-tau mAbs (BIIB076, JNJ-63733657, and LY3303560) are currently underway [109].

**9. Conclusion**

Over 5 million Americans suffer from Alzheimer disease, a neurodegenerative disorder that is irreversible. The methods available for diagnosing Alzheimer's disease in patients include positron emission tomography, computed tomography, and magnetic resonance imaging. Clinicians should continue to treat Alzheimer disease in a patient/caregiver-focused manner. A holistic and practical approach using psychoeducation, behavioral, and environmental techniques, advanced planning for future care needs, and appropriate pharmaceutical treatment is not only an effective but also an ethical way to treat Alzheimer disease A patients. This includes building a strong therapeutic alliance with the patient and his or her caregivers.

**Acknowledgements**

I would like to express my sincere appreciation to Sankaralingam Bhuvaneswari College of pharmacy for their invaluable guidance and support during the preparation of this review article. Their expertise and insights have greatly enriched the content.

**Conflicts of interest**

The authors declare that they have no conflict of interest.

**Funding Source**

Nil

**References:**

[1] Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimers Dement 2015; 11(3):322Y384.
[2] Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid $ deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol 2013; 12(4):357Y367. doi:10.1016/ S1474-4422(13)70044-9.
[3] Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9 (1):119Y128. doi:10.1016/ S1474-4422(09)70299-6.
[4] Alzheimer A.U¨ ber eigenartige Krankheitsfa¨lle des spa¨teren Lebensalters. Z Ges Neurol 1911; 4:356Y85
[5] Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. Neurobiol Aging 1997; 18:S1Y2
[6] Montine TJ, Phelps CH, Beach TG, et al. National Institute on AgingY Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: A practical approach. Acta Neuropathol 2012; 123:1Y11
[7] Brookmeyer R, Johnson E, Ziegler-Graham K, et al. (2007) Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement* 3: 186–191.
[8] Prince M, Bryce R, Albanese E, et al. (2013) The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 9: 63–75. e[2]
[9] Alzheimer's Association (2018) 2018 Alzheimer's disease facts and figures. *Alzheimers Dement* 14: 367–429.
[10] Povova J, Ambroz P, Bar M, Pavukova V, et al. Epidemiological of and risk factors for Alzheimer's disease: A review. Biomed Pap Med FacUnivPalacky Olomouc Czech Repub. 2012; 156:108-114.
[11] Blennow K, de Leon MJ and Zetterberg H. Alzheimer's disease. Lancet 2006; 29: 387-40[3]
[12] Yiannopoulou KG and Papageorgiou SG. Current and future treatments for Alzheimer's disease. There Adv Neurol Disord. 2013; 6: 19-3[3]
[13] Lukiw WJ. Amyloid beta (Aß) peptide modulators and other current treatment strategies for Alzheimer's disease (AD). Expert OpinEmerg Drugs. 201[2]
[14] Ballard C and Corbett A Management of neuropsychiatric symptoms in people with dementia. CNS Drugs. 2010; 24: 729-739.
[15] Martinez A Emerging drugs and targets for Alzheimer's disease; Volume 1: Beta-Amyloid, Tau protein and glucose metabolism. Cambridge: The Royal Society of Chemistry. 2010.
[16] O'Brien RJ, Wong PC (2011) Amyloid precursor protein processing and Alzheimer's disease. *Annu Rev Neurosci* 34: 185–204.
[17] Wilkins HM, Swerdlow RH (2017) Amyloid precursor protein processing and bioenergetics. *Brain Res Bull* 133: 71–79.
[18] Vassar R, Kovacs DM, Yan R, et al. (2009) The beta-secretase enzyme BACE in health and Alzheimer's disease: regulation, cell biology, function, and therapeutic potential. *J Neurosci* 29: 12787–12794.
[19] Chen YY, Wang MC, Wang YN, et al. (2020) Redox signaling and Alzheimer's disease: frompathomechanism insights to biomarker discovery and therapy strategy. *Biomark Res* 8: 4[2]
[20] Sabbagh MN, Cooper K, DeLange J, et al. Functional, global and cognitive decline correlates to accumulation of Alzheimer's pathology in MCI and AD. Curr Alzheimer Res 2010;7(4):280Y286. doi:10.2174/156720510791162340.
[21] Apostolova LG, Zarow C, Biado K, et al. Relationship between hippocampal atrophy and neuropathology markers: a 7T MRI validation study of the EADC-ADNI Harmonized Hippocampal Segmentation Protocol. Alzheimers Dement 2015; 11(2):139Y150. doi: 10.1016/j. jalz.2015.01.001.
[22] Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, et al. 2005. Global prevalence of dementia: A Delphi consensus study. Lancet 366: 2112–2117.
[23] Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, Chown MJ, Hebert LE, Hennekens CH, Taylor JO. 1989. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. JAMA 262: 2551–2556.
[24] Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 2007; 29(1Y2): 125Y13[2] doi: 10.1159/000109998.
[25] Plassman BL, Langa KM, Fisher GG, et al. Prevalence of cognitive impairment without dementia in the United States. Ann Intern Med 2008; 148(6):427Y434. doi: 10.7326/0003- 4819-148-6-200803180-00005.
[26] Gurland BJ, Wilder DE, Lantigua R, et al. Rates of dementia in three ethnoracial groups. Int J Geriatr Psychiatry 1999;14(6):481Y49[3] doi:10.1002/(SICI) 1099-1166(199906)14:6G481::AIDGPS9599[3]0. CO;2-5.
[27] Haan MN, Mungas DM, Gonzalez HM, et al. Prevalence of dementia in older latinos: the influence of type 2 diabetes mellitus, stroke and genetic factors. J Am Geriatr Soc 2003;51(2):169Y177. doi: 10.1046/j. 1532-5415.200[3]51054.x.
[28] Manly JJ, Mayeux R. Ethnic differences in dementia and Alzheimer disease. In: Anderson NB, Bulatao RA, Cohen B, eds.Critical perspectives on racial and ethnic differences in health in late life. Washington, DC: National Academies.Press, 2004:95Y14[2]
[29] Barba R, Martinez-Espinosa S, Rodriguez-Garcia E, PondalM,Vivancos J, Del Ser T. 2000. Poststroke dementia: Clinical features and risk factors. Stroke 31: 1494–1501.
[30] deKoning I, DippelDW, vanKooten F,Koudstaal PJ. 2000.A short screening instrument for poststroke dementia: The R-CAMCOG. Stroke 31: 1502–1508.

[31] Desmond DW, Moroney JT, Paik MC, Sano M, Mohr JP, Aboumatar S, Tseng CL, Chan S, Williams JB, Remien RH, et al. 2000. Frequency and clinical determinants of dementia after ischemic stroke. Neurology 54: 1124–1131.
[32] Desmond DW, Moroney JT, Sano M, Stern Y. 200[2] Incidence of dementia after ischemic stroke: Results of a longitudinal study. Stroke 33: 2254–2260.
[33] Zhu L, Fratiglioni L, Guo Z, Basun H, Corder EH,Winblad B, Viitanen M. 2000. Incidence of dementia in relation to stroke and the apolipoprotein E 14 allele in the very old.Findings from a population-based longitudinal study. Stroke 31: 53–60.
[34] Henon H, Durieu I, Guerouaou D, Lebert F, Pasquier F, Leys D. 2001. Poststroke dementia: Incidence and relationship to prestroke cognitive decline. Neurology 57: 1216–122[2]
[35] Klimkowicz A, Dziedzic T, Slowik A, Szczudlik A. 200[2] Incidence of pre- and poststroke dementia: Cracow Stroke Registry. Dement Geriatr Cogn Disord 14: 137–140.
[36] Honig LS, Tang MX, Albert S, Costa R, Luchsinger J, Manly J, Stern Y, Mayeux R. 200[3] Stroke and the risk of Alzheimer disease. Arch Neurol 60: 1707–171[2]
[37] Liebetrau M, Steen B, Skoog I. 200[3] Stroke in 85-year-olds: Prevalence, incidence, risk factors, and relation to mortality and dementia. Stroke 34: 2617–262[2]
[38] Ivan CS, Seshadri S, Beiser A, Au R, Kase CS, Kelly-Hayes M, Wolf PA. 2004. Dementia after stroke: The Framingha Study. Stroke 35: 1264–1268.
[39] Linden T, Skoog I, Fagerberg B, Steen B, Blomstrand C. 2004. Cognitive impairment and dementia 20 months after stroke. Neuroepidemiology 23: 45–5[2]
[40] Srikanth VK, Anderson JF, Donnan GA, Saling MM, Didus E, Alpitsis R, Dewey HM, Macdonell RA, Thrift AG. 2004. Progressive dementia after first-ever stroke: A community-based follow-up study. Neurology 63: 785–79[2]
[41] Tang WK, Chan SS, Chiu HF, Ungvari GS, Wong KS, Kwok TC, Mok V, Wong KT, Richards PS, Ahuja AT. 2004. Frequency and determinants of poststroke dementia in Chinese. Stroke 35: 930–935.
[42] Zhou DH, Wang JY, Li J, Deng J, Gao C, Chen M. 2004. Study on frequency and predictors of dementia after ischemic stroke: The Chongqing stroke study. J Neurol 251: 421–427.
[43] de Koning I, van Kooten F, Koudstaal PJ, Dippel DW. 2005. Diagnostic value of the Rotterdam-CAMCOG in post-stroke dementia. J Neurol Neurosurg Psychiat 76: 263–265.
[44] Kuller LH, Lopez OL, Jagust WJ, Becker JT, DeKosky ST, Lyketsos C, Kawas C, Breitner JC, Fitzpatrick A, Dulberg C. 2005. Determinants of vascular dementia in the Cardiovascular Health Cognition Study. Neurology 64: 1548–155[2]
[45] Gamaldo A, Moghekar A, Kilada S, Resnick SM, Zonderman AB, O'Brien R. 2006. Effect of a clinical stroke on the risk of dementia in a prospective cohort. Neurology 67: 1363–1369.
[46] Jin YP, Di Legge S, Ostbye T, Feightner JW, Hachinski V. 2006. The reciprocal risks of stroke and cognitive impairment in an elderly population. Alzheimer's Dement 2: 171–178.
[47] Simons LA, Simons J,McCallum J, Friedlander Y. 2006. Lifestyle factors and risk of dementia: Dubbo Study of the elderly. Med J Australia 184: 68–70.
[48] Srikanth VK,Quinn SJ, Donnan GA, Saling MM, Thrift AG. 2006. Long-term cognitive transitions, rates of cognitive change, and predictors of incident dementia in a population-based first-ever stroke cohort. Stroke 37: 2479–248[3]
[49] Yip AG, Brayne C, Matthews FE. 2006. Risk factors for incident dementia in England and Wales: The Medical Research Council Cognitive Function and Ageing Study. A population-based nested case-control study. Age Ageing 35: 154–160.
[50] Jin YP, Ostbye T, Feightner JW, Di Legge S, Hachinski V. 2008. Joint effect of stroke and APOE 4 on dementia risk: The Canadian Study of Health and Aging. Neurology 70: 9–16.
[51] Reitz C, Bos MJ, Hofman A, Koudstaal PJ, Breteler MM. 2008. Prestroke cognitive performance, incident stroke, and risk of dementia: The Rotterdam Study. Stroke 39: 36–41.
[52] Rastas S, Pirttila T, Mattila K, Verkkoniemi A, Juva K, Niinisto L, Lansimies E, Sulkava R. 2010. Vascular risk factors and dementia in the general population aged .85 years: Prospective population-based study. Neurobiol Aging 31: 1–7.
[53] Chodosh J, Reuben DB, Albert MS, Seeman TE. 200[2] Predicting cognitive impairment in high-functioning community-dwelling older persons: MacArthur Studies of Successful Aging. J Am Geriat Soc 50: 1051–1060.
[54] Manly JJ, Schupf N, Tang MX, Stern Y. 2005. Cognitive decline and literacy among ethnically diverse elders. J Geriat Psychiat Neurol 18: 213–217.
[55] Evans DA, Beckett LA, Albert MS, Hebert LE, Scherr PA, Funkenstein HH, Taylor JO. 199[3] Level of education and change in cognitive function in a community population of older persons. Ann Epidemiol 3: 71–77.
[56] Evans DA, Hebert LE, Beckett LA, Scherr PA, Albert MS, Chown MJ, Pilgrim DM, Taylor JO. 1997. Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. Arch Neurol 54: 1399–1405.
[57] Letenneur L, Commenges D, Dartigues JF, Barberger- Gateau P. 1994. Incidence of dementia and Alzheimer's disease in elderly community residents of south-western France. Int J Epidemiol 23: 1256–1261.
[58] Letenneur L, Gilleron V, Commenges D, Helmer C, Orgogozo JM, Dartigues JF. 1999. Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. J Neurol Neurosurg Psychiat 66: 177–18[3]
[59] Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. 1994. Influence of education and occupation on the incidence of Alzheimer's disease. JAMA 271: 1004–1010.

[60] White L, Katzman R, Losonczy K, Salive M,Wallace R, Berkman L, Taylor J, Fillenbaum G, Havlik R. 1994. Association of educationwith incidence of cognitive impairment in three established populations for epidemiologic studies of the elderly. J Clin Epidemiol 47: 363–374.
[61] Qiu C, Backman L,Winblad B, Aguero-Torres H, Fratiglioni L. 2001. The influence of education on clinically diagnosed dementia incidence and mortality data from the Kungsholmen Project. Arch Neurol 58: 2034–2039.
[62] Valenzuela MJ, Sachdev P. 2005. Brain reserve and dementia: A systematic review. Psychol Med 25: 1–14.
[63] Sparks DL, Kuo YM, Roher A, Martin T, Lukas RJ. 2000.VAlterations of Alzheimer's disease in the cholesterol-fedVrabbit, including vascular inflammation. PreliminaryVobservations. Ann NY Acad Sci 903: 335–344.
[64] Luchsinger JA, Tang MX, Shea S, Mayeux R. 200[2] Caloric intake and the risk of Alzheimer disease. Arch Neurol 59: 1258–126[3]
[65] Morris MC, EvansDA, Bienias JL, Tangney CC, BennettDA, Aggarwal N, Schneider J, Wilson RS. 200[3] Dietary fats and the risk of incident Alzheimer disease. Arch Neurol 60: 194–200.
[66] Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, Tucker KL, Kyle DJ, Wilson PW, Wolf PA. 2006.VPlasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: The Framingham Heart Study. Arch Neurol 63: 1545–1550.
[67] van Gelder BM, Tijhuis M, Kalmijn S, Kromhout D. 2007. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: The Zutphen Elderly Study. Am J Clin Nutr 85: 1142–1147.
[68] Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A, Witteman JC, Breteler MM. 200[2] Dietary intake of antioxidants and risk of Alzheimer disease. JAMA 287: 3223–3229.
[69] Morris MC, EvansDA, Bienias JL, Tangney CC, BennettDA, Aggarwal N, Wilson RS, Scherr PA. 200[2] Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. JAMA 287: 3230–3237.
[70] Luchsinger JA, Tang MX, Shea S, Mayeux R. 200[3] Antioxidant vitamin intake and risk of Alzheimer disease. Arch Neurol 60: 203–208.
[71] van Praag H, Kempermann G, Gage FH. 1999. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 2: 266–270.
[72] Cotman CW. Berchtold NC. 200[2] Exercise: A behavioural intervention to enhance brain health and plasticity. Trends Neurosci 25: 295–301.
[73] Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. 1990. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proc Natl Acad Sci 87: 5568–557[2]
[74] Carro E, Trejo JL, Busiguina S, Torres-Aleman I. 2001. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insultsof different etiology and anatomy. J Neurosci 21: 5678–5684.
[75] Ford ES. 200[2] Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology 13: 561–568.
[76] Reuben DB, Judd-Hamilton L, Harris TB, Seeman TE. 200[3] The associations between physical activity and inflammatory markers in high-functioning older persons: MacArthur Studies of Successful Aging. J Am Geriatr Soc 51: 1125–1130.
[77] Angevaren M, Aufdemkampe G,Verhaar H, Aleman A,Vanhees L. 2008. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database of Systematic Reviews (Online): CD005381.
[78] Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, Bennett DA. 2002b. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA 287: 742–748.
[79] Wilson RS, Scherr PA, Schneider JA, Tang Y, Bennett DA. 2007. Relation of cognitive activity to risk of developing Alzheimer disease. Neurology 69: 1911–1920.
[80] Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, Ambrose AF, Sliwinski M, Buschke H. 2003b. Leisure activities and the risk of dementia in the elderly. New Engl J Med 348: 2508–2516.
[81] Akbaraly TN, Portet F, Fustinoni S, Dartigues JF, Artero S, Rouaud O, Touchon J, Ritchie K, Berr C. 2009. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. Neurology 73: 854–861.
[82] American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition. Washington, DC: American Psychiatric Publishing, 201[3]
[83] Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7(3):270Y279. doi:10.1016/ j.jalz.2011.0[3]008.
[84] McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7(3):263Y269. doi:10.1016/j.jalz.2011.0[3]005.
[85] Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7(3):280Y29[2] doi:10.1016/j.jalz.2011.0[3]00[3]
[86] Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56(9): 1143Y115[3] doi:10.1212/WNL.56.9.114[3]
[87] C hui H, Zhang Q. Evaluation of dementia: a systematic study of the usefulness of the American Academy of Neurology's practice parameters. Neurology 1997; 49(4):925Y935. doi:10.1212/WNL.49.4.925.
[88] Apostolova LG, Dutton RA, Dinov ID, et al. Conversion of mild cognitive impairment to Alzheimer disease predicted by hippocampal atrophy maps. Arch Neurol 2006;63(5): 693Y699. doi:10.1001/archneur.6[3]5.69[3]
[89] Apostolova LG, Thompson PM, Green AE, et al. 3D comparison of low, intermediate, and advanced hippocampal atrophy in MCI. Hum Brain Mapp 2010;31(5):786Y797. doi:10.1002/hbm.20905.

[90] Jack CR Jr, Shiung MM, Gunter JL, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology 2004;62(2):591Y600. doi:10.1212/ 01.WNL.0000110315.26026.EF.
[91] Apostolova LG, Steiner CA, Akopyan GG, et al. Three-dimensional gray matter atrophy mapping in mild cognitive impairment and mild Alzheimer disease. Arch Neurol 2007;64(10): 1489Y1495. doi:10.1001/archneur.64.10.1489.
[92] Thompson PM, Hayashi KM, de Zubicaray G, et al. Dynamics of gray matter loss in Alzheimer's disease. J Neurosci 2003;23(3): 994Y1005.
[93] Kilroy E, Apostolova L, Liu C, et al. Reliability of two-dimensional and three-dimensional pseudo-continuous arterial spin labeling perfusion MRI in elderly populations: comparison with 15O-water positron emission tomography. J Magn Reson Imaging 2014;39(4):931Y939. doi:10.1002/jmri.24246.
[94] Silverman DH. Brain 18F-FDG PET in the diagnosis of neurodegenerative dementias: comparison with perfusion SPECT and with clinical evaluations lacking nuclear imaging. J Nucl Med 2004;45(4):594Y607.
[95] Silverman DH, Truong CT, Kim SK, et al. Prognostic value of regional cerebral metabolism in patients undergoing dementia evaluation: comparison to a quantifying parameter of subsequent cognitive performance and to prognostic assessment without PET. Mol Genet Metab 2003;80(3):350Y355. doi:10.1016/S1096-7192(03)00139-[2]
[96] What Is A PET Scan? How Does A PET Scan Work? Medical News Today: Health News. 2009.
[97] Small GW Neuroimaging and Genetic Assessment for Early Diagnosis of Alzheimer's disease. Journal of Clinical Psychiatry. 1996; 57: 9-1[3]
[98] Beyenhof and Lauren. How a CT Scan Works. Helium - Where Knowledge Rules. Web. 2010.
[99] Khachaturian, Zaven S, and Teresa SR. Alzheimer's Disease: Cause(s), Diagnosis, Treatment, and Care. Boca Raton: CRC.1996.
[100] Gould, Todd A, and Molly Edmonds Discovery Health "MRI Magnets". Discovery Health. Web. 2010.
[101] Emilien and Grard, et al. Alzheimer Disease: Neuropsychology and Pharmacology. Basel: Birkhauser. 2004.
[102] Mellon EA, Pilkinton DT, Clark CM et al. Sodium MR Imaging Detection of Mild Alzheimer's Disease: Preliminary Study. American Journal of Neuroradiology. 2009; 30: 978-984.
[103] Nordberg A PET Studies and Cholinergic Therapy in Alzheimer's disease. Rev Neurol, National Center for Biotechnology Information. 1999; 4: 53-6[3]
[104] Atri A. Current and future treatments in Alzheimer's disease. *Semin Neurol*. 2019; 39:227-240.
[105] Na R, Yang JH, Yeom Y, et al. A systematic review and meta-analysis of nonpharmacological interventions for moderate to severe dementia. *Psychiatry Investig*. 2019;16:325-335.
[106] Kishita N, Backhouse T, Mioshi E. Nonpharmacological interventions to improve depression, anxiety, and quality of life (QoL) in people with dementia: an overview of systematic reviews. *J Geriatr Psychiatry Neurol*. 2019;33: 28-41.
[107] Hukins D, Macleod U, Boland JW. Identifying potentially inappropriate prescribing in older people with dementia: a systematic review. *Eur J Clin Pharmacol*. 2019; 75:467-481.
[108] Anderson RM, Hadjichrysanthou C, Evans S, Wong MM. Why do so many clinical trials of therapies for Alzheimer's disease fail? *Lancet*. 2017;390:2327-2329.
[109] Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2019. *Alzheimers Dement*. 2019;5:272-29[3]
[110] Doody RS, Raman R, Farlow M, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med*. 2013;369:341-350.
[111] Vandenberghe R, Rinne JO, Boada M, et al. Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials. *Alzheimers Res Ther*. 2016;8:18.
[112] The Lancet Neurology. Solanezumab: too late in mild Alzheimer's disease. *Lancet Neurol*. 2017;16:97.
[113] Burki T. Alzheimer's disease research: the future of BACE inhibitors. *Lancet*. 2018; 391:2486.
[114] Egan MF, Kost J, Voss T, et al. Randomized trial of verubecestat for prodromal Alzheimer's disease. *N Engl J Med*. 2019;380:1408-1420.
[115] Henley D, Raghavan N, Sperling R, Aisen P, Raman R, Romano G. Preliminary results of a trial of atabecestat in preclinical Alzheimer's disease. *N Engl J Med*. 2019;380:1483-1485.
[116] Gauthier S, Albert M, Fox N, et al. Why has therapy development for dementia failed in the last two decades. *Alzheimers Dement*. 2016;12:60-64.
[117] Romero K, Ito K, Rogers JA, et al. The future is now: model-based clinical trial design for Alzheimer's disease. *Clin Pharmacol Ther*. 2015;97:210-214.
[118] Hadjichrysanthou C, Ower AK, de Wolf F, Anderson RM. The development of a stochastic mathematical model of Alzheimer's disease to help improve the Design of clinical trials of potential treatments. *PLoS ONE*. 2018; 13:e0190615.
[119] Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement*. 2016; 12:292-32[3]
[120] Goñi F, Herline K, Peyser D, et al. Immunomodulation targeting of both Aβ and tau pathological conformers ameliorates Alzheimer's disease pathology in TgSwDI and 3xTg mouse models. *J Neuroinflammation*. 2013; 10:150.
[121] Wisniewski T, Goñi F. Immunotherapeutic approaches for Alzheimer's disease. *Neuron*. 2015; 85:1162-1176.
[122] Yoshiyama Y, Lee VM, Trojanowski JQ. Therapeutic strategies for tau mediated neurodegeneration. *J Neurol Neurosurg Psychiatry*. 2013;84 :784-795.
[123] Medina M. An overview on the clinical development of tau-based therapeutics. *Int J Mol Sci*. 2018;19: E1160.
[124] Budur KK, West T, Braunstein JB, et al. Results of a phase 1, single ascending dose, placebo-controlled study of ABBV-8E12 in patients with Progressive Supranuclear Palsy and phase 2 study design in early Alzheimer's disease. *Alzheimers Dement*. 2017; 13:599-600.

[125] Wilcock GK, Gauthier S, Frisoni GB, et al. Potential of low dose leuco-methylthioninium bis (Hydromethanesulphonate) (LMTM) monotherapy for treatment of mild Alzheimer's disease: cohort analysis as modified primary outcome in a phase III clinical trial. *J Alzheimers Dis*. 2018; 61:435-457.
[126] Doody R. Developing disease-modifying treatments in Alzheimer's disease—a perspective from Roche and Genentech. *J Prev Alzheimers Dis*. 2017;4:264-27[2]