The Pharma Innovation Journal 2021; 10(5): 1460-1470

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2021; 10(5): 1460-1470

www.thepharmajournal.com
Received: 02-02-2021
Accepted: 09-03-2021

Ankita Gupta
Shiva Insititute of B. Pharmacy Bilaspur, Himachal Pradesh, India

Vivek Sharma
Baddi University of Emerging Sciences and Technology, Makhnumajra, Baddi, Himachal Pradesh, India

Naveen Singh
Baddi University of Emerging Sciences and Technology, Makhnumajra, Baddi, Himachal Pradesh, India

Corresponding Author:
Vivek Sharma
Baddi University of Emerging Sciences and Technology, Makhnumajra, Baddi, Himachal Pradesh, India

Ongoing clinical trials of new drugs for Alzheimer's disease: A review article

Ankita Gupta, Vivek Sharma and Naveen Singh

Abstract
Alzheimer's disease is the most common cause of dementia worldwide, it occurs continuing to growing in part because of the aging world population. Alzheimer's disease is the most common cause of neurodegenerative disorder in the ageing individuals. It is set to be the largest killer among the growing elderly population. This neurodegenerative disease process is classify through two hallmark pathologies: beta-amyloid plaque deposition and neurofibrillary tangles of hyper phosphorylated tau. Diagnosis is mainly depend upon clinical presentation satisfying several criteria as well as fluid and imaging biomarkers. Clinically, patients primarily present with short-term memory loss, subsequently followed by executive dysfunction, confusion, agitation and behavioral disturbances. Approximately 70% of the risk of developing AD because of genetics. Three causative genes have been related with autosomal dominant familial (APP, PSEN1 and PSEN2) and 1 genetic risk factor (APOEepslon4 allele). However, acquired factors such as cerebrovascular diseases, diabetes, hypertension, obesity and dyslipidemia increases the danger of AD development. At present treatment is currently targeted through symptomatic therapy, although trials are proceeding that aim to reduce the production and overall burden of pathology within the brain. Here, we discuss modern advances in our understanding of the clinical evaluation and treatment of Alzheimer's disease, with updates regarding clinical trials still in progress.

Keywords: Ongoing, clinical, drugs, Alzheimer's, neurodegenerative

Introduction
One of the great tasks faced by neuropsychologists over the past 50 years is to understand the cognitive and behavioral manifestations of dementia and their relationship to underlying brain pathology. This challenge has grown extensively over the years with the aging of the population and the age-related nature of many dementia-producing neurodegenerative diseases. Although the concept of dementia has occurred for thousands of years, it is only early in the past century that the essential clinical syndrome and associated neurodegenerative changes were first discovered. In 1907, Aloysius "Alöis" Alzheimer cautiously described the symptoms of a 51- year-old woman, Auguste Deter, who was under his care at the state asylum in Frankfurt Germany. Alzheimer's description of her symptoms is almost certainly the first neuropsychological characterization of the disease:

"Her memory is totally impaired. If stuffs are shown to her, she names them correctly, but almost immediately afterwards she has forgotten everything. When interpretation a test, she skips from line to line or reads by spelling the words individually, or by making them meaningless through her pronunciation. In writing she repeats separate syllables many times, neglects others and quickly breaks down completely. In speaking, she uses gap-fills and a few paraphrased expressions ("milk- pourer" instead of cup); sometimes it is understandable she cannot go on. Plainly, she does not understand certain questions. She does not remember the use of some objects."

Dementia is a general term that refers to a failure in cognitive ability severe enough to interfere with activities of daily living. Alzheimer disease (AD) is the most common type of dementia, accounting for at least two-thirds of cases of dementia in people age 65 and older. Alzheimer disease is a neurodegenerative disease that produces progressive and disabling impairment of cognitive functions including memory, comprehension, language, attention, reasoning, and judgment. It is the sixth leading cause of death in the United States. Alzheimer disease is characteristically a disease of old age. Onset before 65 years of age (early onset) is rare and seen in less than 10% of Alzheimer disease patients. The most common presenting symptom is selective short-term memory loss. The disease is invariably progressive, eventually leading to

severe cognitive decline. There is no cure for Alzheimer disease, although there are treatments available that may improve some symptoms.

Symptoms of Alzheimer disease depend on the stage of the disease. Alzheimer disease is categorized into preclinical, mild, moderate, and late-stage depending on the degree of cognitive impairment. The original presenting symptom is usually recent memory loss with relative sparing of long-term memory and can be elicited in most patients even when not the presenting symptom. Short-term memory impairment is followed by impairment in problem-solving, judgment, executive functioning, lack of motivation and disorganization, leading to problems with multitasking and abstract thinking. In the early stages, impairment in executive functioning may be subtle. This is followed by language disorder and impairment of visuospatial skills. Neuropsychiatric symptoms like apathy, social withdrawal, disinhibition, agitation, psychosis, and wandering are also common in the mid to late stages. Difficulty performing learned motor tasks (dyspraxia), olfactory dysfunction, and sleep disturbances, extrapyramidal motor signs like dystonia, akathisia, and parkinsonian symptoms occur late in the disease. This is followed by primitive reflexes, incontinence, and total dependence on caregivers [1-3].

Background

Dementia is a clinical syndrome which is characterized by coming decline in 2 or more domains including memory, language, executive and visuospatial function, personality, and behavior, which causes loss of abilities to perform instrumental and/or basic activities of daily living. AD is the main cause for dementia. In United State death rate because of stroke and cardiovascular disease get decline, on the other hand rate of death due to dementia may increases 89% IN 2000 to 2014. There is spend of at least $500 billion per year for diagnose of dementia. For diagnose of AD in living patients 3 main things are focused that are post-mortem evaluation of brain tissue, though cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers combined with several relatively new clinical criteria. Current treatment for dementia includes cholinesterase inhibitors which are suitable for patient of any age. Medication may increases the quality of life of patients and caretaker but does not decline the rate of AD.

Clinical research is proceeding toward more definitive treatment of the hallmark pathology in AD with the expectation that these therapies will attenuate the progressive cognitive decline associated with this illness.

Diagnosis

The clinical indications of AD include disturbances in the areas of memory and language, visuospatial orientation, and higher executive function. No cognitive changes include personality changes, decreased judgment ability, wandering, psychosis, mood disturbance, agitation, and sleep abnormalities.

Patients suspected from AD may comprises (i) a history from a reliable informant (containing general medical history, neurological history, neuropsychiatries history, family history); (ii) physical and neurological examination; (iii) routine laboratory examinations (complete blood count, sequential multiple analysis-21, thyroid function tests, vitamin B12, folate, rapid plasma regain); optional laboratory examinations (erythrocyte sedimentation rate, human immunodeficiency virus (HIV) serology, serology for Lyme's disease, urinalysis, urine drug screen, lumbar puncture, electroencephalography); and (iv) neuroimaging (computed tomography or magnetic resonance imaging). Neuropathological examination (looking for the hallmark senile plaques and neurofibrillary tangles) from autopsy studies suggested 90% accuracy in clinical detection of AD such as those of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM TV) criteria and the National Institute of Neurological and Communicative Diseases and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [5]

Etiology

AD is a regular, progressive neurodegenerative disease caused by neuronal cell death. It is started from entorhinal cortex located in hippocampus. Early and late onset AD can caused due to genetic factor. There are many risk factors for AD. Increasing age is the most common factor of AD. Traumatic head injury, depression, cardiovascular and cerebrovascular disease, higher parental age, smoking, family history of dementia, and presence of APOE e4 allele increases the risk of AD. Higher education, use of estrogen by women, use of anti-inflammatory agents, and regular aerobic exercise may decreases the risk of AD. Individuals having 2 or more than 2 siblings have higher risk that is 3-fold of late onset AD as compared to normal population [6-8].

Comorbidity

Although still AD is the main cause of dementia but still it is comorbid with Lewy-body or vascular dementia. There is limited clinical data of treatment of patients having this type of comorbidity. Patients suffering from AD having medical comorbidity (heart disease, diabetes, cancers) [9].

Epidemiology

AD is mainly divided into familial, irregular, early onset (younger than 65) and later onset (older than 65). In every 6 month AD increases 5.5% to 9%. It may doubles in every 10 years. AD mainly affects people having age 85 or older than 85.

Early recognition of AD is essential for treatment with cholinesterase inhibitors, reduction in caregiver stress, community support, delay in institutionalization, planning of lifestyle, and legal issues.

AD is mainly the disease of old age. Global occurrence of AD is 24 million which is predicted to be 4 times more at 2050. Health care cost in United State is $172 billion per year. In 2011, there are

4.5 million people of United State suffer from AD having age 65 or more. Frequency of patients

may get double after every 10 years especially in case of people having age 65 or more. There are more chances of occurrence of AD in women after age of 85 [10, 11].

Prognosis

AD is the progressive disease. Persons suffer from AD have life expectancy of 4 to 8 years. There are few people who live up to 20 years suffering from AD. Main cause of AD is pneumonia.

Staging

Preclinical: Earliest pathological changes started from entorhinal cortex followed by hippocampus. In this stage,

patient suffer from mild memory loss but there is no functional impairment in their daily life activities. At this stage it is classified as mild cognitive impairment.

Mild Alzheimer Disease

In this stage cognitive impairment begins because disease reaches at cerebral cortex. Along with memory loss, there is a failure to remember new information, forgetting things and appointments, repetitive questions and conversations, confusion, disorientation, personality changes, mood swings, loss of spontaneity, and impairment in reasoning and judgment.

Moderate Alzheimer Disease

In this stage disease starts to spread in more area of cerebral cortex which is responsible for language, reasoning, and sensory processing. There is increasing memory loss and attention, and behavioral problems like wandering off and agitation starts to appear. In this stage patients got difficulty to identify their own family and friends. They have apathy, social withdrawal, and loss of inhibition. They often make repetitive statements and have a loss of impulse control. They also have problems with language, reading, and writing.

Severe Alzheimer Disease

In last stage disease progressed to entire cortex. In this stage patients cannot identify their family and friends and also they depend fully on other for their daily activities Along with other features, they also become incontinent of bladder and bowel and may have difficulty swallowing [12].

Pathology

AD is mainly caused by overproduction and impaired clearance of β-Amyloid. Downstream events are tau hyper phosphorylation and neuronal toxicity. The primary pathologic features of AD are brain atrophy from regional neuronal and synaptic loss, extracellular β-amyloid deposition in the form of neuritic plaques, and intra neuronal tau protein deposition in the form of intra neuronal neurofibrillary tangles. β-Amyloid also deposits in the cerebral blood vessels. Cerebral amyloid angiopathy ranges in severity from small amounts of amyloid to major deposits that distort the artery architecture and cause cortical micro infarcts, micro aneurysms, and cerebral micro hemorrhages or macro hemorrhages

From past 20 years amyloid deposition considered to be main cause of AD [13]. Neurofibrillary tangles are not involve in AD but can be found in other conditions, such as dementia pugilistica and chronic traumatic encephalopathy, prion disease, and in normal aging. Neurofibrillary tangle burden and neuronal loss show a robust association with global cognitive impairment [14, 15].

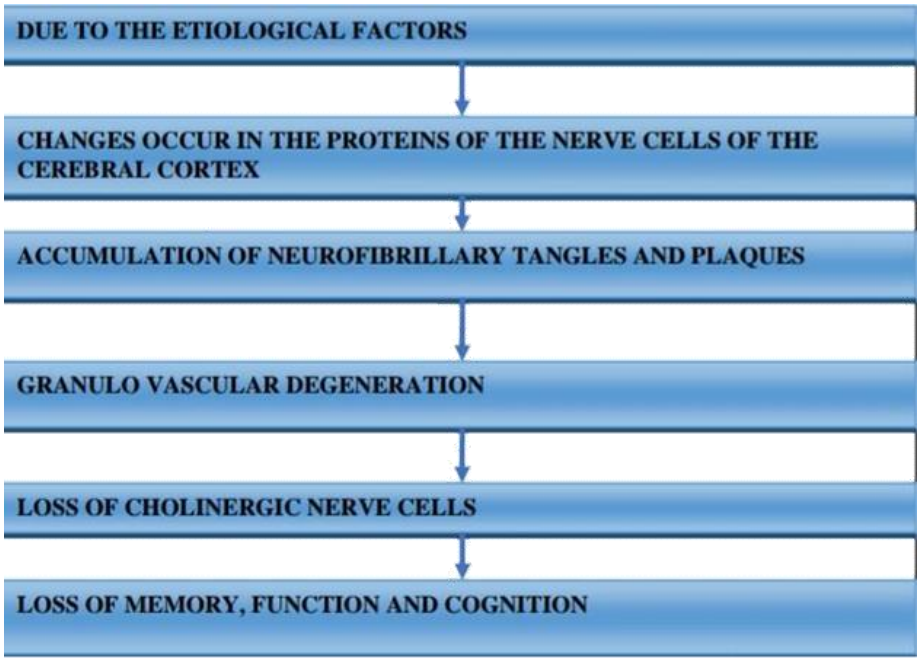


Fig 1: Pathology of Alzheimer Disease

Symptoms

Both EOAD and LOAD are clinically present in dementia and initiates with gradual decline in memory. Disease progression may cause impairment in cognition area (e.g., language, abstract reasoning, and executive function or decision making) and typically it may cause difficulty in work, social situations and household activities. This may also cause change in mood which effect on memory. Delusions and hallucinations are not the sign of AD but may occur any time during course of illness. Neurological symptoms may occur in later stage of AD that are seizures, hypertonia, myoclonus, incontinence, and mutism. Death commonly occurs from general inanition, malnutrition, and pneumonia [16]. Treatment of AD with cholinesterase inhibitors and memantine may result in slowing of cognitive decline in patients who suffer from mild-to- moderate dementia, but current treatments do not modify the course of illness [17, 18].

Treatment: AD requires exact diagnosis as soon as possible and adequate etiological treatment. As it is an incurable age-related disease neurodegenerative disorder so pathophysiological considerations are needed. Therapeutic considerations mainly focused on improving symptoms as well as reducing progression of disease. Although it may not reverse the disease so prevention is the best solution for this public health disease [19, 20].

1. Symptomatic treatment

Acetylcholinesterase inhibitors

It is well known that acetylcholine (ACh) plays an important role for mediating learning and memory [21]. Furthermore, direct interaction between Aβ and cholinergic systems has been proposed, with negative response to the production of the peptide; it has been suggested that the alteration in this negative feedback loop and abnormal accumulation of Aβ reduced cholinergic transmission effectiveness, focused on alpha-7 nicotinic acetylcholine receptors [22, 23].

N-Methyl-D-aspartate Receptor (NMDA) Antagonist

Glutamate-mediated excitotoxicity may result in calcium overload and mitochondrial dysfunction, with increased nitric oxide generation, which can be harmful to cells, forming high levels of oxidants and eliciting neuronal apoptosis. This overstimulation is blocked by NMDA receptor antagonists such as memantine, which was approved in 2003 by the Food and Drug Administration (FDA) for the treatment of moderate-to-severe AD, having a marginal advantageous effect on cognition in mild-to-moderate AD [24-26].

Other neurotransmitter systems

Muscarinic and nicotinic ACh receptors are also considered targets for AD treatment, although selectivity of the agonists has been a problem outcome in clinical trials. EVP-6124 is at present in phase II trial [20].

2. Etiology- Based Treatment

ApoE ε4 is the main genetic risk factor for sporadic AD (the major risk factor is age), although, for disease-modifying treatment based on amyloid cascade hypothesis, efforts are targeting secretase modulation and amyloid binders, and also targeting kinases involved in the hyper phosphorylation of tau protein [25, 24].

Secretase inhibitors

APP is first divided either by α-secretase or by β-secretase enzymes, and the resulting fragments are processed by γ-secretase. The proposal of the "over activation" of β- and γ-secretases, or age-related decreased α-secretase processing, has led to the use of inhibitors for this amyloid genic pathway [27].

Amyloid binders

The deposition of Aβ in AD is concentration-dependent which increased amyloid genic processing of APP and inefficient removal of peptides may be involved in the pathology. There is reduced activity of Aβ- degrading enzymes, such as neprilysin, an insulin-degrading enzyme, as well as the ApoE determinant, which relates well with the proposal of AD as a metabolic disorder [25].

Anti-Aβ Aggregation Compounds

In recent eras, research has focused on developing therapies in which the Aβ peptide formation or its aggregation is prevented. Amongst the small molecule inhibitors of Aβ aggregation in clinical trials are tramiprosate (phase III), clioquinol (phase II), scylloinositol (phase II), and epigallocatechin-3-gallate (phase II/III); although these drugs have achieved stabilization of the Aβ monomers, they have important side effects. Also, synthetic β-sheet breaker peptides of the IAβ5p arrangement such as azetidine-2-carboxylic acid, 3-phenyl azetidine-2-carboxylic acid, β-proline, and β-sulfonylproline controls the cell damage caused by the Aβ exposure by preventing fibril formation and they have shown improved results Aβ with regard to spatial memory.

Stemazole has been shown to protect SH-SY5Y cells from toxicity induced by *in vitro*, reducing Aβ aggregation. Likewise, compounds such as curcumin, T718MA, and SK-PC-B70M protect neurons from Aβ-induced toxicity [28].

Tau Therapies

Prevention of aggregates of paired, helically twisted filaments of hyper phosphorylated tau in neurofibrillary tangles is one of the main objective of this therapy. Immunotherapy has been developed; AADvac1 was the first vaccine in clinical trials, and ACI-35 (another liposomal- based vaccine) trials have begun.

Other Therapies

As an age-related pathology, AD is related with other chronic-degenerative disorders, and coordinated therapies are needed. A type 3 diabetes hypothesis of AD has been developed, and intranasal insulin is included as a possible treatment for the disease, due to its ability to penetrate the brain-blood barrier [25].

3. Nonpharmacological treatments

Nonpharmacological treatments are needed for the prevention of AD or as adjuvants in other treatments. AD prevention strategies can be divided into two groups, the first related with lifestyle and the second with diet and chemical compounds.

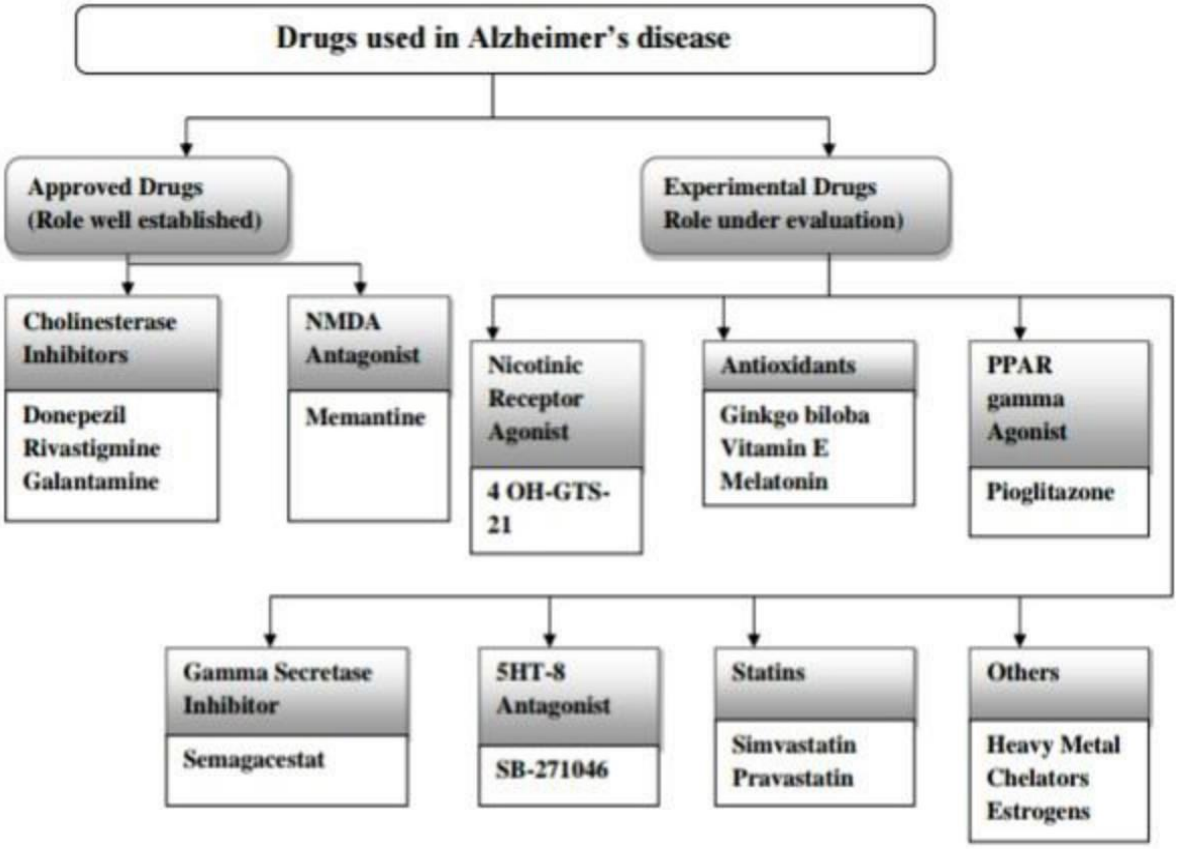
Lifestyle

Lifestyle strategies involve physical activity, mental challenges, energy restriction, and socialization as preventive factors in AD [28]. Physical activity such as aerobic exercise was related with the reduction of AD deficits in a cohort study [29]. This was not reliable with studies that considered a small number of cases [30].

Diet and Chemical Substances

Dietary supplements for prevention of AD were studied with vitamins such as B6, B12, folates, and E, C, and D vitamins. Vitamin B studies produced mixed results; on one hand, a two-year treatment with homocysteine and vitamin B in 271 patients indicated a significant difference as compared to placebo in whole brain atrophy [31], whereas other reports indicate different results [32, 33]. It has been proposed that folic acid has neuroprotective activity through an epigenetic mechanism that inhibits amyloid-β peptide accumulation. Studies with 2000 IU of vitamin E did not indicate a protective effect for AD with three years of treatment [33], nor with the combined treatment with vitamin C. Additionally, does vitamin D supplementation improve cognitive performance [34].

Classification of drugs



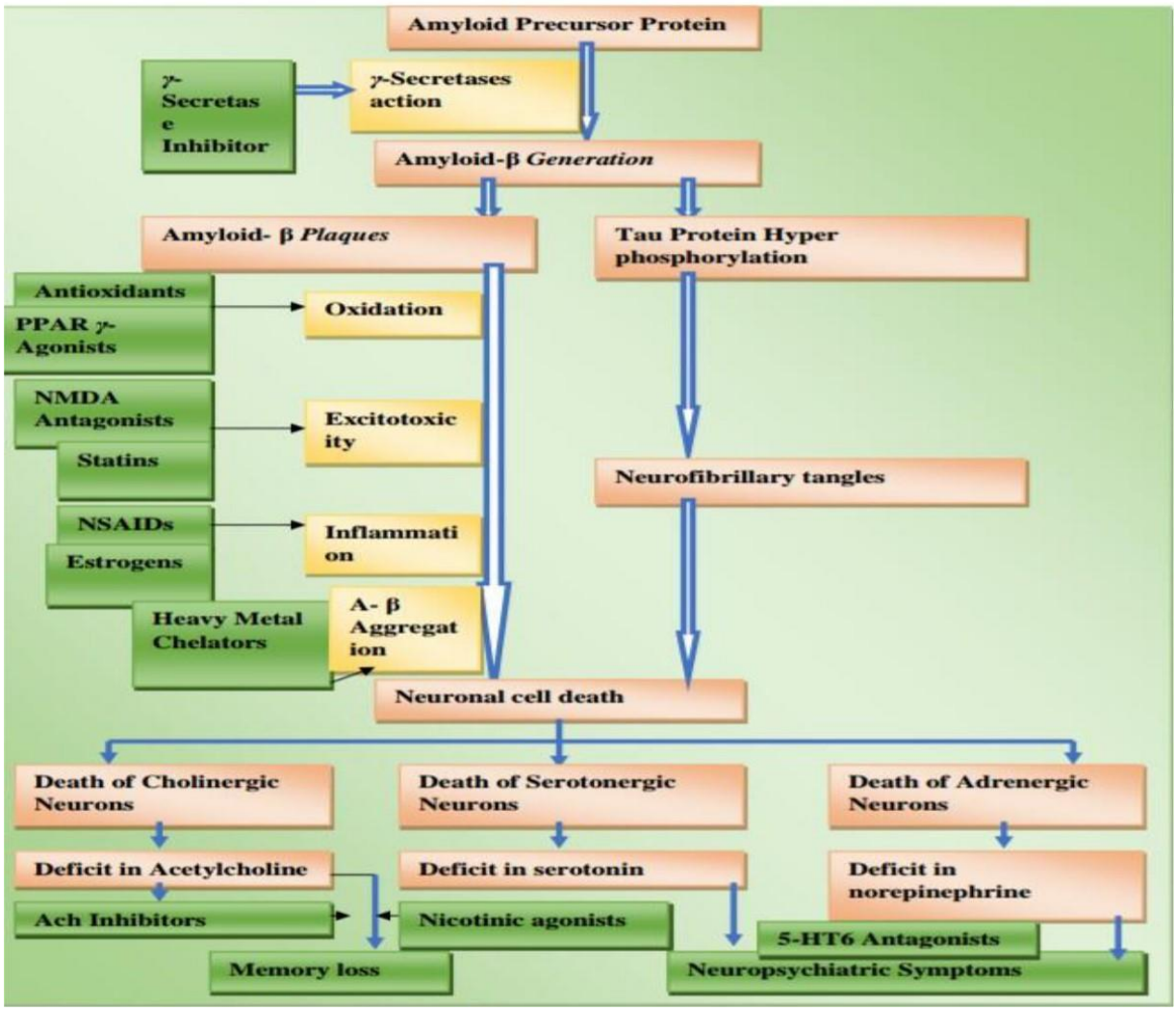


Fig 2: Targets of Drug Action on Ad

Ongoing clinical trials of new drugs for Ad

The World Alzheimer Report 2015 uncovered that 46.8 million individuals overall were living with dementia in 2015, and the all-out worldwide cultural expense of dementia was evaluated to be US $818 billion. Alzheimer illness (AD) is the most well-known dementia type and may represent 60–70% of dementia cases. Promotion normally presents as dynamic memory decay at first, which is joined or followed by other psychological dysfunctions, for example, visuospatial variations from the norm, route challenges, official issues, and language unsettling influence. These intellectual weaknesses further influence day by day life exercises, and numerous conduct mental indications of dementia (BPSD) normally happen during the illness course.

Obsessive proof in regards to AD shows that degeneration in cholinergic neuron–rich districts, to be specific the core basalis of Meynert, frontal cortex, foremost cingulate cortex, and back cingulate cortex, is related with memory misfortune, disturbance, and lack of care. Acetylcholine (ACh) has been demonstrated to be profoundly connected with memory work, including memory encoding, combination stockpiling, and the recovery procedure [35-36]. As of now, in any event three cholinesterase inhibitors (Ache Is) allowed by the US Food and Drug Administration (FDA) are being utilized to treat AD, with some clinical improvement in cognizance and worldwide capacity [37]. In any case, acheIs can just recuperate subjective side effects of AD for a specific period however can't alter the infection course.

The genuine reasons of AD are as yet hazy. Two obsessive characteristics of AD exist, regarding feeble plaques, which comprise of amyloid fibrils made out of the amyloid-beta (Aβ) peptide and neurofibrillary tangles comprising of hyper phosphorylated tau protein [38]. Another critical finding is mind decay, especially in the hippocampus. The suggestion that Aβ gathering is the focal occasion in AD pathogenesis was at first proposed by three free gatherings in 1991. All the freak qualities of innate, autosomal, and predominant familial AD, with amyloid antecedent protein (APP), presenilin 1, and presenilin 2, encode the significant proteins engaged with amyloid digestion [39-40]. Patients with trisomy 21 have APP quality areas with increasingly amyloid amassing and high AD hazard in late life since they have one more duplicate of the APP quality, which brings about expanded amyloid creation [40]. Past examinations have demonstrated that the cerebral testimony of Aβ fibrils can happen periods before an individual shows clinical indications [41]. Atomic imaging studies, for example, those utilizing amyloid positron emanation tomography (PET) have indicated that Aβ affidavit arrives at a level before mind decay can be perceived from basic attractive reverberation imaging (MRI) and subjective side effects [39,42]. The amyloid theory has been the standard clarification for AD pathogenesis for periods, yet all the earlier clinical preliminaries including amyloid weight decrease au collection, which may be a result of neuronal harm, was proposed to start between AD clinical side effect improvement and Aβ gathering. Neurofibrillary tangles and quantitative neuronal misfortune, yet not amyloid plaques, have been found to relate with infection seriousness and dementia term. In addition, PET investigations have indicated that the spatial examples of tau tracer restricting are firmly identified with neurodegeneration designs and the clinical introduction in patients with AD [43]. Recently, biomarkers of amyloid, tau, and neurodegeneration were utilized for correctly diagnosing AD [44].

Anti-amyloid therapy

A rare approaches reduce the amyloid burden have been developed. Aβ is produced from APP, which is digested by gamma-secretase and beta-secretase [45-46]. Both gamma-secretase and beta-secretase inhibitors have been the targets of new drug development [46, 47]. Aβ is damaged by a few enzymes, including neprilysin, and has also been considered for new drug development. Removing Aβ through immunotherapy is also a reasonable strategy.

In 2019, nine phase 3 trials for eight drugs directing amyloid are underway. Two of these enrolled patients with preclinical AD; one trial required positive amyloid PET, and the other required genetic mutation or strong genetic risks. Four trials enrolled patients with prodromal AD with positive biomarkers, with one trial for prodromal and mild AD and two for mild to moderate stages of AD- related dementia. The inclusion criteria for these trials were positive amyloid PET or cerebrospinal fluid (CSF) biomarker results showing sign of early AD. Such results consisted of reduced CSF Aβ- 42, increased CSF tau, and, using the definition given by the National Institute on Aging at National Institutes of Health and the Alzheimer's Association (NIA-AA), a diagnosis of mild cognitive impairment (MCI) due to AD (MCI-AD) or mild dementia due to AD. No ongoing drug trials have enrolled patients with advanced AD, which reflects the present consensus that anti-amyloid therapy is not beneficial for patients in the late stage of AD. Compared with 2017 and 2018, the number of anti-amyloid phase 3 drug trials was lower in 2019, and anti-amyloid trials have also moved to the early stages of AD, including the prodromal or even preclinical stage. AD surrogate biomarkers have been used often as secondary outcome measures. The most common outcome biomarkers in trials have been CSF amyloid, CSF tau, volumetric MRI, and amyloid PET [48]. AD Composite Score (ADCOMS), which combines scores on items derived from the AD Assessment Scale–cognitive subscale (ADAS-cog), clinical dementia rating (CDR) score, and Mini-Mental Status Examination (MMSE), has been a useful measure of cognitive outcome in trials concerning early-stage AD with limited cognitive deficits.

AN-1792 is the first active immunotherapy strategy for AD that consists of an artificial full-length Aβ peptide. In 2002, an AN-1792 trial was ended. In a phase 2 study, 6% of patients developed aseptic meningoencephalitis as a side effect [49]. In 2019, only one active immunotherapy trial combined CAD106 and CNP520 to treat individuals with the ApoE4 allele and amyloid burden without cognitive impairment. CAD106 combines multiple copies of Aβ1–6 peptide derived from the N-terminal B cell epitope of Aβ, coupled to a Qβ virus-like particle [50]. Orally ingested CNP520 (umibecestat) is a small-molecule inhibitor of aspartyl protease and beta-scretase-1 (BACE-1). It is aimed to interfere with the upstream process of the amyloid cascade to inhibit Aβ production. The Alzheimer's Prevention Initiative Generation Program (Generation Study 1), which consists of a CAD106 injection arm versus a placebo or oral CNP520 (50 mg) arm versus a placebo, has announced that the CNP520 arm showed a worsening of cognitive function. However, the CAD106 treatment arm is ongoing. Bapineuzumab was the first monoclonal antibody used for passive immunotherapy strategy to focus on Aβ in AD. Further trials were dropped after the first two trials were completed and yielded no treatment effect on either cognitive or functional outcomes [51]. In 2019, five drug trials were conducted using monoclonal

antibody targeting Aβ, namely aducanumab, crenezumab, gantenerumab, and solanezumab, and one trial with a combination of gantenerumab andsolanezumab. Aducanumab focuses aggregated Aβ forms. Within the brain, it preferentially binds to parenchymal over vascular amyloid. Studies have shown that amyloid deposition was reduced in all treatment groups at 26 weeks and further reduced by the end of the first year. Additionally, amyloid was cleared from the six cortical regions of interest, namely the frontal, parietal, lateral temporal, sensorimotor, anterior, and posterior cingulate areas.

The most common side effect was amyloid-related imaging abnormalities (ARIA). In ARIA, the white spots within the MRI, which signifyvasogenic edema, were mostly found within the ApoE4 carriers and in participants receiving high doses. In 2017 and 2018, the long-term open-label extension phase of the Multiple Dose Study of Aducanumab (BIIB037) (Recombinant, Fully Human Anti-Aβ IgG1 mAb) in Participants With Prodromal or Mild Alzheimer's Disease (PRIME study), which is a phase 1b study evaluating the safety, tolerability, and pharmacokinetics/pharmacodynamics of aducanumab in patients with prodromal/mild AD aged 50–90 years with positive amyloid PET scan, was reported to be continuing to show dose-dependent amyloid removal and also slowing cognitive decline. However, in March 2019, Biogen and Eisai announced the termination of the phase 3 ENGAGE (221 AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease) and EMERGE (221 AD302 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease) trials of aducanumab because a futility analysis concluded that these trials would fail to reach their primary endpoint—slowing of disease progression as measured by the CDR-Sum of Boxes (CDR-SB). The futility analysis was based on data available as of on December 26, 2018 from 1748 patients. However, additional data from these studies became available thereafter and it resulted in a large dataset consisting of a total of 3285 patients, including 2066 with the full 18 months of treatment. The updated analysis revised the results of EMERGE to be statistically significant, mainly for the patients treated with a high dose of aducanumab. Those patients showed a significant reduction in decline of global functions from baseline in CDR-SB scores at 78 weeks (23% versus placebo, $P = 0.01$), the ADAS-Cog 13 (27% versus placebo, $P = 0.01$), and AD Cooperative Study–Activities of Daily Living Inventory, Mild Cognitive Impairment version (40% versus placebo, $P = 0.001$). Amyloid plaque deposition Imaging in EMERGE demonstrated that amyloid plaque burden decreased with low- and high-dose aducanumab when compared with placebo at 26 and 78 weeks ($P < 0.001$). The company announced its plan to file a Biologics License Application in early 2020. Solanezumab is a humanized IgG1 monoclonal antibody that targets the central region of Aβ. In phase 3 trials, the Mild Alzheimer's Disease progression in Participants on Solanezumab Versus Placebo EXPEDITION 1, EXPEDITION 2, and EXPEDITION 3 studies had enrolled patients with mild to moderate AD with intravenous solanezumab infusions, which failed to show effectiveness with regard to cognitive and functional outcomes. Analysis of Florbetapir PET did not show any reduction in brain amyloid deposits with solanezumab. Furthermore, solanezumab is being tested in protective paradigms in the ADCS A4 and DIAN-TU trials. Gantenerumab is an entirely human recombinant monoclonal IgG1 antibody that binds to both amino-terminal and central regions of Aβ. For Aβ oligomers and fibrils Gantenerumab shows a higher affinity than for Aβ monomers. The Marguerite RoAD study assessed monthly subcutaneous injections of gantenerumab in patients with mild AD. Preliminary results from open- label extension studies indicated that gantenerumab has an acceptable safety profile at a high dose [52]. Furthermore, gantenerumab is being assessed in the Safety and Efficacy Study of Gantenerumab in Participants with Early Alzheimer's Disease (GRADUATE) 1, GRADUATE 2, and Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) trials. Crenezumab is a humanized anti-Aβ monoclonal IgG4 with particular affinity for all pentameric, oligomeric and fibrillary amyloid [53]. Crenezumab is being assessed in the CREAD (A Study of Crenezumab Versus Placebo to Evaluate the Efficacy and Safety in Participants with Prodromal to Mild Alzheimer's diseasetrials concerning prodromal to mild AD. E2609 (elenbecestat) is a BACE-1 inhibitor. A phase 2b study on elenbecestat in amyloid-PET-positive patients with MCI, prodromal AD, or mild AD showed reduced CSF Aβ levels in a dose-dependent manner but no significant improvements in the Alzheimer's Disease Composite Score or CDR-SB score [54,55]. The effectiveness of elenbecestat is being evaluated in the A 24-Month Study to Evaluate the Efficacy and Safety of Elenbecestat in Subjects With Early Alzheimer's Disease (MISSION AD1) and MISSION AD2 trials concerning prodromal AD. These trials will remain until December 2023. GV-971 (sodium oligo-mannurarate) can bind to multiple sites of amyloid, further destabilize and inhibit Aβ aggregation, and then Aβ clearance is increased. GV-971 also can reform gut microbiota and suppress dysbiosis-induced neuroinflammation [55]. A phase 3 study, which began in April 2014, examined the effects of GV-971 in mild to moderate AD. The primary endpoint is the change in ADAS-Cog 12 score. Reports from this trial showed that GV-971 provides important cognitive benefits. On November 2, 2019, Shanghai Green Valley Pharmaceuticals announced that China National Medical Product Administration (NMPA) had provisionally approved GV-971 for the treatment of mild to moderate AD [56]. The dihydropyridine calcium channel has a blocker known as Nilvadipine. The functions of neuroprotection and anti-inflammation of nilvadipine may contribute to the decline of Aβ production and the enhancement of Aβ clearance.

Anti-neuro inflammation therapy

Azeliragon is an inhibitor of RAGE. RAGE controls many physical activities and also take part in transportation process and blood flow. The therapeutic effect of Azeliragon has been proved in clinical trials studies. Some clinical trials shown the effect of it and other trials are in progress.

Anti-tau therapy: Tau proteins are involved in Parkinson's as well as Alzheimer disease. The tau proteins involve in neurotransmitter production in pre and post synaptic ganglia. The anti tau therapy involves the use of medicinal agents against the tau proteins. The clinical trials has been undergoing on the use of TRX0237 and LMTX in Alzheimer disease. This clinical trials expected to be ended in Dec 2020.

Neuroprotection therapy

Neuroprotection is always needed in the Alzheimer disease and other CNS disorders. In this therapy the clinical trials are undergoing which are expected to be ended in 2023. The drug of choice for this activity is Trorilazole which is glutamate modulator.

Cognitive enhancer

Cognitive enhancers are the medical agent's binds to 5HT receptor present on post synaptic ganglia. The main mechanism of these agents involves inhibition of signals which take part in excitation and inhibition of neurotransmitter. The drug of choice in cognitive enhancer is Interpredine.

BPSD- relieving therapy

BPSD therapy involves use of 2 combinations of medications i.e. Dextromethorphan and Bupropion. In which one act on NMDA receptor and other act on glutamate. Both of these drugs act on signaling receptor. The clinical trials are under process which may ended in 2024.

Table 1: Ongoing Clinical Trials List

Sr. No.	Drug Name	Mechanism Of Action	Uses	On Going Clinical Trials	
				Started In	Ending In
1	Anti amyloid Drugs Solenezumab Gantenerumab	Targets Aggregated Amyloid and amyloid monomers	Dementia, Alzheimer, Parkinson's	2018	2022 (Phase- 3)
2	Anti -neuro Inflammation Drugs Azeliragon Cyclohexylbenzamide	Inhibition of RAGE-Amyloid binding	Dementia, Alzheimer	2016	2023 (Phase- 3)
3	Anti-tau Therapy TMRX0237 LMTX	Inhibition of tau Proteins	Dementia, Alzheimer, Parkinson's	2017	2020 (Phase- 2)
4	Neuroprotection Therapy Trorilazole	Glutamate Modulating actvity	Dementia, Alzheimer Other CNS Disorders	2017	2022 (Phase-3)
5	Cognitive Enhencer Interpredine	Blocks 5HT receptors at pre and post synaptic Ganglia	Dementia, Alzheimer Other CNS Disorders	2018	2023 (Phase-3)
6	BPSD Relieving Therapy Dextromethorphen Bupropion	NMDA and Glutamate Receptor Inhibiotrs	Dementia, Alzheimer Other CNS Disorders	2018	2023 (Phase-3)

Discussion

There are 132 agents in clinical trials for the treatment of AD. Twenty-eight agents are in 42 phase 3 trials; 74 agents are in 83 phases 2 trials; and 30 agents are in 31 phase 1 trials. There is an increase in the number of agents in each phase compared with that in the 2018 pipeline. Nineteen agents in trials target cognitive enhancement, and 14 are intended to treat neuropsychiatric and behavioral symptoms. There are 96 agents in disease modification trials; of these, 38 (40%) have amyloid as the primary target or as one of several effects. Eighteen of the antiamyloid agents are small molecules, and 20 are monoclonal antibodies or biological therapies. Seven small molecules and ten biologics have tau as a primary or combination target (18%). Amyloid is the most common specific target in phase 3 and phase 2 disease modification trials. Novel biomarkers (e.g., neurofilament light), new outcomes (e.g., AD Composite Score [ADCOMS]), enrollment of earlier populations, and innovative trial designs (e.g., Bayesian adaptive designs) are new features in recent clinical trials.

Drug development continues robustly at all phases despite setbacks in several programs in the recent past. Continuing unmet needs require a commitment to growing and accelerating the pipeline.

Conclusion

Current or disease-modifying drugs for AD are still lacking. The molecular and clinical events, involving amyloid accumulation, neuroinflammation, tau accumulation, neural degeneration, cognitive decline, and occurrence of behavioral psychological symptoms, develop along with AD progression. The clinical trials directing these events are under evaluation. Because the trials of anti-amyloid failed in recent years, the research emphasis has shifted to populations at prodromal or preclinical stages with positive diagnostic biomarkers. Meanwhile, the amyloid hypothesis has been challenged, and the number of anti-amyloid phase 3 trials was reduced significantly in 2019. The targets of phase 1 and 2 trials are diverse, and the trends show increased directing of neuroprotection and antineuroinflammation in phase 1 and phase 2 trials, respectively. Chronic progressive disorders usually require two or more drugs to efficiently slow down the disease progression. Prospectively, it may be judicious to conduct trials with "dirty drugs" which have actions at multiple targets, namely anti-amyloid and anti-tau effects, neurotransmitter modification, anti-neuroinflammatory and neuroprotective effects, and cognitive enhancement.

Abbreviations Used

AD – Alzheimer Disease PSEN1 – Presenillin 1 APOE – Apolipoprotein E CSF – Cerebrospinal Fluid

PET – Polyethylene Terephthalate

DSMTV – Diagnostic and Statistical Manual of Mental Disorders

NINCDS – national Institute of Neurological and Communicative Disorders and Stroke

References

1. Tang Y, Lutz MW, Xing Y. A systems-based model of Alzheimer's disease. Alzheimer's Dement 2019;15(1):168-171. [PubMed]
2. Zilberzwige-Tal S, Gazit E. Go with the Flow-Microfluidics Approaches for Amyloid Research. Chem Asian J 2018;13(22):3437-3447. [PubMed]

3. Maccioni RB, González A, Andrade V, Cortés N, Tapia JP, Guzmán-Martínez L. Alzheimer´s Disease in the Perspective of Neuroimmunology. Open Neurol J. 2018;12:50-56. [PMC free article] [PubMed]
4. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stacllan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939-91. [PubMed] [Google Scholar]
5. Nicolas G, Acuña-Hidalgo R, Keogh MJ, Quenez O, Steehouwer M, Lelieveld S *et al*. Somatic variants in autosomal dominant genes are a rare cause of sporadic Alzheimer's disease. Alzheimers Dement. 2018; 14(12):1632-1639. [PMC free article] [PubMed]
6. Liljegren M, Landqvist Waldö M, Rydbeck R, Englund E. Police Interactions among Neuropathologically Confirmed Dementia Patients: Prevalence and Cause. Alzheimer Dis Assoc Disord 2018;32(4):346-350. [PubMed]
7. Tong BC, Wu AJ, Li M, Cheung KH. Calcium signaling in Alzheimer's disease & therapies. Biochim Biophys Acta Mol Cell Res 2018;1865(11 Pt B):1745-1760. [PubMed]
8. Poorkaj P, Bird TD, Wisjsman E *et al*. Tau is a candidate gene for chromosome 17 frontotemporal dementia. Ann Neurol 1998;43:815-825. [PubMed] [Google Scholar]
9. Verma M, Wills Z, Chu CT. Excitatory Dendritic Mitochondrial Calcium Toxicity: Implications for Parkinson's and Other Neurodegenerative Diseases. Front Neurosci 2018;12:523. [PMC free article] [PubMed]
10. Wallace L, Theou O, Rockwood K, Andrew MK. Relationship between frailty and Alzheimer's disease biomarkers: A scoping review. Alzheimer's Dement (Amst) 2018;10:394-401. [PMC free article] [PubMed]
11. Barnes J, Bartlett JW, Wolk DA, van der Flier WM, Frost C. Disease Course Varies According to Age and Symptom Length in Alzheimer's disease. J. Alzheimer's Dis 2018;64(2):631-642. [PMC free article] [PubMed]
12. Villemagne VL, Burnham S, Bourgeat P *et al*. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol 2013;12(4):357-367. Doi: 10.1016/S1474-4422(13)70044-9. [PubMed] [Google Scholar]
13. 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):280-286. Doi: 10.2174/156720510791162340. [PMC free article] [PubMed] [Google Scholar]
14. 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. Alzheimer's Dement 2015;11(2):139-150. doi:10.1016/j.jalz.2015.01.001. [PMC free article] [PubMed] [Google Scholar]
15. Bird TD. Genetic aspects of Alzheimer disease. Genet Med 2008;10(4):231-239. [PMC free article] [PubMed] [Google Scholar]
16. Raschetti R, Albanese E, Vanacore N, Maggini M. Cholinesterase inhibitors in mild cognitive impairment: a systematic review of randomised trials. PLoS Med. 2007;4(11):e338. [PMC free article] [PubMed] [Google Scholar]
17. Raina P, Santaguida P, Ismaila A *et al*. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med 2008;148(5):379-397. [PubMed] [Google Scholar]
18. Chu LW. Alzheimer's disease: early diagnosis and treatment. Hong Kong Medical Journal 2012;18(3):228-237. [PubMed] [Google Scholar]
19. Kumar A, Nisha CM, Silakari C *et al*. Current and novel therapeutic molecules and targets in Alzheimer's disease. Journal of the Formosan Medical Association. 2016;115(1):3-10. doi: 10.1016/j.jfma.2015.04.001. [PubMed] [CrossRef] [Google Scholar]
20. Mitsushima D, Sano A, Takahashi T. A cholinergic trigger drives learning-induced plasticity at hippocampal synapses. Nature Communications. 2013;4. article 2760 doi: 10.1038/ncomms3760. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
21. Puzzo D, Gulisano W, Arancio O, Palmeri A. The keystone of Alzheimer pathogenesis might be sought in Aβ physiology. Neuroscience 2015;307:26-36. doi: 10.1016/j.neuroscience.2015.08.039. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
22. Garcia-Osta A, Alberini CM. Amyloid beta mediates memory formation. Learning and Memory 2009;16(4):267-272. doi: 10.1101/lm.1310209. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
23. Folch J, Petrov D, Ettcheto M *et al*. Current research therapeutic strategies for Alzheimer's disease treatment. Neural Plasticity. 2016; 2016:15. doi: 10.1155/2016/8501693.8501693 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
24. Prentice H, Modi JP, Wu JY. Mechanisms of neuronal protection against excitotoxicity, endoplasmic reticulum stress, and mitochondrial dysfunction in stroke and neurodegenerative diseases. Oxidative Medicine and Cellular Longevity 2015; 2015:7. doi: 10.1155/2015/964518.964518 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
25. Shi X, Lin X, Hu R, Sun N, Hao J, GAO C. Toxicological differences between NMDA receptor antagonists and cholinesterase inhibitors. American Journal of Alzheimer's disease and Other Dementias. 2016;31(5):405-412. doi: 10.1177/1533317515622283. [PubMed] [CrossRef] [Google Scholar]
26. Chen M. The maze of APP processing in Alzheimer's disease: where did we go wrong in reasoning? Frontiers in Cellular Neuroscience 2015, 9, article 186:1–10. doi: 10.3389/fncel.2015.00186. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
27. Jedrziewski MK, Ewbank DC, Wang H, Trojanowski JQ. The impact of exercise, cognitive activities, and socialization on cognitive function: results from the national long-term care survey. American Journal of Alzheimer's Disease & Other Dementias 2014;29(4):372-378. doi: 10.1177/1533317513518646. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
28. Okonkwo OC, Schultz SA, Oh JM *et al*. Physical activity attenuates age-related biomarker alterations in preclinical AD. Neurology 2014;83(19):1753-1760. doi: 10.1212/WNL.0000000000000964. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

29. Verghese J, Lipton RB, Katz MJ *et al*. Leisure activities and the risk of dementia in the elderly. The New England Journal of Medicine 2003;348(25):2508-2516. doi: 10.1056/nejmoa022252. [PubMed] [CrossRef] [Google Scholar]
30. Sun Y, Lu CJ, Chien KL, Chen ST, Chen RC. Efficacy of multivitamin supplementation containing vitamins b6 and b12 and folic acid as adjunctive treatment with a cholinesterase inhibitor in Alzheimer's disease: a 26-week, randomized, double-blind, placebo-controlled study in Taiwanese Patients. Clinical Therapeutics 2007;29(10):2204-2214. doi: 10.1016/j.clinthera.2007.10.012. [PubMed] [CrossRef] [Google Scholar]
31. Petersen RC, Thomas RG, Grundman M *et al*. Vitamin E and donepezil for the treatment of mild cognitive impairment. The New England Journal of Medicine. 2005;352(23):2379-2388. doi: 10.1056/nejmoa050151. [PubMed] [CrossRef] [Google Scholar]
32. Gangwar AK, Rawat A, Tiwari S, Tiwari SC, Narayan J, Tiwari S. Role of Vitamin- D in the prevention and treatment of Alzheimer's disease. Indian Journal of Physiology and Pharmacology 2015;59(1):94-99. [PubMed] [Google Scholar]
33. Rosenberg PB, Nowrangi MA, Lyketsos CG. Neuropsychiatric symptoms in Alzheimer's disease: What might be associated brain circuits? Mol Asp Med 2015;43-44:25-37. Doi: 10.1016/j.mam.2015.05.005. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
34. Boccia MM, Blake MG, Acosta GB, Baratti CM. Atropine, an anticholinergic drug, impairs memory retrieval of a high consolidated avoidance response in mice. Neurosci Lett 2003;345(2):97-100. doi: 10.1016/S0304-3940(03)00493-2. [PubMed] [CrossRef] [Google Scholar]
35. Raina P, Santaguida P, Ismaila A, Patterson C, Cowan D, Levine M *et al*. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. 2008; 148(5):379-397. doi: 10.7326/0003-4819- 148-5-200803040-00009. [PubMed] [CrossRef] [Google Scholar]
36. Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochem Biophys Res Commun. 1984;120(3):885-890. doi: 10.1016/S0006-291X(84)80190-4. [PubMed] [CrossRef] [Google Scholar]
37. Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K. Amyloid plaque core protein in Alzheimer disease and Down syndrome. Proc Natl Acad Sci U S A. 1985;82(12):4245-4249. doi: 10.1073/pnas.82.12.4245. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
38. Gunawardena S, Yang G, Goldstein LS. Presenilin controls kinesin-1 and dynein function during APP-vesicle transport *in vivo*. Hum Mol Genet 2013; 22(19):3828-3843. doi: 10.1093/hmg/ddt237. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
39. Sperling R, Mormino E, Johnson K. The evolution of preclinical Alzheimer's disease: implications for prevention trials. Neuron 2014;84(3):608-622. doi: 10.1016/j.neuron.2014.10.038. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
40. Mormino EC, Kluth JT, Madison CM, Rabinovici GD, Baker SL, Miller BL *et al*. Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. Brain J Neurol. 2009;132(Pt 5):1310-1323. doi: 10.1093/brain/awn320. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
41. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW *et al*. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9(1):119-128. doi: 10.1016/S1474-4422(09)70299-6. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
42. Jack CR, Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB *et al*. NIA- AA research framework: toward a biological definition of Alzheimer's disease. Alzheimer's Dementia: J Alzheimer's Assoc 2018;14(4):535-562. doi: 10.1016/j.jalz.2018.02.018. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
43. Sisodia SS. Beta-amyloid precursor protein cleavage by a membrane-bound protease. Proc Natl Acad Sci U S A. 1992;89(13):6075-6079. doi: 10.1073/pnas.89.13.6075. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
44. Chow VW, Mattson MP, Wong PC, Gleichmann M. An overview of APP processing enzymes and products. NeuroMolecular Med 2010;12(1):1-12. doi: 10.1007/s12017-009- 8104-z. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
45. May PC, Dean RA, Lowe SL, Martenyi F, Sheehan SM, Boggs LN, and *et al*. Robust central reduction of amyloid-beta in humans with an orally available, non-peptidic beta- secretase inhibitor. J Neurosci 2011;31(46):16507-16516. doi: 10.1523/JNEUROSCI.3647- 11.2011. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
46. El-Amouri SS, Zhu H, Yu J, Marr R, Verma IM, Kindy MS. Neprilysin: an enzyme candidate to slow the progression of Alzheimer's disease. Am J Pathol 2008;172(5):1342-1354. doi: 10.2353/ajpath.2008.070620. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
47. Wang Jinping, Logovinsky Veronika, Hendrix Suzanne B, Stanworth Stephanie H, Perdomo Carlos, Xu Lu *et al*. ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials. Journal of Neurology, Neurosurgery & Psychiatry 2016;87(9):993-999. doi: 10.1136/jnnp- 2015-312383. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
48. Wiessner C, Wiederhold K-H, Tissot AC, Frey P, Danner S, Jacobson LH *et al*. The second- generation active Aβ immunotherapy CAD106 reduces amyloid accumulation in APP transgenic mice while minimizing potential side effects. J Neurosci 2011;31(25):9323-9331. doi: 10.1523/JNEUROSCI.0293-11.2011. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
49. Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M *et al*. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med. 2014;370(4):322-333. doi: 10.1056/NEJMoa1304839. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
50. Goure WF, Krafft GA, Jerecic J, Hefti F. targeting the

proper amyloid-beta neuronal toxins: a path forward for Alzheimer's disease immunotherapeutics. Alzheimers Res Ther 2014;6(4):42. doi: 10.1186/alzrt272. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
51. Vos SJ, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant EA *et al*. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. Lancet Neurol. 2013;12(10):957-965. doi: 10.1016/S1474-4422(13)70194-7. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
52. Murakami K, Irie K. Three structural features of functional food components and herbal medicine with amyloid β42 anti-aggregation properties. Molecules. 2019;24(11):2125. doi: 10.3390/molecules24112125. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
53. Wang X, Sun G, Feng T, Zhang J, Huang X, Wang T, *et al*. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. Cell Res. 2019, 1-17. [PMC free article] [PubMed]
54. Paris D, Bachmeier C, Patel N, Quadros A, Volmar CH, Laporte V *et al*. Selective antihypertensive dihydropyridines lower Abeta accumulation by targeting both the production and the clearance of Abeta across the blood-brain barrier. Mol Med (Cambridge, Mass) 2011;17(3, 4):149-162. doi: 10.2119/molmed.2010.00180. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
55. Lawlor B, Segurado R, Kennelly S, Rikkert MGO, Howard R, Pasquier F, *et al*. Nilvadipine in mild to moderate Alzheimer disease: a randomised controlled trial. PLoS Med 2018;15(9):e1002660. doi: 10.1371/journal.pmed.1002660. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
56. Puzzo D, Gulisano W, Arancio O, Palmeri A. The keystone of Alzheimer pathogenesis might be sought in Abeta physiology. Neuroscience 2015;307:26-36. doi: 10.1016/j.neuroscience.2015.08.039. [PMC free article] [PubMed] [CrossRef] [Google Scholar]