Progress in Chemical and Biochemical Research

Journal homepage: www.pcbiochemres.com

Review Article

Potential Plasma Biomarkers for Diagnosis of Alzheimer's Disease: An Overview

Shaikh Abdul Basit Mustak Ahamad, Umesh Pravin Dhuldhaj*

Department of Biotechnology, School of Life Sciences, Swami Ramanand Teerth Marathwada University, Nanded, India 431606

ARTICLEINFO

ARTICLEHISTORY

Submitted:2023-08-26
Revised:2023-12-25
Accepted: 2024-02-14
Available online: 2024-03-18
Manuscript ID:PCBR-2308-1285
Checked for Plagiarism: Yes
Language Editor Checked: Yes
Editor: Dr. S.L. Sanati, Afsaneh

KEYWORDS

Alzheimer's disease
Biological markers
Plasma GFAP
CSF
PET

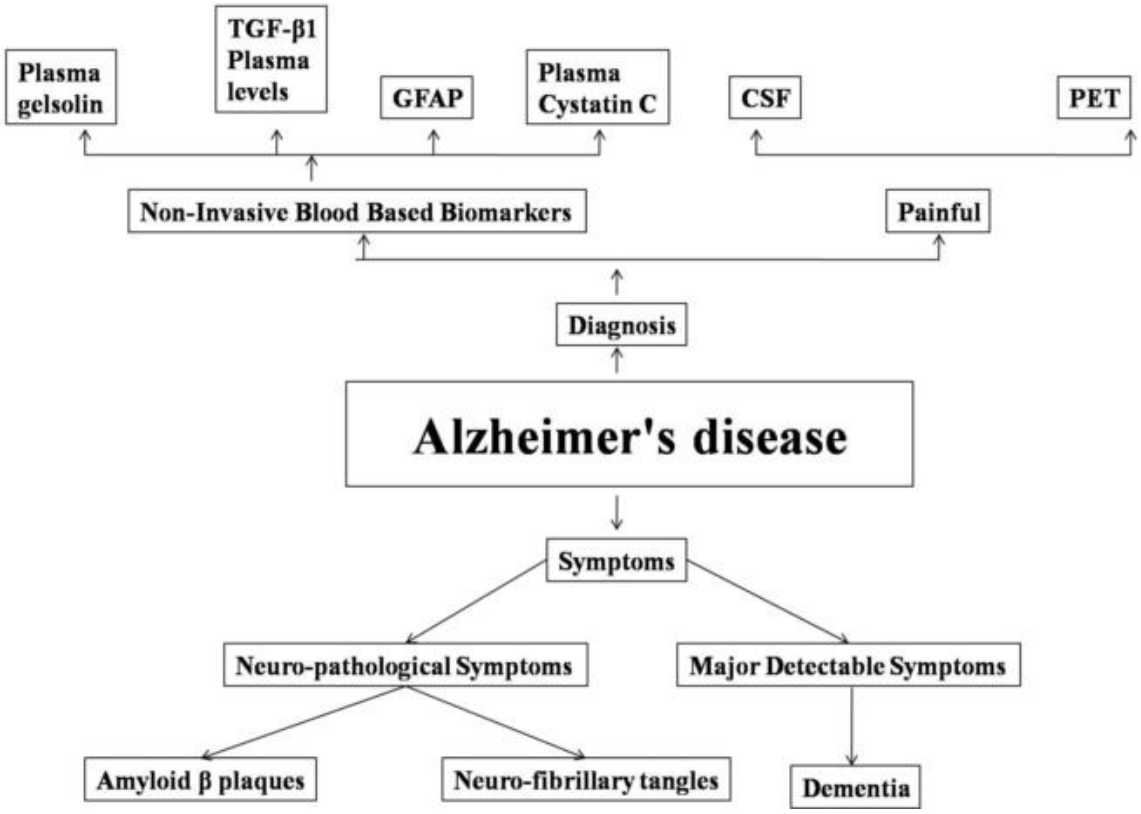
ABSTRACT

Alzheimer's disease (AD) is the widely known neuro-degenerative disease, responsible for cognitive decline and progressive memory loss, results from the brain shrinkage (called atrophy) and degradation of neurons of brain, globally almost 60-70% people are suffering from it and most prevalent amongst older peoples of above 40 years. The major or marker symptoms symptom of this disease is dementia, impairment of thinking, and changes in behavioral pattern. The disease progression commences with short memory loss to severe memory impairment. To cope with this, prior disease diagnosis helps in the prevention and treatment of diseases, as there is no complete treatment and cure available to this disease. Once the patients have been diagnosed with this disease, there are several pharmacological or non-pharmacological treatments can be given. Up to now, the technique available for the AD detection is CSF and PET scan which are painful and expensive. Several blood or plasma biomarkers can be used to detect the progression or prevalence of the diseases, based on non-invasive blood-based biomarker and it is cost-effective technique and with similar efficiency in comparison to classical one.In this investigation, we focus on potential biological markers for the investigation and AD detection. The blood biomarkers can be useful are Plasma GFAP has been found to be the most potential blood biomarker. There is no any standard procedure/test been accepted to be used for the AD diagnosis as a blood biomarker. The other biomarkers can be used along with Plasma GFAP are level of TGF-β1 in plasma and Activity NO synthase in Leukocytes, plasma gelsolin (GSN) and matrix metalloproteinase 3 (MMP3), plasma Cystatin C, and High-Density Lipoprotein.

Citation: Shaikh Abdul Basit Mustak Ahamad, Umesh Pravin Dhuldhaj. Potential Plasma Biomarkers for Diagnosis of Alzheimer's Disease: An Overview. Prog. Chem. Biochem. Res., 7(2) (2024) 114-128
https://doi.org/10.48309/PCBR.2024.413416.1285
https://www.pcbiochemres.com/article_192839.html

* Corresponding author: Umesh Pravin Dhuldhaj
✉ E-mail: umeshpd12@gmail.com
☎ Tel number: +9881395745

GRAPHICAL ABSTRACT



Introduction

The neurodegenerative disease Alzheimer's disease (AD) was first encountered in D. Auguste, one of patient of Alois Alzheimer, which was further named as Alzheimer's disease by Kraepelin [1]. The typical clinical symptoms of AD include memory disturbances, with neuro-pathological detection of Amyloid β (Aβ) plaques and neurofibrillary tangles; are known to be as the hallmark of Alzheimer's disease (AD). The principle detectable symptom of AD is dementia, observed in 50-60% cases, prevalence of dementia is observed to be around 1% in age ranges from 60-64 years and it becomes intense around 24-33% with increase in age around 85 or older [2]. The people aged with 65, 80 and 90 having chances of disease prevalence around 5, 20, and 33% [3]. Loss of memory and inability tocarry normal behavior, results from cerebral atrophy which targets hippocampus and entorhinal cortex [4]. The disease evolves silently and reported that the detection and cognitive impairment observed in the patients after the 10-12 years of onset of disease [5]. The disease prevalence increasing with increasing population and it is to be estimated that up to 2050, the individuals suffering from AD will be 115 million [6].

The conventional diagnosis having around 15% chances to diagnose AD wrongly. Differential diagnosis of dementia can be because of poisoning of carbon monoxide, drug interactions, deficiency of vitamins, and subdural hematoma. The more common cause of dementia is depression, Parkinsonian vascular and fronto-temporal dementia. Hence, differential diagnosis of dementia related to AD is very necessary towards accurate therapeutic treatments [7]. The dementia caused in older life ecause of vascular

or neuro-degeneration is called as Geriatric syndrome [8,9]. The hallmark symptoms of neuropathologic AD are neuron degeneration, synaptic loss, tau protein, and amyloid β rich plaques. The plaques of amyloid β and neurofibrillary tangles formed by phosphorylated tau protein are major sign of AD while cognitive decline is because of synaptic loss or synaptic dysfunction [10].

The risk factor involved in AD can be genetic and epigenetic. Other than increasing older age, the major risk factors involved in intellectual decline is also it may include educational attainment and brain size. Illiteracy and less awareness have been one of the risk factor for prevalence and incidence dementia. Severe cognitive deficit and prevalence of AD symptoms in childhood results in smaller brain size [11]. The environmental factors related to AD are principally aging and other factors involved are head trauma, systemic arterial hypertensions, diabetes, and obesity. The factors which aids in the disease symptoms are depression, social isolation, and smoking and hearing loss [12,13].From the symptoms we can assumed that by changing the lifestyle it can be mitigated.

The second risk factor related to AD is genetic; autosomal dominant mutations results in early onset of AD in 70% of individuals, more often occurrence of disease observed before age 65 years. The autosomal dominant mutations are on the three genes such as presenilin 1, presenilin 2, and amyloid precursor protein (APP) which can be inherited [14]. At molecular level, the expression of disease symptoms of AD is due to these three genes such as amyloid precursor protein (APP) present on chromosome 21, Presenilin 1 (PS 1) present on chromosome 14 and Presenilin 2 (PS 2) present on chromosome 1. Expression of autosomal dominant disease just in the third decades of life is to be observed in the some of the families because of expression of PS 1[15]. More than 50% chances of AD are because of genetic factor APOEε4. The analysis and evaluations of APOEε4 through the autopsy was proved to be responsible for AD dementia [16]. Based on other investigations of autopsy, specific presence of O4 allele indicates 100% confirmation of AD [17-19].

Other factors involved in the expression disease conditions are; lifestyle factors like High diet fat, lack of exercise, etc. and changes in hormonal levels (See Fig 1).

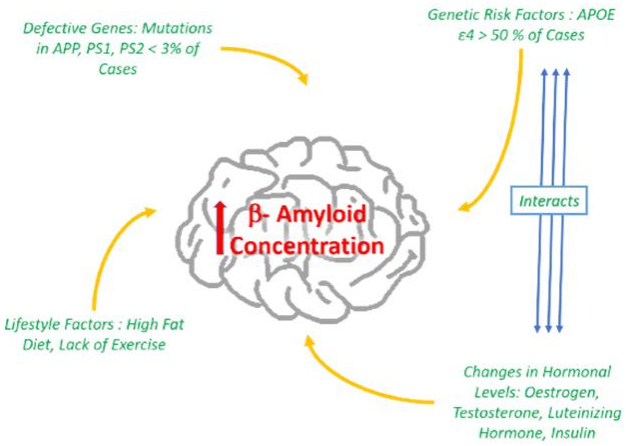


Fig 1. Kinds of Risk factors associated with Aβ concentration increase in the brain and AD

Alzheimer disease variants

Along with the typical AD, its variants have also been detected such as frontal variant, logopenic variant, and posterior cortical atrophy. The logopenic variant of AD is progressive aphasia. The change in behavioral pattern with memory loss for shorter span is linked to frontal variant, these individuals are highly impatient and irritable [20].

The other variant of AD is posterior cortical atrophy which has similar symptoms like Balint-Holmes syndrome and Gerstmann syndrome. Posterior cortical atrophy related to visuospatial dysfunction and apperceptive visual agnosia. The patients with posterior cortical atrophy variants have preserved memory insight, but have develop constructional, dressing and ideomotor apraxia. The patients with logopenic aphasia

variants are having problems with repetitions of anonymous words and poor naming [21].

AD diagnosis and detection

The patients suspected for the AD are classified into three groups' preclinical, mild cognitive impairment (MCI) [22], and dementia [23]. For the AD diagnosis, several methods have been adopted among them most often used is detection amyloid-β deposition responsible for the dementia. AD diagnosis also can be achieved from some clinical parameters like biomarkers present in body fluids such as plasma and cerebrospinal fluid (CBF) or with the direct imaging method (PET) [5]. The AD is diagnosed very lately, it has two sorts of states symptomatic and asymptomatic [24].

The dementia, keymarker symptoms of AD is initiated with cognitive decline and takes long time to reach dementia, the hallmark symptom of AD which indicates greater brain impairment [25].The known method for the detection and diagnosis of AD is done by collecting CSF (Cerebra-Spinal Fluid) sample by lumbar puncture and Positron Emission Tomography (PET) which are expensive and invasive techniques and out of reach of common people. Therefore, it requires thorough study and investigations to find cheaper and non-invasive diagnosis technique for AD which can be affordable to even common people. In this article, we focus on the Plasma Biomarkers for AD diagnosis in a non-invasive technique.

Positron emission tomography (PET)

Diagnosis of clinical symptoms is very essential for the treatment and management of the disease. Other than the clinical symptoms, the AD neuropathology can be detected with positron emission tomography of deposited amyloid [21]. The genetic risk factors are responsible for early onset of AD [26]. In the asymptomatic stages of early onset of AD, the neurodegeneration can be detected with the 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) by monitoring glucose [27]. The patients detected with the AD while monitoring neuronal activity through the CMRglc shown reduction in parietotemporal, frontal, and posterior cingulated cortices [27]. Detection of common symptoms for the all sorts of dementia including AD is hypometabolic regions hence further it can be firmed by applying amyloid PET scan which helps to figure out surface area of amyloid plaques [28].

The major characteristic which makes AD from other diseases and dementia is Amyloid-β (Aβ) plaques and neurofibrillary tangles of tau protein. PET scan of Cerebrospinal fluid using Pittsburgh B (PiB) radiotracer (PiB-PET scan) shows uncontrolled production and clearance of amyloid-β proteins in human brain [29]. Other than amyloid β, pathologic symptoms involved in AD are loss of functions of tau protein by neurofibrillary tangles and phosphorylation, neuroinflammations, uncontrolled glucose metabolism, and oxidative stress [30].

Cerebrospinal fluid (CSF)

Detection of neuropathology have brought about by the scanning CSF biomarkers such as amyloid-β and tau proteins for diagnosis of AD (Fig 2). The biomarkers present in CSF are Aβ42 and Aβ40 and their ratio is decreased in AD positive individuals. Instead of individual Aβ42 and Aβ40, their ratio is more reliable marker for detection of AD [8,31]. The deposition of amyloid plaques results in loss in Aβ42. Other than the amyloid level in CSF, there is other nanodiagnostic approach to detect the AD by monitoring AbO level in CSF. Nanodiagnostic approaches uses nanoparticles as the DNA carrier to monitor the level of AbO in CSF. This technique used the nanoparticles such as magnetic nanoparticles and DNA conjugated with antibody AbO [32].

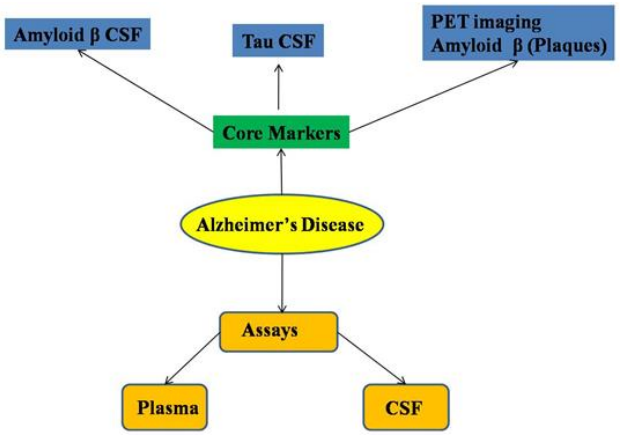


Fig 2. Markers for Alzheimer's disease (adopted from Kerwin et al. [33])

Biological markers [34]

There are several biomarkers present in the biological fluids that can be used for the diseases diagnosis. The major biological markers can be fluids present in human body which includes cerebrospinal fluid and blood or peripheral tissue. These biomarkers can be helpful in the diagnosis and confirmation of disease.

Some peculiarity ideal biomarkers are mentioned as:

- Highly sensitive around 80%
- High specificity around 80%
- Probable positive confirmation around 90%
- Help in neuropathological detection
- Helps in disease diagnosis in childhood
- Reliable, non-invasive, and cost effective
- Easily distinguishes dementia of AD and others

Plasma blood biomarkers

Plasma glial fibrillary acidic protein (GFAP) [35]

Proliferation and abnormal activation of astrocytes can be marked by GFAP during astrogliosis results in neural damage [36]. The GFAP expression in brain tissue suffered with AD associated with Aβ plaque density [37].

In one of the case study of 134 volunteers, which were selected on the basis of inclusive and exclusive criteria regarding AD [38-40] and 105 cases observed through neuro-imaging, neuropsychometric evaluation, and blood collection, and also among them 00 had been found to have Normal Global Cognition on the basis of MMSE [41]. Around 95 cases were detected with Aβ 1 and Aβ 1-42 in their plasma, Plasma GFAP concentrations were detected in 96 and total set of GFAP and Aβ 1 and Aβ 1-42 were detected in of 94.

In this case study, it was observed that, biomarker GFAP elevation found in the high brain Aβ load which serves as blood biomarkers for early detection of diseases. Furthermore, their study also shown how it can be used to distinguish Aβ + and Aβ – individuals on the basis of disease's risk factors such as age, sex, and APOEε4 carriage along with GFAP with 90 % sensitivity and 80% specificity. Individuals having compromised blood-brain barrier have been shown elevated Plasma GFAP levels along with astrogliosis. The study also indicates that the GFAP levels increases with age.

TGF-β1 level in plasma and activity NO synthase in leukocytes [42]

During monitoring of brain activity in AD diagnosis and it was observed that some of the activity can be used as the significant biomarkers which are present in plasma and leucocytes such as levels of TGF-β1 and activity of NO synthase, respectively. In the Central Nervous System (CNS) expression of TGF-β related to several abnormal events related to brain which directly related to events of AD, including brain injury, astrocytosis, regulation of α2M, etc. [43].

The free radical involved in the inflammations is Nitric Oxide (NO) and its excessive productions switch its effect from physiological neuro-modulator to a neuro-toxic effect [44]. In one of the investigations, it was reported that, in AD patients, activity of NO synthesis is enhanced in leucocyts [45]. In one of the investigations there were random 48 subjects with AD (60-89 years old) were chosen and also 23 healthy control subjects (60-92 years old) and in this cases AD

subjects met the criteria recommended by National Institute of Neurological and Communicative disorders and stroke and AD Related Disorders Association (NINCDS-ADRDA). In this study they found, on an average of all control subjects taken into investigations, their functional TGF-β-1 should be lower. In all the 48 AD subjects, they found to have enhanced activity of NOS in Leukocytes. In result of this invesitigation TGF-β-1 and of NOS activity can be possibly used practically to identify all AD subjects and can be used as diagnostic marker in AD Subjects.

Plasma gelsolin (GSN) and matrix metalloproteinase 3 (MMP3) [46]

Plasma gelsolin can be used for diagnosis of AD patients as its concentration significantly dropped in disease conditions [47]. GSN is a 93 kDa protein, involved in de-fibrilization of the Aβ protein and also defibrilize preformed fibrils [48] and it is correlated with disease progression rate estimation by MMSE decline per year [47]. One of the principal GSN-degrading enzyme is Matrix metalloproteinase 3 (MMP3), found in two active forms (45 kDa and 28 kDa) [49], reported to have enhanced concentration in patients suffering from AD [50].

In this study, they had randomly selected total 113 subjects each as Normal as control and AD, which had undergone many inclusive and exclusive parameters. The AD subjects met the criteria of NINCDS-ADRDA for probable AD symptoms. Blood sample were taken and those subjects detected with ε4 allele classified as APOEε4. APOEε4 should be with minimum one copy of ε4 allele. The decreased level of $A\beta_{42/40}$ ratio detected in AD subjects and the plasma GSN levels are negatively co-related with MMP3 activity in AD subjects. The Plasma GSN levels directly related to MMSE scores while dropped concentration of level of GSN in plasma and higher activity of MMP3 activity gives probable of confirmation of AD diseases, hence GSN level and MMP3 activity can be used as the significant biomarker for AD detection with accuracy, sensitivity, and specificity of around in the range of 76.1%, 77%, and 75.2%, respectively.

Plasma cystatin C and high-density lipoprotein [51]

The cystatins (Cys) are the major group of protein in neurological disorder more often called as cysteine protease inhibitor. Predominantly Cys B and Cys C are detected for the Vascular Dementia (VaD) and AD. Cys B involved in the regulation of Aβ peptide and maintenance of auto-fluorescence associated with lipofuscin and giant lipid of autolysosomes involved in AD [52]. Lipoproteins can be helps in the restoration of cognitive functions [53], among them HDL (High Density Lipoprotein) present in systemic circulation. Lipoprotein helps in the lipid related molecules present all over the body can be effectively delivered and cleared [54].

In this study, the researchers have tried to check whether High Density Lipoprotein or Plasma Cystatin C can be used as a reliable biomarker to differentiate dementia of AD and others and these biomarkers investigated in VaD and AD. Therefore, they had recruited 88 subjects with dementia. 43 subjects with AD, whose diagnosis was confirmed using NINCDS-ADRDA and 45 subjects as normal control group were selected. Further Blood sample measurement of all subjects was carried out to measure level of Cys C along with the concentrations of HDL in the plasma and they found that elevated level of plasma CysC in AD subjects.

Drug treatments in alzheimer's disease

Drug therapy was recommended for the treatment of AD was aducanumab, and it is setback because of its side effects. There is still hope to develop drug therapies for the treatment in future time for disease-modifying treatment (DMT) for AD [55]. BAN2401 was recommended

drug for the cognitive decline after Phase II trial. The Recommended drugs for the treatment of AD should be used in initial period of AD and to prevent further progression and manifestation of disease and dementia. Such treatment needs to find patients with early stages of AD, hence for such therapies patient should be diagnosed, evaluated, and treated for prior disease condition [29]. Aducanumab was the initially approved drug for disease-modifying treatment (DMT) by Food and Drug Administration (FDA, USA) targeting to targeting amyloid beta (Aβ) plaques. However, this drug does not full access all over globe by European Medicines Agency as they recommended further clinical trial for the efficacy of the drug [33].

The drugs available now days are based on the prevention of symptoms and their control, the therapy are based on four targets such as acetylcholinesterase inhibitors and tau hyperphosphorylation, diabetes, and psychological help [5]. The drugs recommended for disease modifying treatments are based on their approach of disease modification such as neuroprotection or neurotrophic, which mainly consist of anti-amyloid therapy [56] (Table 1).

Anti-amyloid therapy

As the hallmark symptoms of AD is accumulation of amyloid, hence majority of treatment therapies target to the amyloid protein. The principal approach used to target amyloid is passive immunization by provision of exogenous monoclonal antibodies (mAbs) [57].

Cholinesterase inhibitors

The currently available drug therapy approved by FDA are based on cholinesterase inhibitions consists of four drugs for the treatment of AD viz., tacrine, donepezil, galantamine, and rivastigmine, all of which are cholinesterase inhibitors. These drugs are helps in improvement of neurotransmission by keeping intact acetylcholine. The cholinergic neurotransmitter have vital role in cognition and memory comes with several side effects such as nausea, diarrhea and vomiting [67]. Other than the targeted cholinesterase inhibition, other drugs recommended are N-methyl-D-aspartate (NMDA)-receptor antagonists [68].

Table 1. Disease-Modifying Treatments for Alzheimer's Disease (Lam et al.) [29]

Therapy	Candidate	Target
Anti-Aβ Antibodies[57]	Gantenerumab [58]	β-amyloid pathology
	BAN2401[59]	
	LY3002813 (Donanemab) [60]	
Anti-tau antibodies	Humanized ABBV-8E12 [61]	Reduces brain atrophy
	RO7105705 (Semorinemab) [62]	
BACE inhibitors	Elenbecestat (E2609) [63]	Prolonged reductions in plasma beta-amyloid levels
	CNP520 (Umibecestat) [64]	
Vaccines	CAD106 (Second Generation) [65]	Reduces amyloid accumulation
	AADvac1 (Active immunotherapy)[66]	
Cholinesterase inhibitors[68]	Tacrine	Improvement of neurotransmission
	Donepezil	
	Galantamine	
	Rivastigmine	

Tacrine or tetra-hidro-aminoacridine (THA)

One of cholinesterase inhibitor recommended and approved by FDA is Tacrine, having reversible inhibitions of cholinesterase. The tacrine having half-life up to 4 hours and can be metabolized in liver through cytochrome. There are investigation have been conducted to detect the efficacy of this drug since 1981 and each study have shown its significant effectiveness [69] and also shown improvement [70].

Donepezil

The second recommended drug as the cholinesterase inhibitor is Donepezil, which is more potent than Tacrine. In one of the case study in which around 900 patients were treated with this drug and observed positive outcome in 15 to 30 weeks such as cognitive improvement and doses, were administered for this investigations were 5 to 10 mg [71].

Rivastigmine

Rivastigmine is another cholinesterase inhibitor drug involved in specific carbamates acetylcholinesterase activity in brain. The drug induces pseudoirreversible, helps in consistent prevention of acetylcholinesterase activity, even after the removal of the drug. The half-life of these drugs is up to 1 hour and efficacy of the drugs can be lasts for up to 10 hours [72].

Galantamine

Galantamine is one more cholinesterase inhibitor acts on nicotine receptors through the allosteric modulatory action. This drug has dual action like cholinesterase inhibitor and presynaptic activation for the secretion of acetylcholine, glutamate, monoamines, and GABA. The drug has shown significant recovery in case of cognitive decline and psychiatric symptoms [73-74].

Conclusion and future prospective

Blood biomarkers are the important source of non-invasive diagnosis of AD, but unfortunately the specificity and sensitivity of CSF biomarkers remain higher than that of Blood Biomarkers. Indeed, it is necessary to produce a biomarker to predict AD before symptoms arise. Genetic risk factors and neuro-imaging will definitely play a vital role in AD biomarker. Even after an extensive study research in this area, yet there is no potential standard blood biomarker available for AD diagnosis. On the basis of reports available from various study groups, GFAP can be considered one of the most potential biomarkers with a sensitivity of 90% and specificity of 80%, which also matches with the condition and parameters for an ideal biomarker. Based on the results, it can be concluded that Cystatin and high density lipoproteins can be used to detect AD subjects from normal subjects.

The progress and development therapeutics for the AD treatment with the help of antibody can be one of the beneficial approaches which have shown significant mitigation but yet failed to pheasible clinical translations [75-80] may be because of secondary effect of antibodies. Therefore, the application of antibody approach needs thorough investigation to increase the therapy efficacy [81]. The antibody approach used to diagnosis and treatment of AD have some other issue also like drug molecules involved can cross blood-brain barrier (BBB) and targets other molecules can cause other pathologies [82]. There is need of development modern therapy for the complete mitigation of AD as the dementia can be symptoms of AD and other diseases. Hence, there be wrong diagnosis more often has been done regarding this. To mitigate AD along with pharmacological treatment also requires special care to individuals suffering from it as bio-psychosocial aspects.

For future, there is urgent need to develop which can use biomarkers from peripheral blood or plasma which helps in the rapid diagnosis of AD. As the protein like amyloid, tau and neuro-filament protein involved in AD, hence we require accurate and sensitive technique to monitor the level of such molecules in body fluids

for rapid diagnosis of AD with respect to amyloidogenesis and neurodegeneration [24,83-84].

Acknowledgments

Authors are thankful to the Department of Biotechnology, School of Life Sciences, Swami Ramanand Teerth Marathwada University, Nanded for laboratory and other necessary facilities.

Conflict of interest

The authors declare that they have no conflict of interest.

Declaration of ethical studies

No actual animal studies were performed in the present investigations.

Orcid

Shaikh AbdulBasit MustakAhamad
https://orcid.org/0000-0003-3280-5981
Umesh Pravin Dhuldhaj
https://orcid.org/0000-0002-7439-4669

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Declarations

Conflict of interest: The authors have no relevant financial or non-financial interests to disclose.

Ethical approval: Not applicable.

Consent to participate: Not applicable.

Consent for publication: Not applicable

References

1. Graeber MB. The case described by Alois Alzheimer in 1911. European Archives of Psychiatry and Clinical Neuroscience. 1998 Jul 1;248(3):111. [Crossref], [Google Scholar], [Publisher]
2. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. The Lancet. 2006 Jul 29;368(9533):387-403. [Crossref], [Google Scholar], [Publisher]
3. Hajipour MJ, Santoso MR, Rezaee F, Aghaverdi H, Mahmoudi M, Perry G. Advances in alzheimer's diagnosis and therapy: The implications of nanotechnology. Trends in biotechnology. 2017 Oct 1;35(10):937-53. [Crossref], [Google Scholar], [Publisher]
4. Wanleenuwat P, Iwanowski P, Kozubski W. Alzheimer's dementia: pathogenesis and impact of cardiovascular risk factors on cognitive decline. Postgraduate medicine. 2019 Oct 3;131(7):415-22. [Crossref], [Google Scholar], [Publisher]
5. García-Morales V, González-Acedo A, Melguizo-Rodríguez L, Pardo-Moreno T, Costela-Ruiz VJ, Montiel-Troya M, Ramos-Rodríguez JJ. Current understanding of the physiopathology, diagnosis and therapeutic approach to Alzheimer's disease. Biomedicines. 2021 Dec 14;9(12):1910. [Crossref], [Google Scholar], [Publisher]
6. Corbett A, Pickett J, Burns A, Corcoran J, Dunnett SB, Edison P, Hagan JJ, Holmes C, Jones E, Katona C, Kearns I. Drug repositioning for Alzheimer's disease. Nature Reviews Drug Discovery. 2012 Nov;11(11):833-46. [Crossref], [Google Scholar], [Publisher]
7. Boss MA. Diagnostic approaches to Alzheimer's disease. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2000 Jul 26;1502(1):188-200. [Crossref], [Google Scholar], [Publisher]
8. Briggs R, Kennelly SP, O'Neill D. Drug treatments in Alzheimer's disease. Clinical medicine. 2016 Jun;16(3):247. [Crossref], [Google Scholar], [Publisher]
9. Ravona-Springer R, Davidson M, Noy S. Is the distinction between Alzheimer's disease and vascular dementia possible and relevant?. Dialogues in clinical neuroscience. 2003 Mar 31;5(1):7-15. [Crossref], [Google Scholar], [Publisher]
10. Coleman P, Federoff H, Kurlan R. A focus on the synapse for neuroprotection in Alzheimer disease and other dementias. Neurology. 2004 Oct 12;63(7):1155-62. [Crossref], [Google Scholar], [Publisher]

11. Mortimer JA, Snowdon DA, Markesbery WR. Head circumference, education and risk of dementia: findings from the Nun Study. Journal of clinical and experimental neuropsychology. 2003 Aug 1;25(5):671-9. [Crossref], [Google Scholar], [Publisher]
12. Robinson M, Lee BY, Hane FT. Recent progress in Alzheimer's disease research, part 2: genetics and epidemiology. Journal of Alzheimer's Disease. 2017 Jan 1;57(2):317-30. [Crossref], [Google Scholar], [Publisher]
13. Burns A. Citicoline in the treatment of acute ischaemic stroke: An international, randomised, multicentre, placebo-controlled study (ICTUS trial). The Lancet. 2020 Jul 30;396(10248):413-46. [Crossref], [Google Scholar], [Publisher]
14. Kim JH. Genetics of Alzheimer's disease. Dementia and neurocognitive disorders. 2018 Dec 1;17(4):131-6. [Crossref], [Google Scholar], [Publisher]
15. Mayeux R. Epidemiology of neurodegeneration. Annual review of neuroscience. 2003 Mar;26(1):81-104. [Crossref], [Google Scholar], [Publisher]
16. Mayeux R, Saunders AM, Shea S, Mirra S, Evans D, Roses AD, Hyman BT, Crain B, Tang MX, Phelps CH. Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. New England Journal of Medicine. 1998 Feb 19;338(8):506-11. [Google Scholar], [Publisher]
17. Kakulas BA, Wilton SD, Fabian VA, Jones TM. Apolipoprotein-E genotyping in diagnosis of Alzheimer's disease. The Lancet. 1996 Aug 17;348(9025):483. [Crossref], [Google Scholar], [Publisher]
18. Saunders AM, Hulette C, Welsh-Bohmer KA, Schmechel DE, Crain B, Burke JR, Alberts MJ, Strittmatter WJ, Breitner JC, Rosenberg C, Scott SV. Specificity, sensitivity, and predictive value of apolipoprotein-E genotyping for sporadic Alzheimer's disease. The Lancet. 1996 Jul 13;348(9020):90-3. [Crossref], [Google Scholar], [Publisher]
19. Welsh-Bohmer KA, Gearing M, Saunders AM, Roses AD, Mirra S. Apolipoprotein E genotypes in a neuropathological series from the Consortium to Establish a Registry for Alzheimer's Disease. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1997 Sep;42(3):319-25. [Crossref], [Google Scholar], [Publisher]
20. Johnson JK, Head E, Kim R, Starr A, Cotman CW. Clinical and pathological evidence for a frontal variant of Alzheimer disease. Archives of neurology. 1999 Oct 1;56(10):1233-9. [Crossref], [Google Scholar], [Publisher]
21. Apostolova LG. Alzheimer disease. Continuum: Lifelong Learning in Neurology. 2016 Apr;22(2 Dementia):419. [Crossref], [Google Scholar], [Publisher]
22. Chetelat G, Desgranges B, De La Sayette V, Viader F, Eustache F, Baron JC. Mild cognitive impairment: can FDG-PET predict who is to rapidly convert to Alzheimer's disease?. Neurology. 2003 Apr 22;60(8):1374-7. [Crossref], [Google Scholar], [Publisher]
23. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC. 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. Alzheimer's & dementia. 2011 May 1;7(3):263-9. [Crossref], [Google Scholar], [Publisher]
24. Bateman RJ, Blennow K, Doody R, Hendrix S, Lovestone S, Salloway S, Schindler R, Weiner M, Zetterberg H, Aisen P, Vellas B. Plasma biomarkers of AD emerging as essential tools for drug development: an EU/US CTAD task force report. The journal of prevention of Alzheimer's disease. 2019 Jul;6:169-73. [Crossref], [Google Scholar], [Publisher]
25. Lesne SE, Sherman MA, Grant M, Kuskowski M, Schneider JA, Bennett DA, Ashe KH. Brain amyloid-β oligomers in ageing and Alzheimer's disease. Brain. 2013 May 1;136(5):1383-98. [Crossref], [Google Scholar], [Publisher]
26. Kennedy AM, Frackowiak RS, Newman SK, Bloomfield PM, Seaward J, Roques P,

Lewington G, Cunningham VJ, Rossor MN. Deficits in cerebral glucose metabolism demonstrated by positron emission tomography in individuals at risk of familial Alzheimer's disease. Neuroscience letters. 1995 Feb 15;186(1):17-20. [Crossref], [Google Scholar], [Publisher]

27. Mosconi L, Berti V, Glodzik L, Pupi A, De Santi S, de Leon MJ. Pre-clinical detection of Alzheimer's disease using FDG-PET, with or without amyloid imaging. Journal of Alzheimer's Disease. 2010 Jan 1;20(3):843-54. [Crossref], [Google Scholar], [Publisher]
28. Vandenberghe R, Adamczuk K, Van Laere K. The interest of amyloid PET imaging in the diagnosis of Alzheimer's disease. Current Opinion in Neurology. 2013 Dec 1;26(6):646-55. [Crossref], [Google Scholar], [Publisher]
29. Lam J, Hlávka J, Mattke S. The potential emergence of disease-modifying treatments for Alzheimer disease: the role of primary care in managing the patient journey. The Journal of the American Board of Family Medicine. 2019 Nov 1;32(6):931-40. [Crossref], [Google Scholar], [Publisher]
30. Teipel S, Gustafson D, Ossenkoppele R, Hansson O, Babiloni C, Wagner M, Riedel-Heller SG, Kilimann I, Tang Y. Alzheimer Disease: Standard of Diagnosis, Treatment, Care, and Prevention. Journal of Nuclear Medicine. 2022 Jul 1;63(7):981-5. [Crossref], [Google Scholar], [Publisher]
31. Anoop A, Singh PK, Jacob RS, Maji SK. CSF biomarkers for Alzheimer's disease diagnosis. International journal of Alzheimer's disease. 2010 Jun 23;2010. [Crossref], [Google Scholar], [Publisher]
32. Georganopoulou DG, Chang L, Nam JM, Thaxton CS, Mufson EJ, Klein WL, Mirkin CA. Nanoparticle-based detection in cerebral spinal fluid of a soluble pathogenic biomarker for Alzheimer's disease. Proceedings of the National Academy of Sciences. 2005 Feb 15;102(7):2273-6. [Crossref], [Google Scholar], [Publisher]
33. Kerwin D, Abdelnour C, Caramelli P, Ogunniyi A, Shi J, Zetterberg H, Traber M. Alzheimer's disease diagnosis and management: Perspectives from around the world. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2022;14(1):e12334. [Crossref], [Google Scholar], [Publisher]
34. El Kadmiri N, Said N, Slassi I, El Moutawakil B, Nadifi S. Biomarkers for Alzheimer disease: classical and novel candidates' review. Neuroscience. 2018 Feb 1;370:181-90. [Crossref], [Google Scholar], [Publisher]
35. Chatterjee P, Pedrini S, Stoops E, Goozee K, Villemagne VL, Asih PR, Verberk IM, Dave P, Taddei K, Sohrabi HR, Zetterberg H. Plasma glial fibrillary acidic protein is elevated in cognitively normal older adults at risk of Alzheimer's disease. Translational psychiatry. 2021 Jan 11;11(1):27. [Crossref], [Google Scholar], [Publisher]
36. Colangelo AM, Alberghina L, Papa M. Astrogliosis as a therapeutic target for neurodegenerative diseases. Neuroscience letters. 2014 Apr 17;565:59-64. [Crossref], [Google Scholar], [Publisher]
37. Muramori f, kobayashi k, nakamura i. A quantitative study of neurofibrillary tangles, senile plaques and astrocytes in the hippocampal subdivisions and entorhinal cortex in Alzheimer's disease, normal controls and non-Alzheimer neuropsychiatric diseases. Psychiatry and clinical neurosciences. 1998 Dec;52(6):593-9. [Crossref], [Google Scholar], [Publisher]
38. Nasreddine ZS, Rossetti H, Phillips N, Chertkow H, Lacritz L, Cullum M, Weiner M. Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sampleAuthor Response. Neurology. 2012 Mar 6;78(10):765-6. [Google Scholar], [Publisher]
39. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC. 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. Alzheimer's & dementia. 2011 May

1;7(3):263-9. [Crossref], [Google Scholar], [Publisher]
40. Kim KS, Lee SJ, Suh JC. Numerical simulation of the vortical flow around an oscillating circular cylinder. InISOPE International Ocean and Polar Engineering Conference 2005 Jun 19 (pp. ISOPE-I). ISOPE. [Google Scholar], [Publisher]
41. Chatterjee P, Goozee K, Sohrabi HR, Shen K, Shah T, Asih PR, Dave P, ManYan C, Taddei K, Chung R, Zetterberg H. Association of plasma neurofilament light chain with neocortical amyloid-β load and cognitive performance in cognitively normal elderly participants. Journal of Alzheimer's Disease. 2018 Jan 1;63(2):479-87. [Crossref], [Google Scholar], [Publisher]
42. De Servi B, La Porta CA, Bontempelli M, Comolli R. Decrease of TGF-β1 plasma levels and increase of nitric oxide synthase activity in leukocytes as potential biomarkers of Alzheimer's disease. Experimental gerontology. 2002 Jun 1;37(6):813-21. [Crossref], [Google Scholar], [Publisher]
43. Mattson MP, Barger SW, Furukawa K, Bruce AJ, Wyss-Coray T, Mark RJ, Mucke L. Cellular signaling roles of TGFβ, TNFα and βAPP in brain injury responses and Alzheimer's disease. Brain research reviews. 1997 Feb 1;23(1-2):47-61. [Crossref], [Google Scholar], [Publisher]
44. Torreilles F, Salman-Tabcheh S, Guérin MC, Torreilles J. Neurodegenerative disorders: the role of peroxynitrite. Brain Research Reviews. 1999 Aug 1;30(2):153-63. [Crossref], [Google Scholar], [Publisher]
45. Dorheim MA, Tracey WR, Pollock JS, Grammas P. Nitric oxide synthase activity is elevated in brain microvessels in Alzheimer′ s disease. Biochemical and biophysical research communications. 1994 Nov 30;205(1):659-65. [Crossref], [Google Scholar], [Publisher]
46. Peng M, Jia J, Qin W. Plasma gelsolin and matrix metalloproteinase 3 as potential biomarkers for Alzheimer disease. Neuroscience letters. 2015 May 19;595:116-21. [Crossref], [Google Scholar], [Publisher]
47. Güntert A, Campbell J, Saleem M, O'Brien DP, Thompson AJ, Byers HL, Ward MA, Lovestone S. Plasma gelsolin is decreased and correlates with rate of decline in Alzheimer's disease. Journal of Alzheimer's Disease. 2010 Jan 1;21(2):585-96. [Crossref], [Google Scholar], [Publisher]
48. Ray I, Chauhan A, Wegiel J, Chauhan VP. Gelsolin inhibits the fibrillization of amyloid beta-protein, and also defibrillizes its preformed fibrils. Brain research. 2000 Jan 24;853(2):344-51. [Crossref], [Google Scholar], [Publisher]
49. Okada YA, Nagase HI, Harris Jr ED. A metalloproteinase from human rheumatoid synovial fibroblasts that digests connective tissue matrix components. Purification and characterization. Journal of Biological Chemistry. 1986 Oct 25;261(30):14245-55. [Crossref], [Google Scholar], [Publisher]
50. Horstmann S, Budig L, Gardner H, Koziol J, Deuschle M, Schilling C, Wagner S. Matrix metalloproteinases in peripheral blood and cerebrospinal fluid in patients with Alzheimer's disease. International psychogeriatrics. 2010 Sep;22(6):966-72. [Crossref], [Google Scholar], [Publisher]
51. Wang R, Chen Z, Fu Y, Wei X, Liao J, Liu X, He B, Xu Y, Zou J, Yang X, Weng R. Plasma cystatin C and high-density lipoprotein are important biomarkers of Alzheimer's disease and vascular dementia: a cross-sectional study. Frontiers in aging neuroscience. 2017 Feb 7;9:26. [Crossref], [Google Scholar], [Publisher]
52. Yang DS, Stavrides P, Mohan PS, Kaushik S, Kumar A, Ohno M, Schmidt SD, Wesson DW, Bandyopadhyay U, Jiang Y, Pawlik M. Therapeutic effects of remediating autophagy failure in a mouse model of Alzheimer disease by enhancing lysosomal proteolysis. Autophagy. 2011 Jul 1;7(7):788-9. [Crossref], [Google Scholar], [Publisher]
53. Ray L, Khemka VK, Behera P, Bandyopadhyay K, Pal S, Pal K, Basu D, Chakrabarti S. Serum homocysteine, dehydroepiandrosterone sulphate and lipoprotein (a) in Alzheimer's disease and

vascular dementia. Aging and disease. 2013 Apr;4(2):57. [Google Scholar], [Publisher]
54. Hottman DA, Chernick D, Cheng S, Wang Z, Li L. HDL and cognition in neurodegenerative disorders. Neurobiology of disease. 2014 Dec 1;72:22-36. [Crossref], [Google Scholar], [Publisher]
55. Selkoe DJ. Alzheimer disease and aducanumab: adjusting our approach. Nature Reviews Neurology. 2019 Jul;15(7):365-6. [Crossref], [Google Scholar], [Publisher]
56. Desai AK, Grossberg GT. Diagnosis and treatment of Alzheimer's disease. Neurology. 2005 Jun 28;64(12 suppl 3):S34-9. [Crossref], [Google Scholar], [Publisher]
57. Van Dyck CH. Anti-amyloid-β monoclonal antibodies for Alzheimer's disease: pitfalls and promise. Biological psychiatry. 2018 Feb 15;83(4):311-9. [Crossref], [Google Scholar], [Publisher]
58. Bateman RJ, Cummings J, Schobel S, Salloway S, Vellas B, Boada M, Black SE, Blennow K, Fontoura P, Klein G, Assunção SS. Gantenerumab: an anti-amyloid monoclonal antibody with potential disease-modifying effects in early Alzheimer's disease. Alzheimer's Research & Therapy. 2022 Dec;14(1):1-7. [Crossref], [Google Scholar], [Publisher]
59. Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RY, Lannfelt L, Bradley H, Rabe M, Koyama A, Reyderman L. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimer's research & therapy. 2021 Dec;13:1-4. [Crossref], [Google Scholar], [Publisher]
60. Lowe SL, Duggan Evans C, Shcherbinin S, Cheng YJ, Willis BA, Gueorguieva I, Lo AC, Fleisher AS, Dage JL, Ardayfio P, Aguiar G. Donanemab (LY3002813) phase 1b study in Alzheimer's disease: rapid and sustained reduction of brain amyloid measured by florbetapir F18 imaging. The Journal of Prevention of Alzheimer's Disease. 2021 Sep;8:414-24. [Crossref], [Google Scholar], [Publisher]
61. West T, Hu Y, Verghese PB, Bateman RJ, Braunstein JB, Fogelman I, Budur K, Florian H, Mendonca N, Holtzman DM. Preclinical and clinical development of ABBV-8E12, a humanized anti-tau antibody, for treatment of Alzheimer's disease and other tauopathies. J Prev Alzheimers Dis. 2017 Jan 1;4(4):236-41. [Crossref], [Google Scholar], [Publisher]
62. Teng E, Manser PT, Pickthorn K, Brunstein F, Blendstrup M, Bohorquez SS, Wildsmith KR, Toth B, Dolton M, Ramakrishnan V, Bobbala A. Safety and efficacy of semorinemab in individuals with prodromal to mild Alzheimer disease: a randomized clinical trial. JAMA neurology. 2022 Aug 1;79(8):758-67. [Crossref], [Google Scholar], [Publisher]
63. Lynch SY, Kaplow J, Zhao J, Dhadda S, Luthman J, Albala B. P4-389: elenbecestat, E2609, a bace inhibitor: results from a phase-2 study in subjects with mild cognitive impairment and mild-to-moderate dementia due to Alzheimer's disease. Alzheimer's & Dementia. 2018 Jul;14(7S_Part_31):P1623-.[Crossref], [Google Scholar], [Publisher]
64. Neumann U, Ufer M, Jacobson LH, Rouzade-Dominguez ML, Huledal G, Kolly C, Lüönd RM, Machauer R, Veenstra SJ, Hurth K, Rueeger H. The BACE-1 inhibitor CNP 520 for prevention trials in Alzheimer's disease. EMBO molecular medicine. 2018 Nov;10(11):e9316. [Crossref], [Google Scholar], [Publisher]
65. Vandenberghe R, Riviere ME, Caputo A, Sovago J, Maguire RP, Farlow M, Marotta G, Sanchez-Valle R, Scheltens P, Ryan JM, Graf A. Active Aβ immunotherapy CAD106 in Alzheimer's disease: A phase 2b study. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2017 Jan 1;3(1):10-22. [Crossref], [Google Scholar], [Publisher]
66. Novak P, Zilka N, Zilkova M, Kovacech B, Skrabana R, Ondrus M, Fialova L, Kontsekova E, Otto M, Novak M. AADvac1, an active immunotherapy for Alzheimer's disease and non Alzheimer tauopathies: an

overview of preclinical and clinical development. The journal of prevention of Alzheimer's disease. 2019 Jan;6:63-9. [Crossref], [Google Scholar], [Publisher]
67. Grossberg GT. Diagnosis and treatment of Alzheimer's disease. Journal of Clinical Psychiatry. 2003 Jan 1;64:3-6. [Google Scholar], [Publisher]
68. Dafre R, Wasnik Sr P. Current diagnostic and treatment methods of Alzheimer's disease: a narrative review. Cureus. 2023 Sep 20;15(9). [Crossref], [Google Scholar], [Publisher]
69. Monczor M. Diagnosis and treatment of Alzheimer's disease. Current Medicinal Chemistry-Central Nervous System Agents. 2005 Mar 1;5(1):5-13. [Crossref], [Google Scholar], [Publisher]
70. Davis KL, Thal LJ, Gamzu ER, Davis CS, Woolson RF, Gracon SI, Drachman DA, Schneider LS, Whitehouse PJ, Hoover TM, Morris JC. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. New England Journal of Medicine. 1992 Oct 29;327(18):1253-9. [Google Scholar], [Publisher]
71. Kumar A, Gupta V, Sharma S. Donepezil. InStatPearls [Internet] 2023 Aug 17. StatPearls Publishing. [Google Scholar], [Publisher]
72. Birks JS, Evans JG. Rivastigmine for Alzheimer's disease. Cochrane Database of systematic reviews. 2015(4). [Crossref], [Google Scholar], [Publisher]
73. Razay G, Wilcock GK. Galantamine in Alzheimer's disease. Expert review of neurotherapeutics. 2008 Jan 1;8(1):9-17. [Crossref], [Google Scholar], [Publisher]
74. Olin J, Schneider L. Galantamine for Alzheimer's disease. The Cochrane database of systematic reviews. 2002 Jan 1(3):CD001747.[Crossref], [Google Scholar], [Publisher]
75. Abbott A, Dolgin E. Leading Alzheimer's theory survives drug failure. Nature. 2016 Dec 1;540(7631):15-7. [Crossref], [Google Scholar], [Publisher]
76. Imbimbo BP. Why did tarenflurbil fail in Alzheimer's disease?. Journal of Alzheimer's Disease. 2009 Jan 1;17(4):757-60. [Crossref], [Google Scholar], [Publisher]
77. Reardon S. Alzheimer antibody drugs show questionable potential. Nat Rev Drug Discov. 2015 Sep 1;14(9):591-2. [Crossref], [Google Scholar], [Publisher]
78. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's research & therapy. 2014 Aug;6(4):1-7. [Crossref], [Google Scholar], [Publisher]
79. Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, Raman R, Sun X, Aisen PS, Siemers E. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. New England Journal of Medicine. 2014 Jan 23;370(4):311-21. [Google Scholar], [Publisher]
80. Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, Sabbagh M, Honig LS, Porsteinsson AP, Ferris S, Reichert M. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. New England Journal of Medicine. 2014 Jan 23;370(4):322-33. [Google Scholar], [Publisher]
81. ManafiRad A, Farzadfar F, Habibi L, Azhdarzadeh M, Aghaverdi H, Tehrani KH, Lotfi M, Kehoe PG, Sheidaei A, Ghasemian A, Darzi ER, Mahmoodi R, Mahmoudi M. Is amyloid-β an innocent bystander and marker in Alzheimer's disease? Is the liability of multivalent cation homeostasis and its influence on amyloid-β function the real mechanism? Journal of Alzheimer's Disease. 2014 Jan 1;42(1):69-85. [Crossref], [Google Scholar], [Publisher]
82. Krol S, Macrez R, Docagne F, Defer G, Laurent S, Rahman M, Hajipour MJ, Kehoe PG, Mahmoudi M. Therapeutic benefits from nanoparticles: the potential significance of nanoscience in diseases with compromise to the blood brain barrier. Chemical reviews. 2013 Mar 13;113(3):1877-903. [Crossref], [Google Scholar], [Publisher]
83. Blennow K. A review of fluid biomarkers for Alzheimer's disease: moving from CSF to blood. Neurology and therapy. 2017

Jul;6:15-24. [Crossref], [Google Scholar], [Publisher]

84. Henriksen K, O'Bryant SE, Hampel H, Trojanowski JQ, Montine TJ, Jeromin A, Blennow K, Lönneborg A, Wyss-Coray T, Soares H, Bazenet C. The future of blood-based biomarkers for Alzheimer's disease. Alzheimer's & dementia. 2014 Jan 1;10(1):115-31. [Crossref], [Google Scholar], [Publisher]