CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.6550027

Available online at: http://www.iajps.com *Review Article*

ALZHEIMER'S DISEASE NOVEL DRUGS: A REVIEW

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Article Received: March 2022 **Accepted:** April 2022 **Published:** May 2022

Abstract:

Alzheimer's disease (AD) is a neurological illness that causes the majority of dementia cases. In today's increasingly ageing population, the prevalence of Alzheimer's disease has increased, putting a great strain on families and society. Despite the devastating symptoms of Alzheimer's disease, present treatments are unable to generate sufficient therapeutic benefits or halt the illness's progression. Finding new treatments for Alzheimer's disease has become critical. In this research, we looked at five different types of innovative therapeutic approaches: anti-amyloid therapy, anti-tau therapy, anti-neuroinflammatory therapy, neuroprotective drugs such as N-methyl-D-aspartate (NMDA) receptor modulators, and brain stimulation. The focus of therapeutic development is changing away from a single disease target and toward more complicated mechanisms like neuroinflammation and neurodegeneration. The review focus on Novel Drug used for treatment of alzheimer's disease.

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*Please cite this article in press Sunayana Kesharwani et al,**Alzheimer's Disease Novel Drugs: A Review.,**Indo Am. J. P. Sci, 2022; 09(5).*

INTRODUCTION: [1,2]

Alzheimer's disease (AD) is an age-related neurodegenerative disease that is characterized by a progressive loss of memory associated with other cognitive sphere deficits interfering with social and occupational functioning. The global prevalence of AD was estimated at 26.55 million in 2006 [1]. During several years preceding the diagnosis of dementia, there is a gradual cognitive decline with a continuum from the predementia stage to the other stages of the disease. Current treatment strategies address impairments of cholinergic and glutamatergic systems. The cholinergic hypothesis was initially presented over 25 years ago and suggests that a dysfunction of acetylcholine containing neurons in the brain contributes substantially to the cognitive decline observed in those with AD.

The cholinergic hypothesis of AD states that cholinergic neurons in the basal forebrain are severely affected in the course of the disease, and that the resulting cerebral cholinergic deficit leads to memory loss and other cognitive and noncognitive symptoms, which are characteristic of the disease. Thus, cholinesterase inhibitors (ChEIs) have long been the cornerstone of treatment for patients with AD [2]. Excessive glutamate levels in the cerebral cortex of AD patients have also been hypothesized to contribute to cognitive deficits in AD. Memantine, a moderate affinity N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, is postulated to counteract this effect [3]. However, the effects of these treatments are limited or controversial and they do not modify disease progression [4].

Currently available evidence strongly supports the position that AD is mainly characterized neuropathologically by the presence of two kinds of protein aggregates: extracellular plaques of Abeta-peptide and intracellular neurofibrillary tangles (NFTs). The initiating event in AD could be related to abnormal processing of ß-amyloid (Aß) peptide, ultimately leading to formation of Aß plaques in the brain. This process occurs while individuals are still cognitively normal. Abeta is a highly aggregatory neurotoxic peptide, derived from the enzymatic cleavage of a membrane protein, the amyloid precursor protein (APP). The 42-residue form of the peptide (Abeta-42) is more prone to aggregation than the shorter and less hydrophobic 40-residue form (Abeta40) [5].

The pathological long term accumulation of toxic oligomeric Abeta assemblies could have a causal role in the onset and progression of the disease. APP is processed by beta and gamma-secretases via the amyloidogenic pathway to produce the toxic variety of Abeta (Abeta-42). The non-amyloidogenic pathway results from alpha-secretase cleavage within the Abeta sequence of APP . According to ABeta peptide cascade hypothesis, ABeta triggers all of the pathological features of the disease, from tau hyperphosphorylation to synaptic dysfunction and neuronal cell death. Even though ABeta has an important role in the AD pathogenesis, different findings speak in favour of a less linear pathophysiology. [6]

Patients with sporadic cerebral amyloid angiopathy show great levels of amyloid pathology which is not correlated with cognitive symptoms, and old cognitively normal individuals sometimes exhibit cortical Abeta with almost no tangles. This suggests that amyloid alone is insufficient to explain AD phenotype. Another hypothesis states that Abeta toxicity could be tau dependent or acts in parallel with tau. After a lag period, which varies from patient to patient, neuronal dysfunction and neurodegeneration become the dominant pathological processes. Neurofibrillary tangles are intraneuronal aggregates of paired helical filaments (PHFs) composed of an abnormally hyperphosphorylated intracellular tau protein [7].

Tau normally binds and stabilizes microtubules, the main component of the cellular cytoskeleton. Hyperphosphorylated and aggregated tau lacks its functions and disrupts neuronal transport. It also acts as a toxic stimuli that has an important impact on the viability of neurons: proteolytic cleavage of free tau could generate neurotoxic fragments and abnormal tau sequesters normal tau, MAP1 and MAP2 [8]

In AD, the interaction between deposition of Abeta and hyperphosphorylation of tau is still controversial. Tau could become hyperphosphorylated in response to a disturbance in the balance of physiological kinase/phosphatase activities, which may be initiated by a neurotoxic onset. Abeta and tau could interfere in an original way contributing to a cascade of events leading to the activation of the apoptotic cell death cascade, neuronal death, and transmitter deficits . In the same way, abnormal tau could potentiate Abeta toxicity as disruption of tau processing remains a necessary event in the neurodegenerative cascade and post mortem analyses show that the degree of tau-related pathology correlates much better with the severity of the dementia than does the Abeta burden [9]

Recent advances in understanding AD pathogenesis have led to the development of numerous compounds

that might modify the disease process. Investigation for novel therapeutic approaches targeting the presumed underlying pathogenic mechanisms is a major focus of research on AD and it is expected that disease-modifying medications will emerge. Cerebrospinal fluid (CSF) concentrations of Abeta-42 and tau protein could provide good accuracy in discriminating patients with Alzheimer's disease from control subjects , especially for early stages of the disease. These biomarkers give new possibilities for early clinical trials in AD. This article exposes general classes of potential disease-modifying therapies under clinical investigation for the treatment of AD. [10]

Antiamyloid agents:
Antiamyloid agents target production, accumulation, clearance, or toxicity associated with Abeta peptide [11].

Immunization:
Active immunization of APP transgenic (Tg) mice before they had amyloid plaque deposits resulted in significantly reduced amyloid deposits and neuritic pathology while Abeta immunization of older mice with pre-existing plaques, also resulted in a reduction in plaque pathology. This suggests that this approach is able to slow the progression of amyloid deposition and even reverse it . Subsequent studies have shown that Abeta immunization can also prevent or improve learning deficits in AD Tg mice. A phase I human trial using an active immunisation strategy against Abeta was promising but the phase IIa immunization trial with a synthetic Abeta peptide called AN-1792 was stopped after reports of meningoencephalitis in 6% of the treated patients [12].

The first analysis of efficacy in this trial, reported for a small subset of patients, was suggestive of a slowing cognitive decline, particularly in patients generating the highest antibody titres . A more recent and complete analysis of all treated patients demonstrated no significant efficacy but in the small subset of subjects who had CSF examinations, CSF tau was decreased in antibody responders vs placebo subjects ($p < 0.001$). Immunization strategies research in transgenic mouse models has been refocused to establish safer therapeutic approaches [13].

Classical human immunoglobulins (Igs) preparation can also be investigate as a passive immunization therapy in AD, as a small percentage of antibodies are directed against Abeta peptide sequences. Intravenous infusion of Igs in five AD patients over a 6-month period prevented further cognitive decline , suggesting this approach could potentially act like a passive immunotherapy. Human trials of passively administered anti-Abeta antibodies are now being initiated. Other antibodies have recently reached clinical evaluation: GSK933776A, PF-04360365, PLY2062430. [14]

Secretases modulation:
APP processing by alpha secretase is a non-amyloidogenic pathway, because the alpha-secretase cleavage site is within the Abeta sequence of APP. Enhanced cleavage at this site may represent a potential disease modifying strategy . To our knowledge no human clinical trials are underway. Beta-secretase has been shown to be a transmembrane aspartic protease, beta-site APP cleaving enzyme 1 (BACE1). BACE-1 processing of beta-amyloid precursor protein is the first step in the pathway leading to the production of amyloid-beta. BACE-1 knockout mice develop normally, and appear to have completely abolished Abeta production (31). A selective BACE-1 inhibitor, GSK188909, reduced levels of secreted and intracellular Abeta40 and Abeta42 in vitro as well as in APP transgenic mice brains . Other beta-secretase inhibitors are under investigation [15].

Thiazolidinediones also act as ß-secretase inhibitors by stimulating PPARγ (see below). To our knowledge, at this time, there are no clinical trials with Beta-secretase in humans. Inhibition of gamma-secretase targets the generation of Abeta 42, but other proteins are also substrates of this enzyme, and particulary the transmembrane Notch receptor, involved in vital functions. Abnormalities in the gastrointestinal tract, thymus and spleen in animal models result from inhibition of Notch cleavage . Preclinical studies establish that gamma-secretase inhibitors can reduce brain Abeta and reverse Abeta-induced cognitive deficits in transgenic mice. LY450139 dihydrate, a gamma-secretase inhibitor, inhibits Abeta formation in vitro and in vivo. [16]

In phase 1 volunteer studies, a dose-dependent reduction in plasma Abeta was demonstrated. However, Abeta concentrations were unchanged in CSF. In an AD patients randomized controlled trial (RCT) with LY450139 dihydrate, Abeta40 decreased significantly in plasma, and decreased in a non significant manner in CSF. Single doses of GSI-953, a selective gamma-secretase inhibitor, also produce dose dependent reductions of plasma but not CSF Aß peptides in humans. Protein Kinase C (PKC) plays an important role in many types of learning and memory. Its impact is further emphasized by a

regulatory role of PKC enzymes in amyloid production and accumulation [17].

Bryostatin 1, a macrolide lactone, exhibits high affinity for PKC and dramatically enhances the secretion of the alpha-secretase product in patients' fibroblasts . Tarenflurbil is the pure R-enantiomer of flurbiprofen and is the first in a novel class of selective Abeta-42 lowering agent. It modulates gamma secretase and is highly specific for its effects on Abeta -42 and, unlike the gamma secretase inhibitors, does not interfere with the function of Notch. In a phase II study, tarenflurbil was well tolerated for up to 24 months of treatment in 210 AD patients, with evidence of a dose-related effect on measures of daily activities and global function in patients with mild AD , but phase III clinical trial was negative. [18]

Abeta degradation enhancement:
Insufficient clearance of brain Abeta could be another hypothesis to explain Abeta accumulation in AD. Several Abeta 42-cleaving proteases have been identified including neprilysin and its homologue endothelin-converting enzyme, insulysin, matrix metalloproteinase-9, and insulin-degrading enzyme (IDE). In addition, the serine proteinase, plasmin, may participate in extracellular metabolism of the amyloid peptide under regulation of the plasminogen-activator inhibitor . IDE knockout mice demonstrate an elevation of brain Abeta levels, and transgenic mice overexpressing IDE or neprilysin show a reduction of amyloid burden as an improved survival . The level of neprilysin mRNA has been found significantly reduced in the hippocampus and temporal cortex of AD patients . Level of Abeta in brains of nepri lysine knockout mice is elevated and neprilysin administration in transgenic APP mice shows a reduction of cortical amyloid deposits [19].

Somatostatin up-regulates brain neprilysin activity, resulting in a decrease of Abeta levels. A genetic deficiency of somatostatin altered hippocampal neprilysin activity and increased Abeta-. Strategies targeting somatostatin receptors may be effective in AD . FK962, a somatostatin releaser had shown cognitive enhancing properties in vivo, reached phase II clinical trial few years ago but its development seems to be over. PAI-1 inhibits the activity of tissue plasminogen activator (tPA), an enzyme that cleaves plasminogen to generate plasmin, a protease that degrades Abeta oligomers and monomers. The inhibitor of PAI-1, PAZ-417, has shown promising results in vivo and has reached clinical evaluation, but its development seems to be over. [20]

Anti-aggregation and anti-fibrillization agents:
An alternative approach to secretase inhibition, which raises the problem of interfering with normal enzymatic reactions, is to inhibit Abeta aggregation into neurotoxic oligomers. Tramiprosate or NC-531 or 3APS is a glycosaminoglycan mimetic that binds to Abeta and inhibits amyloid plaque formation . Preclinical data have shown that tramiprosate reduces brain and plasma levels of Abeta and prevents fibril formation [21].

In a phase II trial, longterm administration of tramiprosate was safe, well tolerated and reduced CSF Abeta42 levels in patients with AD . Tramiprosate has reached phase III clinical trials . However, phase III in the United States was negative (unpublished data) and stopped in Europe. Dysregulation of cerebral metal ions (Fe(2+), Cu(2+) and Zn(2+)), and their interactions with Abeta may contribute to AD by playing a role in the precipitation and cytotoxicity of Abeta . Metal ions are required for Abeta protein oligomerisation and recent studies show that metal chelators could produce a significant reversal Abeta deposition in vitro and in vivo . XH1 and DP-109, both metal chelators, attenuated Abeta pathology inAPP transgenic mice [22].

Receptor for advanced glycation end products inhibitors:
The receptor for advanced glycation end products (RAGE) is a cell-bound receptor of immunoglobulin which may be activated by a variety of pro-inflammatory ligands including advanced glycation end products leading to secretion of cytokines, which may link the amyloid pathway to the inflammatory pathway. RAGE-mediated inflammation caused by glial cells and subsequent changes in neuronal glucose metabolism are likely to be important contributors to neurodegeneration in AD [23].

Tau-related therapies:
Microtubule associated protein (MAP) tau is abnormally hyperphosphorylated in AD. Several kinases are reported to phosphorylate tau in vitro including glycogen synthase kinase (GSK-3), cyclin-dependant kinase-5 (Cdk-5), mitogen activated protein kinase family members (MAPK), casein kinase, calcium calmodulin-dependant kinase II, protein kinase A andothers . Some of them, like GSK3, could be also involved in Abeta generation promoting cell death, production of inflammatory molecules and cell migration. Phosphoseryl /phosphothreonyl protein phosphatase-2A (PP2A), which is colocalized with tau and microtubules in the brain, is apparently the most active enzyme in dephosphorylating the abnormal tau to a normal-like

state (8082). Other phosphatases have also been implicated [24].

Reducing abnormal phosphorylation, restoring or stimulating phosphatase activity are promising therapeutic strategies. Lithium reduces tau phosphorylation in vitro, promotes microtubule assembly through inhibition of GSK3 , and has been shown to reduce tau phosphorylation in APP transgenic mice [25].

Neuroprotective agents:
Another alternative approach involves protection against cellular damage caused by oxidative, inflammatory or other toxic stressors.

Antioxidants:
Genetic and lifestyle-related risk factors for AD could be associated with an increase in oxidative stress, suggesting that oxidative stress is involved in the early stage of the pathology . Individuals with mild cognitive impairment or very mild AD show increased levels of lipid peroxydation and nucleic acid oxydation in postmortem brain and plasma . Free radicals and oxidative injury to neurons could chronologically precede Abeta plaque deposition and tau phosphorylation [26].

Several antioxidants that have been investigated for their potential to reduce the risk of AD include vitamins A , C and E , coenzyme Q , selenium, polyunsaturated fatty acid and others. In an AD trial published in 1997, vitamin E had been show to slow progression of the disease in patients with moderately severe AD . However, recent meta-analysis and trial results suggest that vitamin E increases morbidity and mortality and the Cochrane review does not support the use of vitamin E to treat AD . The lack of consistent efficacy data for vitamin C and its questionable safety could also discourage its use [27].

Anti-Inflammatory drugs:
Laboratory evidence shows that inflammatory mechanisms contribute to neuronal damage in AD . Epidemiological evidence , suggests that non steroidal antiinflammatory drugs (NSAIDs) may favourably influence the course of the disease. In a 1993 trial, indomethacin appeared to protect AD patients from cognitive decline according to the authors (138) but this point of view is not shared by Cochrane reviewers . Another trial with indomethacin failed to show any efficacy in the progression of AD. Ibuprofen, celexocib, rofecoxib and naproxen did not slow the progression of AD [28].

In a phase II AD clinical trial with (R)flurbiprofen, a few subset of patients who had high blood concentrations of this drug demonstrated a benefit in cognitive and behavioral performance. However, Myriad Company has discontinued the development of (R)-flurbiprofen (Flurizan or MPC-7869). Cyclophosphamide is a potent antiinflammatory and immunomodulatory drug acting primarily by inhibiting proliferation of immune cells . Excess tumor necrosis factor-alpha (TNF-alpha) has been shown to mediate the disruption in synaptic memory mechanisms caused by betaamyloid in addition to its proinflammatory functions . Etanercept, an antagonist of TNF-alpha, delivered by perispinal administration in AD patients, shown a great potential in a pilot study . Among traditional medicine products, Resveratrol, a component of grapes, berries and other fruits, is a polyphenol that has been shown to mediate its effects through modulation of many different pathways. For instance, Resveratrol has been shown to reduce the expression of inflammatory biomarkers and induce antioxidant enzymes . Lastly, curcumin, a polyphenolic molecule safely used as a food coloring, proved to be immunomodulatory and has shown Abeta40 aggregation inhibition properties in vitro and in vivo [29].

Glutamate mediated neurotoxicity:
The glutamatergic system has long been recognized for its role in learning and memory, and recent studies indicate the involvement of glutamate mediated neurotoxicity in the pathogenesis of AD . The neurotransmitter glutamate activates several classes of receptors and especially three major types of ionotropic receptors: alpha-amino-3-hydroxy-5-methyl4-isoxazolepropionic acid (AMPA), kainate and Nmethyl-Daspartate (NMDA). Chronic activation of receptors, in particular of the NMDA type, ultimately leads to neuronal damage. Complete NMDA receptor blockade has also been shown to impair neuronal plasticity. Thus, both hypo and hyperactivity of the glutamatergic system leads to dysfunction . Memantine is an uncompetitive NMDA receptor antagonist and has been approved for the symptomatic treatment of AD. Most other centrally acting NMDA antagonists have been unattended because of severe psychomimetic and cardiovascular adverse effects [30].

A series of second-generation memantine derivatives are currently in development and may have greater neuroprotective properties than memantine . Neramexane is a new NMDA receptor antagonist that is currently under development. In vivo neramexane enhances long-term spatial memory in adult rats . Its clinical development seems to be over. Another way

of action is the positive modulation of AMPA receptors . LY404187, a selective positive modulator of AMPA receptors, improved performance of cognitive function in animal models . LY451395, an AMPA receptor potentiator, administered to AD patients did not show a statistically significant difference versus placebo on cognitive functions in a clinical trial [31].

Neurorestorative approaches: neurotrophin and cell therapy:

Nerve growth factor (NGF) promotes survival and differentiation of neurons and neurotrophic factors have been suggested as contributors of AD pathophysiology (160). In rhesus monkeys, aging is associated with a significant reduction in cortical cholinergic innervation but this reduction is reversible by NGF delivery to cholinergic somata in the basal forebrain (161). Phenotypic knockout of NGF activity in transgenic anti-NGF mice results in a progressive neurodegenerative AD type phenotype and the neurodegeneration induced by the expression of anti-NGF antibodies can be largely reversed by NGF delivery [32].

Results suggested improvement in the rate of cognitive decline after a mean follow-up of 22 months . AIT-082 (Neotrofin) increase levels of NGF and stimulate nerve sprouting in the brain. A phase I study of AIT-082 was conducted in 36 mild AD patients with no significant side effects . Growth factor modulators such as CERE-110 are also under clinical development for AD treatment .

Animal studies show that human neural stem cells transplanted into animals brains differentiated into neural cells and significantly improved the cognitive functions. Neural stem cell grafts present a potential strategy of treatment. It raises the possibility to stimulate inherent precursor cells to replace lost neurons. Stem cell-related approaches are now under investigation [33].

Impact on cholinergic deficit:

The mainstays of current pharmacotherapy for AD are compounds aimed at increasing the levels of acetylcholine (ACh) in the brain, thereby facilitating cholinergic neurotransmission through inhibition of the cholinesterases. These drugs, known as acetyl cholinesterase inhibitors (AChEIs), were first approved by the U.S. Food and Drug Administration in 1995. Other drugs which can increase the ACh levels in brain include ACh precursors, muscarinic agonists and nicotinic agonists.

Acetyl cholinesterase and butyryl cholinesterase inhibitors:

Recent reports suggest that AChEIs could affect the underlying disease processes through neuroprotective and disease-modifying property. Huperzine A is a selective AChEIs with potential properties that include modification of beta-amyloid peptide processing,reduction of oxidative stress, neuroprotection, and regulation of NGF expression. Clinical trials of its derivative, ZT1, have demonstrated an improvement in cognitive function of AD patients. Phenserine, a derivative of physostigmine, has a dual mode of action: AChEIs and inhibitor of the formation of beta amyloid precursor protein[34].

Phenserine is dose-limited in animals by its cholinergic actions. The (+)-phenserine enantiomer (Posiphen) which has weak activity as an AChEIs and is potent on Abeta levels and amyloid processing can be dosed much higher , but clinical trials are required. Butyrylcholinesterase may play a role in attention, executive function, emotional memory and behavior. Furthermore, butyryl cholinesterase activity progressively increases as the severity of dementia advances, while acetylcholinesterase activity declines. Therefore, inhibition of butyryl cholinesterase may provide additional benefits . Structural analogues of phenserine, cymserine and bisnorcymserine, proved to be potent inhibitors of human butyryl cholinesterase in comparison to phenserine [35]

Muscarinic M1 agonist and neuronal nicotinic receptor ligands:

Several M1 receptor agonists have been tested in clinical trials without much success . Recent studies which suggest the role of muscarinic agonists in regulating the production of Abeta raise again the possibility that selective M1 agonists could be useful in AD . The M1 muscarinic agonists are neurotrophic, elevate the nonamyloidogenic APP in vitro, decrease Abeta levels in vitro and in vivo and restore cognitive impairments in animal AD models . Talsaclidine, a M1 agonist that stimulates the nonamyloidogenic alphasecretase processing in vitro and decreases CSF Abeta in AD patients following chronic treatment holds potential disease modifying properties.

To our knowledge no clinical trials are registered. Nicotinic acetylcholine receptors (nAChRs), which are essential for learning and memory, are reduced in AD brains and research implicates a role for nAChRs in neuroprotection. Several selective ligands for nAChRs have been developed but a challenge has

been the reduction of side effects . ABT-089, a selective neuronal nicotinic receptor modulator which shows positive effects in rodent and primate cognitive models , is a candidate for further evaluation as a treatment for AD . GTS-21 (DMXBA) is a selective agonist of alpha7 nicotinic receptors which enhances a variety of cognitive behaviors in mice, monkeys, rats and rabbits. It also displays neuroprotective activity in vitro and has shown promising characteristics during phase I clinical tests [36].

Ispronicline (TC-1734, AZD-3480) is a selective neuronal nicotinic agonist that is neuroprotective in vitro and exhibits memory enhancing properties in vivo. Ispronicline also had a beneficial effect on cognition in subjects with age associated memory impairment in phase II trial [37].

Insuline, glitazones and hormonal therapy:

Epidemiologic studies have shown a greater prevalence of AD in patients with type II diabetes . Possible mechanisms through which the risk of cognitive impairment is increased include the effects of peripheral hyperinsulinemia, CNS inflammation, increased formation of advanced glycation end products and regulation of the beta-amyloid peptide . The thiazolidinediones have a potent insulin-sensitising action that appears to be mediated through the peroxisome proliferator-activated receptor-gamma (PPAR-gamma). PPARgamma agonists, such as rosiglitazone, also have antiinflammatory effects . Thiazolidinediones are under evaluation in AD but recent data have shown a potential higher risk of myocardial infarction with these compounds [38].

Other treatments:

Attention and short-term memory enhancing effects of H3 receptor antagonists are well described . GSK239512, an H3 antagonist, is now under phase I evaluation in AD. Dimebon is a molecule previously approved in Russia as a non-selective antihistamine but its most potent pharmacological activities established in-vivo is the stabilization of mitochondrial membrane depolarization in the setting of molecular stress and neurite outgrowth which may be a consequence of its mitochondrial action. Dimebon demonstrated cognition enhancing properties in vivo and in a human pilot clinical trial in AD. In a randomized, doubleblind, placebo-controlled study , it showed a significant drug-placebo difference in change from baseline on the ADAScog at week 26 which was not driven by worsening in the placebo group as patients given dimebon were improved from their baseline values.

Even in the absence of vitamin B deficiency, homocysteine levels can be reduced by administration of highdose supplements of vitamin B. However, in a randomized controlled trial recently published, high-dose B vitamin supplements failed to show any effect incognitive decline in AD . Folate deficiency also induces an imbalance of Sadenosyl-L-methionine (SAM) which could have an impact on cognitive functions. Dietary supplementation with SAM in the absence of folate attenuated these consequences in vivo [39].

CONCLUSION:

For the treatment of Alzheimer's disease, numerous techniques are being researched. Clinical trials are underway for immunotherapies that target amyloid-beta plaques, tau protein, and brain circuits. Furthermore, antisense oligonucleotide techniques are being considered as treatments. Phytopharmaceuticals and nutraceuticals are also gaining popularity in the fight against Alzheimer's disease symptoms. The current review paper finds that both novel and traditional medicines provide future hope for the treatment of Alzheimer's disease.

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