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# Investigational Drugs in treatment of Alzheimer's Disease: A Systematic Review

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**ABSTRACT**

*Alzheimer's disease (AD) is a chronic neurodegenerative disease affecting elderly between age 65-85 years and is characterized by progressive dementia sufficient to interfere with social and occupational functioning pathophysiologically there is loss of neurons, synaptic function and formation of amyloid plaques and neurofibrillary tangles with profound deficit of Acetylcholine in brain. Presently, exiting treatments are acetylcholinesterase inhibitors and Mementine effective in mild AD. This review summarizes the upcoming investigational drugs in treatment of AD.*

**KEYWORDS: Alzheimers Disease, Anti-amyloid drugs, Dementia**

**Introduction:**

Alzheimer's disease is a chronic neurodegenerative disease characterized by brain atrophy, loss of neurons and synaptic function secondary to amyloid plaques and neurofibrillary tangles resulting in progressive dementia. Alzheimer's disease (AD) is characterized by profound memory loss sufficient to interfere with social and occupational functioning. AD is the leading cause of disability in the elderly between ages 65-85 years. Worldwide 37 million people are suffering from Alzheimer's disease. In India prevalence of Alzheimer disease is >3.5 million. The first neurotransmitter defect discovered in AD involved acetylcholine (ACh), the deficiency of which is responsible for dementia and behavioural changes in AD. Clinical drug trials in patients with AD have focused on drugs that augment levels of ACh in the brain to compensate for the loss of cholinergic function. These drugs include Ach precursors, muscarinic agonists, nicotinic agonists, and acetylcholinesterase inhibitors. Current FDA approved drugs do not prevent or reverse the disease but provide only symptomatic relief. With the growing understanding of the molecular pathophysiology of Alzheimer's disease, a number target drugs in development has increased in recent years. Primary targets include beta-amyloid and tau proteins, whose accumulation in the brain is thought to contribute to the development of Alzheimer's disease. Other agents include gamma secretase inhibitor to reduce beta amyloid formation, agents preventing assembly of amyloid oligomers and immunotherapy for clearing amylod. Although some FDA-approved drugs are available for the treatment of Alzheimer's disease, the outcomes are often unsatisfactory. Herbal drugs like ginkgo biloba,huperzine A have come up with encouraging results. The aim of this review is to discuss the upcoming investigational drugs for treatment of Alzheimer's disease with brief summary of existing treatment modalities.

Symptomatic Treatments:The available treatments for Alzheimer's disease are cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and an *N*-methyl-D-aspartate receptor antagonist (memantine). The cholinesterase inhibitors enhance deteriorating cholinergic function and improve cognitive and global function in many patients, but their efficacy wanes over time (Lockhart et al, 2009) Memantine, NMDA antagonist is currently the only symptomatic treatment approved for moderate to severe Alzheimer's disease, protects against the neurodegenerative effects of the excitatory neurotransmitter glutamate. Combination therapy with memantine plus donepezil given for 6 months in patients with moderate to severe Alzheimer's disease significantly improved cognition, activities of daily living, and behavior compared with placebo. Symptomatic treatments may temporarily improve cognition and behavior by improving specific neurotransmitter deficits (Porsteinsson et al, 2008). Research is going on to find drugs which target the pathological process of AD, but no agent has yet been successfully tested in clinical trials.

Anti-amyloid disease modifying treatments: Disease modifying treatment is aimed to interrupt early pathological changes by decreasing amyloid beta production or increasing amyloid clearance. Other treatments may block events occurring due to Aβ production (eg, cholinergic atrophy, neurofibrillary tangle formation) that affect some aspects of the disease. Several different classes of potential anti-amyloid disease-modifying treatments are currently being evaluated in phase II or III clinical trials, including immunotherapies, secretase inhibitors, selective Aβ42-lowering agents, anti-Aβ aggregation agents, peroxisome proliferator-activated receptor-gamma agonists, and others (Henry et al, 2010). Tramprosate: Tramiprosate is anti amyloid drug resembling glycosaminoglycan binding to monomeric Aβ, thereby reducing aggregation and neurotoxicity, promoting clearance from brain. Phase III study conducted in north America in patients with mild to moderate AD, randomly assigned to receive placebo or 100 mg or 150 mg twice daily of tramiprosate. Tramiprosate was well tolerated, but the study failed to demonstrate a beneficial effect on the primary outcome and cognition (Aisen et al, 2008).

Immunotherapy: Targeting the amyloid is a leading approach to disease-modifying treatment. A phase II trial of the first-generation amyloid vaccine AN-1792, with aggregated amyloid peptide as the immunogen, reduced Aβ accumulation in brain by enhancing clearance of amyloid in patients with AD by inducing antibody response over a 12-month period. Aseptic meningoencephalitis in 6% of the patients lead to discontinuation of the vaccine. A second-generation vaccine, ACC-001 in phase II clinical trial has been engineered to have an improved safety profile with a short Aβ sequence as the immunogen to combact toxic immune response. (Ghochikyan et al, 2009)

Passive immunization: incorporates regular intravenous administration of anti-Aβ antibodies to offer better safety and efficacy. A number of monoclonal antibodies against Aβ like Bapineuzumab and solanezumab are now being investigated for their role in AD in phase III trials as phase II study of bapinezumab yielded some encouraging results. A small phase II trial of pooled human immunoglobulin which contains naturally occurring anti-amyloid antibodies showed evidence of cognitive and clinical benefit (Salloway et al, 2009).

RAGE (Receptors for advanced glycated end products) Inhibitor: Amyloid is also known to bind to receptors for advanced glycated endproducts (RAGE) on the surface of cells and at the blood-brain barrier. This binding may contribute to inflammation and neuronal death.By blocking amyloid-RAGE binding, amyloid accumulation and neurotoxicity can be reduced. PF-04494700 is an orally bioavailable small molecule antagonist of RAGE. It is now being investigated in a phase II clinical study to determine its potential in AD therapy (Kojro et al, 2009).

Tarenflurbil: Tarenflurbil, the enantiomer of the non-steroidal anti-inflammatory drug flurbiprofen, modulates the activity of gamma-secretase, thereby reducing Aβ. In a phase II trial in patients with mild-to-moderate AD, tarenflurbil has shown possible benefit of treatment of mildly affected patients with the highest dose tested. A large 18-month Phase III trial showed no benefit of treatment probably because oral administration produced insufficient brain concentrations, to reduce Aβ to a significant extent (Gordon K Wilock et al, 2008).

Gamma-secretase inhibitors: Another approach to lowering the level of Aβ in the brain is to decrease its production. Gamma-secretase is a transmembrane enzyme complex that cleaves the amyloid precursor protein at one end of the Aβ sequence; its activity is required for Aβ generation in brain. A large Phase III study with semagacestat, a gamma-secretase inhibitor, demonstrated significant reduction of amyloid peptide generation in blood and cerebrospinal fluid of patients with AD treated with tolerable doses. Other anti-amyloid compounds are entering clinical trials include beta-secretase inhibitors (the second endopeptidase involved in

Aβ cleavage from its precursor protein) considered to be the most promising target as it may be essential component of the amyloid cascade with minimum adverse effects (Bateman et al, 2009).

Targeting tau protein: Tau is a microtubule-associated protein, in neurons, which stabilizes tubulin to assemble into microtubules. Hyperphosphorylation of tau interferes with its normal functioning and can result in self-assembly to form intraneuronal fibrillary tangles progressing to development of AD. GSK-3 inhibitor, lithium has also been shown to target tau along with certain antioxidants like vitamin E, vitamin B, curcumin, isoflavone etc (Lee et al, 2005).

Methylene blue: Methylene blue, a widely used histological stain is being investigated for its role to interfere with tau aggregation in AD. A phase II study has been completed, suggesting drug benefit in subsets of participants. Pivotal phase III trials are planned for definitive evidence of the efficacy and safety of this approach (Necula et al, 2007).

NAP (Neurotrophic protein): A small peptide called NAP (AL-108) cerebrolysin, derived from a natural neurotrophic protein, can be delivered to the central nervous system via intranasal administration. Animal studies indicate that intranasal NAP markedly reduces tau phosphorylation and preliminary human studies have shown encouraging results. Recently virus vector loaded with NGF gene or mRNA, implanted into brain parenchyma of animals of AD model, brought exciting results. These results lead to phase I and II studies on the CERE-110 (AVV2- NGF), an adeno-associated viral gene delivery vector that encodes human NGF. The CERE-110 delivered to human nucleus basalis of Meynert through stereotactic surgery, is currently assessed for safety, tolerability and biologic activity for a minimum of two-year period (Kim et al, 2004).

Neuroprotection using Antioxidants: The term neuroprotection refers to mechanisms that protect neurons from degeneration, following any kind of brain injury. AD and other neurodegenerative disorders are associated with oxidative and inflammatory stress along with mitochondrial dysfunction. While trials of antioxidants (vitamin E and vitamin B) and anti-inflammatory treatments have provided modest or no beneficial effects, efforts to develop effective neuroprotectants continue (Nishida et al, 2009). Hormonal Regulation: Raloxifene, a SERM, has shown to improve cognition, but limits utility owing to adverse effects of raloxifene. Rosiglitazone, PPAR-alpha agonist may also prove benefit by enhancing utility of insulin (Yaffe et al, 2005) Overall results have been disappointing so far.

Dimebon: Dimebon is a antihistaminic studied in Russia for treatment for AD, based on in vitro studies of cholinesterase inhibition and NMDA receptor antagonism. But efficacy of Dimebon in AD appears to be unrelated to these actions, rather related to a unique mechanism of action involving stabilization of mitochondria. In a 6-month phase 2 trial of Dimebon (20 mg three times a day) in 183 patients with mild to moderate AD conducted in Russia, the drug showed significant improvement in all cognitive, behavioral and global outcome measures suggesting the possibility of a disease-modifying effect (Grigor'ev et al, 2009).

Indomethacin: In a 6-month double-blind, placebo-controlled study, 1100 to 150 mg/d indomethacin appeared to protect mild to moderate Alzheimer's disease patients(1.3%) from the degree of cognitive decline exhibited by a well-matched, placebo-treated. Adverse reactions to indomethacin limited scale of the trial (Tabet, 2002).

**About AC-1204**: AC-1204 targets the metabolic deficits and imbalances associated with Alzheimer's disease by providing ketone bodies as an alternative energy source for brain cells that have defective glucose metabolism. This approach has been shown to improve cognitive function and memory in AD patients and in pre-clinical animal models of dementia. Acetyl-L-carnitine: Acetyl-L-carnitine is an amino acid (a building block for proteins) that is naturally produced in the body. It has been shown to improve cognition and delays the progression of AD over duration of 3 months (Montgomery, 2003). MW151 and MW189: These drugs work by preventing the overproduction of brain proteins called proinflammatory cytokines. Overproduction of these proteins contributes to the development of much degenerative neurological disease as well as to the neurological damage caused by traumatic brain injury and stroke.

Ginkgo biloba: Ginkgo biloba is an herbal medicine that has been used to treat a variety of ailments for thousands of years in China. An extract of Ginkgo biloba has been found in several studies to improve the symptoms and slow the progression of AD. A study of 309 patients with mild dementia was performed. The patients were given either 120 mg of Ginkgo biloba extract or placebo every day for up to a year. At the end of 6 months, 27% of those using Ginkgo biloba had moderate improvement on a variety of cognitive tests. Ginkgo biloba appears to be most effective in the early AD and probably acts by normalizing Ach receptors in hippocampus of brain as seen in experimental studies in aged animals (Colciaghi et al, 2004). Huperzine A: Huperzine A is an alkaloid derived from club moss. Huperzine A is sold as a dietary supplement for memory loss and mental impairment in china. According to three Chinese double-blind trials enrolling a total of more than 450 people, use of huperzine A can significantly improve symptoms of AD and related dementia (Colciaghi et al, 2004).

Conclusion: A better understanding of the natural history of AD has been achieved and appropriate trial designs and outcomes for the various stages of this condition have been developed. With the better understanding of pathophysiology of AD, there is clear evidence of the benefits for the treatment of symptoms in mild to moderately severe AD using anticholinesterase inhibitors and memantine. Currently, the anti-amyloid strategies are proceeding with the greatest number of candidate drugs. Numerous candidate disease-modifying therapies that target the underlying pathogenic mechanisms of AD are currently in clinical trials. While it is not possible to predict the success of any individual class of drugs, one or more are likely to prove effective. Indeed, it seems reasonable to predict that in future, a synergistic combination of agents will have the capacity to alter the neurodegenerative cascade and reduce the global impact of this devastating disease. Treatment guidelines must be constantly updated to take into account new evidence.

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