Original Article

FUTURE PHARMACOLOGICAL ARMAMENTARIA IN MANAGEMENT OF ALZHEIMER DISEASE

Megha H Shah[1], Hetal D Shah[2], Vipul P Chaudhari[3]

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Author's Affiliation:
[1]Assistant Professor, Department of Pharmacology, B.J. Medical College, Ahemedabad; [2]Consultant Cardiac Anesthetic, Narayana Hrudalaya, Ahmedabad; [3]Assistant Professor, Department of Community Medicine, Government Medical College, Surat.

Correspondence:
Dr. Megha Shah,
Email: mkshah_80@yahoo.com

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ABSTRACT

Introduction: Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder and common cause of dementia in elderly. With advancing age, number of people suffering from AD is also increased. Exact aetiology of AD was not known and therapy was focused mainly on increasing central cholinergic transmission with drugs like donepazil, reivastigmine and galantamine. With the generation of amyloid hypothesis, extracellular amyloid plaques, consisting of amorphous extra cellular deposits of β-amyloid protein (known as Aβ) and intraneuronal neurofibrillary tangles(Tau) mainly in the hippocampus and frontal cortex ,altered processing of amyloid protein from its precursor (amyloid precursor protein, APP) recognised as the key to the pathogenesis of AD. But, now various studies have shown that etiology may be multifactorial. Inspite of having identified many potential targets, currently no drug modifying disease pathology is available .Advancement of the early diagnostic methods like positron emission tomography (PET) scan and measurement of various biomarkers like NO tagged proteins, ADAM-10 in c.s.f. could potentiate research to develop disease modifying drugs. Drugs modifying Y secretase, tyrosine kinase inhibitors, sigma receptor agonists, anti-Aβ monoclonal Abs are in the various stages of drug development and could become the cornerstone in the management of AD in future.

Methods: Reviews from index journals and books were taken in this study. In this process, we identified 276 possible sources of information which, upon further scrutiny, were eventually reduced to 30 appropriate studies for inclusion in the review.

Conclusion: Understanding the role and extent of factors causing AD, robust designing of RCTs with use of various biomarkers and multitargeted therapeutic approach are required to develop disease modifying drug which can ameliorate suffering of alzheimer disease patients.

Key words: Alzheimer Disease, Management, New Targets, Dementia

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and a commonest cause of dementia in elderly people. It is one of the major health problems in the United States and the developed world. Because the presence

of clinical AD doubles with every 5 years after 60, preventing the onset of clinical AD by 5 years would reduce the AD population by half. About 5.5 million persons in the United States have AD, and the odds of receiving a diagnosis of AD after the age of 85 exceeds one in three.[1] With increasing population of elderly people, prevalence of AD is also increased. As a disease which makes patient dependent, is booming, effective treatment for that is the need of the hour. The U.S. Senate has passed National *Alzheimer's Project Act (NAPA)* to combat this major problem. NAPA calls for a coordinated effort across the federal government and from research, care, and institutional services and to home and community based programs to combat the crisis across the broad spectrum of the disease.

Initially, loss of cholinergic neurons in the hippocampus and frontal cortex was thought to underlie the cognitive deficit and loss of short-term memory in AD patients and so treatment was based mainly on increasing central cholinergic transmission with cholinergic drugs. Tacrine followed by donepezil, rivastigmine and galantamine were mainly used. For many years, treatment was based only on a single factor. Therapy provided limited therapeutic benefits. Later on two microscopic characteristic features of the disease i.e. extracellular amyloid plaques, consisting of amorphous extra cellular deposits of β-amyloid protein (known as Aβ), and intraneuronal neurofibrillary tangles, comprising filaments of a phosphorylated form of a microtubule-associated protein (Tau) discovered. They appear also in normal brains, although in smaller numbers. The early appearance of amyloid deposits presages the development of AD, although symptoms may not develop for many years. Altered processing of amyloid protein from its precursor (amyloid precursor protein, APP) by B and Y secretase enzymes is recognised as the key to the pathogenesis of AD. The genetic analysis of certain rare types of familial AD discovered mutations of the APP gene, or of other genes that control amyloid processing. The APP gene resides on chromosome 21, which is duplicated in Down's syndrome; in which early AD-like dementia occurs in association with over expression of APP.[2] Recent studies have shown that AD is a complex disease and the aetiology may be multifactorial. [3]

Though research succeeded in identifying many potential targets for AD, its causes might not yet be understood at a level adequate for discovering disease modifying drugs. Inability to identify potential targets and penetrating blood brain barrier, absence of early diagnostic and prognostic methods are important factors leading to failure of clinical trials for developing disease modifying drugs. Early detection and treatment of Alzheimer's disease is essential for better outcome. But, conventional methods of diagnosis such as cognitive tests are helping to catch the disease at its advanced stages, when the patient is already suffering from distinct cognitive impairments.

METHODS

We document the pharmacological aspects associated with Alzheimer's disease. To provide a context for the review, we first present the key questions and analytic framework. Next we describe the methods used to identify articles relevant to our key questions, our inclusion/exclusion criteria.

Data source are MEDLINE® and the Cochrane Database of Systematic Reviews. Additional studies were identified from reference lists and technical experts.

Key Questions:

1. Which are the newer /latest diagnostic tools for Alzheimer's disease?
2. Which are the different criteria By National Institute on Aging and the Alzheimer's Association?
3. What are the therapeutic aspects for Alzheimer's disease?
4. Which are the different drugs useful in Alzheimer's disease and it's mechanism of action?

Inclusion and Exclusion criteria:

1. Pharmacological study for Alzheimer's disease.
2. Time period: 2007 to June 2012
3. Publication language: English
4. Good quality systematic reviews that addressed a question of interest and used eligibility criteria consistent with our inclusion /exclusion criteria.

   Original research studies that provide sufficient detail regarding methods and results to enable use of the data and results; relevant outcomes must be able to be abstracted from data presented in the papers.

For all questions, we were interested in new targets and latest information. We included primary literature to update eligible reviews or when good quality reviews were unavailable.

Using the pre-specified inclusion/exclusion criteria, titles/abstracts were examined relevance to the key questions. Articles included by underwent full-text screening. In this process, we identified 276 possible sources of information which, upon further scrutiny, were eventually reduced to 30 appropriate studies for inclusion in the review.

RESULTS

Identification of multifactorial aetiology, recent development of early diagnostic methods could serve as a ray of hope for disease modifying anti alzheimer drugs. Newer methods for early diagnosis of AD may become the main cornerstone in patient management. (Table-1)

Table 1: Newer Diagnostic tools for Alzheimer's disease

Tool	USE
Positron emission tomography (PET) scan	It is a molecular imaging technique, is used to detect the formation of beta-amyloid plaques in the brain. Subjects had PET scans using 11C Pittsburgh Compound-B (11C-PIB), a PET imaging agent that binds to beta-amyloid in neural tissues. Patients with a strong family history of Alzheimer's or who show mild signs of memory loss could be screened for the development of the disease in order to help them plan for the future. This imaging technique could also be used to evaluate the effectiveness of new treatments as they become available [2]
Radioactive dye, Amyvid	The dye binds to clumps of a beta amyloid plaque and light up on a positron emission tomography, or scan.[4]
Biomarkers	Use of various biomarkers indicative of the AD pathophysiological process Like CSF Ab42, CSF tau, both total tau and phosphorylated tau (p-tau); decreased 18fluorodeoxyglucose (FDG) uptake on PET in temporo–parietal cortex will allow scientists to test treatments or preventions far earlier in the disease, when they could be more effective. These newer methods may be more useful for research and in specialized medical centres for diagnosing patients with symptoms of Alzheimer's dementia. It requires proper standardization of these methods and appropriate cut-off level before routine clinical use. Biomarker test results can fall into three categories–clearly positive, clearly negative, and indeterminate.

The NINCDS-ADRDA criteria, describing clinical diagnosis of AD, proposed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's disease and Related Disorders Association (ADRDA) have been quite successful, surviving for over 27 years. However, with advancement of understanding the pathophysiology of AD and invention of new targets, these criteria requires revision. Therefore, the National Institute on Aging and the Alzheimer's Association workgroup has proposed revised the criteria and to classify individuals with dementia caused by AD in to three category(1) Probable AD dementia, (2) Possible AD dementia, and (3) Probable or possible AD dementia with evidence of the AD pathophysiological process. The first two are intended for use in all clinical settings. The third is currently intended for research purposes. [5]

Here, we are trying to provide a review of important new targets and drugs (table-3) for treatment of AD.

1) Cholinergic drugs: Inspite of wide use of cholinergic in AD, various clinical trials have not been able to develop any potential drug. Trials with muscarinic receptor agonists has had limited success owing to unavoidable side effects.[6] Ispronicline (AZD-3480) is a selective agonist of the nicotinic receptor α4β2.I n Phase-2 trial neither it nor donepezil showed significant effect on the primary outcome (ADAS-cog) after 12 weeks of treatment, but post-hoc analysis suggested a positive effect on ADAS-cog at the 20 mg dose.[7] However, two recent developments occurred in existing cholinergic therapy.

Table 2: Proposed Revised Criteria By National Institute on Aging and the Alzheimer's Association[5]

AD Category	Criteria
Probable AD dementia	1)Insidious onset(months to years), 2)worsening of cognition by report or observation, 3)initial and prominent cognitive deficits involving one of the following domains: – Amnesia(in learning and recall of recently learned information) , – Nonamnestic(Language, Visuospatial) – Executive dysfunction (impaired reasoning, judgment, and problem solving. 4) Deficits in other cognitive domains mentioned in Criteria for all-cause dementia i.e. Impaired reasoning and handling of complex tasks, poor judgment or Changes in personality, behavior, comportment should be present. Criteria **should not** be applied when there is evidence of substantial concomitant cerebrovascular disease or evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.
Possible AD dementia	1) Atypical course *course meets* the core clinical criteria of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline, Or 2) Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence of (a) concomitant cerebrovascular disease or (b) Dementia with Lewy bodies or (c) evidence for another neurological or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition
Probable AD dementia with evidence of the AD pathophysiological process	To increase the certainity of diagnosis, In addition to core clinical criteria , also depends on **two Classes of** Biomarkers 1) of brain amyloid-beta (Ab) protein deposition like low CSF **Ab42 and positive PET** amyloid imaging 2) biomarkers of downstream **neuronal degeneration or injury**. The three in this category are elevated CSF tau, both total tau and phosphorylated tau (p-tau); decreased 18fluorodeoxyglucose (FDG) uptake on PET in temporo– parietal cortex; and disproportionate atrophy on structural magnetic resonance imaging in me-dial, basal, and lateral temporal lobe, and medial parietal cortex.

Table-3 Current Status Of Some Important Targets For Alzheimer Disease

Cholinergic drugs	Higher-Dose donepezil HCl 23 mg Tablet	Approved by U.S.FDA
	Rivastigmine patch	Approved by U.S.FDA
Y secretase modulators	Tarenflurbil	Phase 3
α-secretase activators	Etazolate (EHT 0202)	Positive results in Phase2
	Bryostatin-1	Phase 2
	ADAM10 protein	Preclinical
β secretase inhibitors	PPAR-Y agonists type-II antidiabetic drugs	Failed due to cardiotoxicity
Increasing Aβ removal	Monoclonal antibody – Bapineuzumab	Phase 3
	Human immune globulin	Phase 3
	Vaccination	Failed in Phase 2
Drugs targeting Tau protein	AL-108	Phase 2
Tyrosine kinase inhibitors	Masitinib	Phase 3
Sigma1 receptor agonists	ANAVEX 2-73	Phase 1

Higher-dose donepezil HCl

Donepezil HCl is the first and only prescription medication approved by the FDA for the treatment of all stages of AD—mild, moderate and severe. It was prescribed as 5 mg -10 mg tablet once a day. The recommended starting dose is 5 mg once daily and can be increased to 10 mg once daily after four to six weeks. The U.S.FDA approved a new once-daily, higher-dose donepezil HCl (Aricept) 23 mg tablet for the treatment of moderate-to-severe Alzheimer's disease (AD). Moderate-to-severe AD patients who are established on a regimen of 10 mg donepezil tablet for at least three months are candidates for dose escalation to 23 mg . A large study of donepezil HCl 23 mg tablet versus 10

mg tablet in 1,400 patients with moderate-to-severe AD demonstrated a statistically significant improvement in cognition measure, Severe Impairment Battery (SIB), but no significant improvement in Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+), a measure of global function. Nausea, vomiting, diarrhea, difficulty in sleeping, anorexia and weight loss were the most common adverse events noted with 23 mg donepezil tablet. Incidence of nausea and vomiting was more in patients taking 23 mg/day donepazil versus 10 mg/day.[8]

Rivastigmine transdermal patch

Rivastigmine transdermal patch provides an innovative way to deliver an effective medicine for mild to moderate AD patients instead of an oral capsule. It is applied to the back, chest or upper arm and provides smooth and continuous delivery of medication over 24 hours. Patch showed similar efficacy to capsules and the recommended dose (9.5 mg/24 hours) was generally well tolerated by patients. Patch not only improves compliance but also reduces common gastrointestinal side effects of cholinesterase inhibitors.[9] Rivastigmine transdermal patch is approved by the U.S.FDA for treating mild to moderate Alzheimer's disease.

2) Drugs decreasing Aβ generation

γ-secretase modulators: γ-secretase is the enzyme responsible for the final step in Aβ generation. The reasons which could inversely affect development are collateral effects of γ-secretase inhibitors like haematological and gastrointestinal

toxicity, skin reactions, and changes to hair colour, mainly caused by inhibition of the notch signalling pathway, which is involved in cell differentiation.

Tarenflurbil is a modulator of the activity of γ-secretase and decreases Aβ42 .It is a derivative of flurbiprofen, a NSAIDs. In a phase 2 trial in 210 mild AD patients, receiving 800 mg tarenflurbil twice per day had lower rates of decline in activities of daily living and global function compared with placebo.[10] The results stimulated a large multicentre, phase 3 trial of tarenflurbil in 1,684 subjects with mild AD at doses of either 400 or 800 mg twice daily or placebo. 18 months score on the Alzheimer's disease Assessment Scale showed tarenflurbil had no beneficial effect on the primary or secondary outcomes. The discrepant findings between the phase 2 subgroup analyses and the phase 3study may be due to low dose and requires strongly caution against designing trials and analysis.[11]

α-secretase activators: APP is also cleaved in a non amyloidogenic pathway by α-secretase within the Aβ domain thereby preventing the formation of Aβ. **Etazolate** (EHT 0202) is in a new class of disease modifying therapies which stimulate the α-secretase pathway, thus enhancing the production of the procognitive and neuroprotective sAPPα fragment of APP. Preclinical and Phase I studies demonstrated good tolerability of EHT 0202. Recently published results of EHT 0202 phase IIa study showed clinical safety and tolerability in mild to moderate Alzheimer's disease patients. The effect of two different doses of EHT 0202 (either 40 or 80 mg twice a day) as adjunctive therapy to one acetylcholinesterase inhibitor was evaluated in comparison to placebo.[12]

Bryostatin-1, another α-secretase activator is in phase 2 to evaluate safety in patients with mild-to-moderate Alzheimer's disease (NCT00606164).

ADAM10 protein:

Processing of APP by α-secretase generates the soluble APPsα ectodomain, which may have neuroprotective and neurotrophic properties. The resulting membrane-bound C-terminal fragment is further cleaved by γ-secretase to produce p3, an N-terminal truncated Aβ derivative. Three members of the ADAM (a disintegrin and metalloprotease) family of metalloproteases are described to have α-secretase activity, namely ADAM9, ADAM10 and ADAM17. This is in accordance with Peer-Hendrik Kuhn et al who concluded When ADAM10 is less active; the precursor protein is more likely to be cleaved in a way that promotes the formation of beta-amyloids.[13]

In contrast, a large-scale (n = 576: Controls, 271; AD, 305) resequencing study of ADAM10 in sporadic AD do not support a significant role for ADAM10 mutations in AD.[14] Further studies are required to determine the role of ADAM proteins in AD.

β secretase inhibitors:

Developing β secretase inhibitors is challenging because the enzyme has wide substage variability which can affect other functions also including myelination. The type-II antidiabetic drugs rosiglitazone and pioglitazone showed β

secretase inhibition but their cardictoxicity failed further development.[15]

3) Increasing Aβ removal:

Monoclonal antibody - Bapineuzumab is a humanized anti-Aβ monoclonal antibody. It is directed against the N-terminus of Aβ and is hypothesized to bind to Aβ in the brain to facilitate its removal. A phase 2 multiple-ascending-dose trial in mild to moderate AD tested the safety and efficacy of bapineuzumab.[16] A safety concern was the occurrence of reversible vasogenic edema. Results of phase-II were not conclusive and phase-III studies are ongoing. However, a recent study showed that treatment with bapineuzumab for 78 weeks reduced fibrillar amyloid burden in subjects with AD, shown by Pittsburgh compound B positron emission tomography ((PiB-PET) [17]

Vaccination in a phase 2a trial (NCT00021723) resulted in encephalitis[18], and follow-up of immunized patients showed no cognitive or survival benefit despite diminution of plaques.

4) Drugs targeting Tau protein: AL-108 inhibits hyperphosphorylaiton of tau and formation of neurofibrillary tangles. AL-108 given intranasally by spray also resulted in a significant improvement.[19] AL-108 (10mg twice daily) gave a statistically significant improvement in the delayed match-to-sample test (DMTS 12s) in a phase 2 study after 12 weeks of treatment. With low dose (5 mg) AL-108 did not produce any significant results.[20]

5) Tyrosine kinase inhibitors

Neuroinflammation is thought to be important in Alzheimer's disease pathogenesis. Mast cells are a key component of the inflammation and participate in the regulation of the blood-brain barrier's permeability. Masitinib is a new orally administered tyrosine kinase inhibitor of mast cells. It effectively inhibits the survival, migration and activity of mast cells. Masitinib administered as an add-on therapy to standard care for 24 weeks to 35 patients in a phaseII trial showed significant decrease in the cognitive decline compared to placebo, with an acceptable tolerance profile. The rate of clinically relevant cognitive decline according to ADAS-Cog response (increase >4 points) after 12 and 24 weeks was significantly lower with masitinib (6% versus 50% for both time points; p=0.040 and p=0.046, respectively. Adverse events occurred more with masitinib treatment (65% versus 38% of patients); however, the majority of events were of mild or moderate severity and transitory. Masitinib also lead to gastrointestinal disorders, oedema, and rash. Although the sample size was too small to make any definitive conclusions about treatment efficacy, the evidence is sufficiently compelling to warrant further phase 3 investigation.[21]

6) Sigma1 receptor agonists: Sigma1 receptors are ligand regulated receptors on endoplasmic reticulum**,** involved in alzheimer's disease, stroke, amnesia, pain, ethamphetamine or cocaine addiction, depression, HIV infection and cancer. Sigma1 receptors cause modulation of ion channels, including Ca2+-, K+-, Na+, Cl−, and also NMDA and IP3 receptors. Various studies showed the role of Sigma 1 receptors in AD. Donepezil, a potent acetylcholinesterase inhibitor is also a potent sigma-1 receptor ligand.[22]

Tetrahydro-N, N-dimethyl-5, 5-diphenyl-3-furanmethanamine hydrochloride (ANAVEX 2-73) is the first compound which act through sigma-1 receptor agonism, muscarinic cholinergic effects and modulation of endoplasmic reticulum. It has demonstrated potent neuroprotective, anti-amnesic, anti-convulsive and anti-depressive activity in pre-clinical studies and prepared to enter in phase-1 clinical trials.[23] It could be the gleam of hope for patients of alzheimer's disease.

7) Others

NIPSNAP1: Hemachand Tummala and colleagues[24] observed that in Alzheimer's disease, mitochondria are damaged and lose their function. This happens long before the appearance of symptoms. Study on mice showed APP directly interacts with the neuron-specific mitochondrial protein, 4-nitrophenylphosphatase domain and non-neuronal SNAP25-like protein homolog 1 (NIPSNAP1) and may thereby regulate mitochondrial function in neurons. Drugs targeting NIPSNAP1 could prevent early onset and progression of AD.

Presenilin 1 Gene: Presenilin 1(PS1) plays a key role in "macroautophagy". It is a process for digesting and recycling unwanted proteins and essential for neuron survival. Mutations of PS1can lead to defective lysosomal proteolysis, pathogenic protein accumulations and neuronal cell death in AD and suggests previously unidentified therapeutic target. The other mechanism could be disruption of calcium

homeostasis by increase release of calcium from endoplasmic reticulum in to cytoplasm.[25]

Statins: Role of statins is appealing but controversial and the exact mechanism is still not clear. A defect in cholesterol metabolism is an appealing hypothesis because it ties together the apolipoprotein E (*APOE*) genetic risk, amyloid production and aggregation, and vasculopathy of Alzheimer's disease. Glial-derived APOE is the primary cholesterol transporters in the brain[3] · A single E4 allele increases the risk of AD.

However, a large observational study has found statins appear to cut the risk of developing Alzheimer's disease by up to 56%, even among those with the high-risk apolipoprotein E4 allele. Also, the association between statin use and risk reduction was consistent for both lipophilic and hydrophilic agents, but absent in non-statin cholesterol-lowering drugs. Simvastatin followed by atorvastatin and pravastatin were commonly prescribed. The proposed mechanisms are improved endothelial functioning, reduced atherosclerosis and oxidative stress.[26]

However, no significant clinical benefit on cognition or global functioning was shown for atorvastatin in a 72-week, phase 3 RCT in patients with mild-to-moderate alzheimer's disease already taking donepezil.[27]

5 LOX inhibitors A study found that the genetic absence of 5-LOX in mice resulted in a significant reduction in brain Aβ levels and deposition.[28] Zileuton, used in asthma, (5 LOX inhibitor) had a significant reduction in the amount of Aβ formed and deposited in mice brains. It is in preclinical stage and needs more clinical studies to confirm.

Antioxidants: R-lipoic acid delivered in the plasma can cross the blood brain barrier and be reduced to DHLA.DHLA a very powerful intracellular antioxidant[1]. It also increases glucose uptake and glucose metabolism, improving the energetic state of cells. DHLA is also an effective chelator of iron. It also is able to regenerate vitamin C, vitamin E, and glutathione from their oxidized products.[29] Also, combination of R-lipoic acid (300 mg) with vitamin-c could be beneficial to the patients. Intramuscular administration of deferoxamine, an iron chelator, significantly improved daily living skills and slowed the clinical progression of dementia in a two-year single blind study in patients under 74 years of age with probable AD.[1]

Human umbilical cord blood cells (HUCB):

According an in vitro-culture study by Ning Chen and colleagues,[30] on the brains of adult and aged rats, HUCBs were not only able to protect hippocampal neurons (an area for long term memory) but also promoted the growth of dendrites - the branching neurons acting as signalling nerve communication channels - as well as induced the proliferation hippocampal neurons. These effects may be a function of growth factors and cytokines produced by the HUCB cells.

CONCLUSION

Present alzheimer therapy is only providing limited symptomatic relief to patients. Researchers have identified potential targets and are at preclinical or clinical stages of drug development. Though results of several RCTs are disappointing, turned focus towards identifying potential errors in conducting RCTs. Proper selection and number of patients is must to avoid influence of multifactorial etiology and genetic polymorphism. Use of various biomarkers instead of using subjective rating scale could be more effective measure of efficacy of disease modifying antialzheimer drugs. Understanding the role and extent of factors causing AD, robust designing of RCTs with use of various biomarkers and multitargeted therapeutic approach are required to develop disease modifying drug which can ameliorate suffering of alzheimer disease patients.

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