New treatment in dementia

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Alzheimer’s disease (AD) is a frail neurodegenerative disease and is the commonest form of dementia prevalent in older individuals in the age group of 65 or above that has an exponential escalation in its incidence with each passing year.
preclinical

Mild cognitive impairment

Dementia
Alzheimer’s is currently ranked as the sixth leading cause of death in the United States, but recent estimates indicate that the disorder may rank third, just behind heart disease and cancer, as a cause of death for older people. It is an alarming fact that over 5.3 million Americans of all age groups are known to have AD by 2015 which is expected to rise to 7.1 million by 2025, tripling to about 13.8 million by 2050. AD is the only disease that tops the list of deadliest diseases in USA that are not cured, treated or prevented
The deposition of *neurofibrillary tangles* and *b-amyloid plaques* constitutes the essential hallmarks of AD.

Based on these prominent hallmarks, two hypotheses have been postulated in the pathogenesis of AD:

- **Cholinergic hypothesis**
- **amyloid cascade hypothesis**
Currently available treatment for Alzheimer’s rests upon:

- Acetylcholinesterase inhibitors (AChEIs) (tacrine, donepezil, rivastigmine)
- NMDA receptor antagonists (memantine)

• Side effects
• Only a symptomatic effect and does not alter the progression of the disease
disease-modifying therapy (DMD)

obstruct the pathogenic steps accountable for the appearance of clinical symptoms like:
deposition of amyloid plaques
appearance of neurofibrillary tangles
inflammation, oxidative injury and cholesterol metabolism
The most favourable time to initiate DMD is in the *presymptomatic phase* when the disease is still concealed.
Mutation in APP or presenelines
Or Faulty Amyloid beta clearance

Overall increase in the level of Ab42

Aggregation of Ab42 to form oligomers which impede synaptic productivity

Microglial and Astrocyclic activation and accompanying inflammatory reaction

Disturbance in neuronal homeostasis leading to oxidative damage

Changes in the activity of kinases and phosphatases leading to formation of tangles

Synaptic and neuronal losses

Dementia
Current pharmacotherapy for Alzheimer’s disease

Acetylcholinesterase inhibitors (AChEIs)

Four AChEIs have been approved by the U.S. FDA for the treatment of AD:
- Tacrine
- Donepezil
- Rivastigmine
- Galantamine
• The first indication of AChEIs has always been Alzheimer’s but with the passage of time this has been implicated in various other forms dementia and CNS disorders like mild cognitive impairment, dementia with Lewy bodies, Parkinson’s dementia, Down’s syndrome, vascular dementia and Korsakoff disease.

• Various structurally diverse motifs are now being explored, tried and tested as potential acetylcholinesterase inhibitors. Modifications in the structure of already approved AChEIs have been done and the resultant compounds have shown significant improvement in the activity against AChE with fewer side effects.
The need for an efficacious but a safer therapeutic option has led to the switch over of interest from synthetic to natural products. A variety of plants have been reported to show AChE inhibitory activity and thus seem promising for the treatment of neurodegenerative disorders such as AD. Phytoconstituents such as alkaloids, glycosides, terpenoids, polyphenols, flavonoids, coumarins, sesquiterpene glycosides, and saponins have shown significant acetylcholinesterase inhibitory properties and thus offer avenues for further exploration in this domain of research.
Antiglutaminergic therapy (NMDA receptor antagonist)

**Memantine** is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that fortifies the neurons from the glutamate overactivity, thus blocking the excitotoxic effects of the glutamate.
Donepezil (Aricept®) Approved in 1996 for all stages of AD

Rivastigmine (Exelon®) Approved in 2000 for all stages of AD

Galantamine (Razadyne®) Approved in 2001 for mild to moderate stages

Memantine (Namenda®) Approved in 2003 for moderate to severe stages

Donepezil and Memantine (Namzarin®) Approved in 2014 for moderate to severe stages
Combination therapy of *memantine and donepezil* for the patients of *moderate to severe form of AD* showed remarkable improvement in the cognitive behavior of patients in comparison to placebo.
Molecular docking studies of a number of synthetic derivatives of 1-benzyl-1,2,3,4-tetrahydro-carboline, phenyl-amidine, and triazolyl-amidine derivatives have been validated on NMDA receptor which can serve as lead molecules in the development of NMDA receptor antagonists.
Disease-modifying therapy for Alzheimer’s disease

three strategies of paramount importance in anti-amyloid therapy are

- minimize Aβ production
- avert Aβ aggregation
- encourage Aβ clearance
Inhibiting Aβ production: b-secretase inhibitor (BACE inhibitors)

LY2886721 was the first BACE-1 inhibitor to reach the clinical trials and was selective for inhibiting BACE-1. The outcomes of the phase 1 trial were positive which was carried out with 150 healthy volunteers and patients with AD at a dose of 1–70 mg, with observed decline in the levels of Ab and sAPPb in the CSF. Fourteen days of daily dosing reduced BACE-1 activity by 50–75 %, and CSF Ab42 by 72 %. Favorable outcome of the phase 1 trials led to the phase 2, with a dose of 15 and 35 mg of LY2886721 in 128 patients with mild cognitive impairment, which was voluntarily aborted by the company owing to observed anomalous hepatic biochemistries which were unrelated to the inhibition of the BACE-1, thus being a non-target-related side effect.
**MK-8931** is a small molecule BACE-1 and BACE-2 inhibitor currently under phase 3 clinical trial. Phase 1 trial includes 68 healthy controls and patients with mild to moderate AD, at a single dose of 450 mg and multiple doses of 12–150 mg/day resulting in the decrease in the levels of CSF Ab. Two phase 1/2 dose ranging trials of MK-8931 to assess the tolerability and pharmacology of single and multiple doses in 88 healthy volunteers at a dose ranging from 2.5 to 550 mg/day were carried out. It resulted in around 90 % decrease in CSF Ab.

In 2012, an EPOCH phase 2/3 trial for 18 months comparing 12, 40 and 60 mg/day in 200 patients expanding to 1960 in phase 3 was conducted which passed in terms of safety. In 2014 and 2015, additional Phase 2/3 and Phase 3 trials started in European and Asian countries, as well as New Zealand.
Another BACE-1 inhibitor, **AZD3293** is under clinical trial. The phase 1 study conducted started in December 2012 and continued till 2013–2014 in six additional studies to evaluate the safety and efficacy of the AZD3293 which yielded fruitful results with no incidences of undesirable toxic effects. This was in confirmation with the decrease in the levels of observed biomarkers. The clinical testing of this compound will be stretched in an extensive combined phase 2/3 trial named Amaranth. The trial has already begun enrolling people who meet the desired criteria and is set to run for 5 years.
**E2609** is a BACE-1 inhibitor developed with the aim of decreasing the generation of Ab peptide. Eight phase 1 trials have been completed in March 2015, in 500 healthy volunteers and those with early signs of AD. The single oral ascending-dose study of 5–800 mg drug showed a reduction of Ab levels in plasma; a 14-day ascending dose study of 25–400 mg showed a dose-dependent reduction of up to 80 % in CSF Ab levels. E2609 was found to be safe with reports of only headache and dizziness as the major adverse effects. Phase 2 began in late 2014 enrolling around 700 patients reported to have MCI due to AD or prodromal AD who have a positive amyloid PET scan.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Clinical trial status</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY2886721</td>
<td>Phase 1 clinical trial completed; Phase 2 clinical trial discontinued</td>
<td>Eli Lily and Company</td>
</tr>
<tr>
<td>MK-8931</td>
<td>Phase 3 trial ongoing</td>
<td>Merck</td>
</tr>
<tr>
<td>AZD3293</td>
<td>Phase 1 completed; phase 2 and 3 are planned</td>
<td>Astra Zeneca and Eli Lily</td>
</tr>
<tr>
<td>E2609</td>
<td>Phase 1 trial completed and phase 2 trial commenced in December 2014</td>
<td>Eisai Co. Ltd. and Biogen</td>
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Inhibiting Aβ production: gamma secretase inhibitors and modulators

γ-secretase is a transmembrane protease responsible for the final cleavage of the APP and thus serves as a promising target for the therapeutics of AD.

The main drawback associated with the development of γ-secretase inhibitors is that more than 50 different substrates are present apart from APP to interact with the enzyme, many of which are cytoskeletal and signaling protein. Among these, Notch is one of them. Blockade or inhibition of notch for a chronic period of time may prove detrimental and is manifested in the form of gastrointestinal mucoid enteropathy and abnormal lymphocyte differentiation. These serious adverse effects posed severe limitations in clinical trials and many of the compounds have failed in various stages of clinical development.
Semagacestat (LY450139), is a non-selective c-secretase inhibitor developed by Eli lily. A phase 3 trial conducted by Doody et al. led to the inference that in comparison with the placebo, semagacestat did not show any improvement in the management of cognitive dysfunction and has deleterious side effect. The patients receiving semagacestat also exhibited loss of weight and reports of skin cancers and infections also appeared.
**BMS-708163(Avagacestat)**, is a highly selective Notch sparing γ-secretase inhibitor and reached up to phase II trials and carried with it expectation to develop a promising new candidate for Alzheimer’s therapy even though it displayed significant side effects at a higher dose restricting its development at lower dose.

In November 2012, Bristol-Myers Squibb terminated this trial and announced its decision to end further development of avagacestat due to its ineffectiveness and association of adverse side effects.
With the constant failures in the arena of GSI, scientists are looking forward to an approach where the activity of the c-secretase is attuned instead of completely thwarting it. This line of thought led to the emergence of gamma secretase modulators (GSM).

This strategy suggested that levels of pathogenic Aβ42 can be decreased without causing the unwanted toxic effects that are associated with full-length inhibition of c-secretase by altering the cleavage specificity of the enzyme. In other words, GSMs are small molecule, fostering a product shift from the toxic Aβ42 towards less toxic smaller Aβ fragments.
Classical non-steroidal anti-inflammatory drugs (NSAIDs) formed the very first class of GSMs and thus many of recently developed GSMs have features similar to NSAIDs.

These compounds are produced either by direct adaptation of the classical NSAIDs or are derived from NSAID-like scaffolds.

The main drawback associated with GSMs is their ineffectiveness in exhibiting Ab42-lowering activity.
Inhibiting Aβ production: α-secretase potentiation

Except *Etazolate*, no compound from this therapeutic class has progressed into clinical trials. Of late, the role of etazolate has been seen in traumatic brain injury (TBI).

Etazolate produced a dose-dependent anti-inflammatory and anti-edematous effect in conjunction with improved cognitive performance in the mouse model of TBI.
Inhibiting Aβ aggregation: anti-aggregation agents

*Tramiprosate (Alzhemed, homotaurine)*, This is the first anti-amyloid drug to reach the phase III in clinical trials but subsequently it failed to demonstrate any significant improvement in cognitive dysfunction when compared in treatment and placebo group.

*Scyllo inositol (ELND005)* stabilizes an oligomeric aggregate of Aβ and prevents Aβ-induced neurotoxicity. The phase II trial of the molecule carried by the transition therapeutics has shown its effective safety and tolerability profile and the company has taken a step forward in discussing and executing the phase III trial for AD patients with agitation and aggression.
AN1792 was the first active immunotherapy developed for the treatment of AD. Phase I trial was conducted with around 80 patients. The vaccine developed amyloid antibody response in nearly 50% of the patients. The randomized phase II trial also exhibited some promising results but about 6% of the patients enrolled in the study showed incidence of meningoencephalitis and thus the trial had to be terminated.

New forms of vaccines were developed in which there was absence of amino acid portion responsible for T cell-mediated encephalitis.
A second-generation active amyloid vaccine, CAD106, developed by Novartis and the V950 whose trial was initiated by Merck, are under phase II clinical trial. In animal model, it resulted in decreased amyloid burden without any significant inflammatory response.
Alternative approach to avoid T cell-mediated inflammation as a source of side effect is **passive immunization** technique. This happens by passive infusion of anti-Aβ antibodies in patients that generate an immune response without causing pro-inflammatory T cell activation. This resulted in the conduct of clinical trials using monoclonal antibodies targeting amyloid-β.

**Bapineuzumab**(AAB-001) is a fully humanized monoclonal antibody showing specificity to N-terminal of the amyloid β. Side effects of the therapy like vasogenic edema (which is more common in higher dose group) and microhaemorrhage limited further exploration of Bapineuzumab but subcutaneous and intravenous forms of treatment are under investigation.
<table>
<thead>
<tr>
<th>Approach</th>
<th>Therapeutic</th>
<th>How it lowers Aβ levels</th>
<th>Clinical Trial Phase completed</th>
<th>Clinical Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>CAD-106</td>
<td>An antigen that mimics the amino acids 1-6 of Aβ; produces anti-Aβ antibodies</td>
<td>Phase II</td>
<td>Undetermined</td>
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<tr>
<td>Antibodies</td>
<td>Bapineuzumab</td>
<td>Binds to soluble and fibrillar forms of Aβ</td>
<td>Phase III</td>
<td>Limited efficacy; discontinued because of side-effects</td>
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<tr>
<td></td>
<td>Solanezumab</td>
<td>Binds to soluble Aβ only</td>
<td>Phase III</td>
<td>Shows some efficacy in mild AD</td>
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<tr>
<td></td>
<td>Crenezumab</td>
<td>Binds to soluble and fibrillar forms of Aβ</td>
<td>Phase III</td>
<td>Shows some efficacy in mild AD</td>
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<td></td>
<td>Aducanumab</td>
<td>Binds to fibrillar and plaque, but not soluble forms of Aβ</td>
<td>Phase III</td>
<td>No efficacy in mild to moderate AD</td>
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<tr>
<td></td>
<td>Gantenerumab</td>
<td>Binds to fibrillar and plaque, but not soluble forms of Aβ</td>
<td>Phase II</td>
<td>Undetermined, phase III trial is ongoing</td>
</tr>
<tr>
<td></td>
<td>MK-8931</td>
<td>Blocks production of Aβ by inhibiting β-secretase enzyme</td>
<td>Phase II/III</td>
<td>Undetermined, phase III trial is ongoing</td>
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<tr>
<td>β-secretase</td>
<td>AZD3293</td>
<td>Blocks production of Aβ by inhibiting β-secretase enzyme</td>
<td>Phase I</td>
<td>Undetermined, phase II/III trial is ongoing</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>E2609</td>
<td>Blocks production of Aβ by inhibiting β-secretase enzyme</td>
<td>Phase I</td>
<td>Undetermined, phase II/III trial is ongoing</td>
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Tau-directed therapy

Tau pathology can be modified by either:

* prevention of tau aggregation and hyperphosphorylation
  or by
  employing immunotherapy that is aimed at removing tau as NFTs and oligomers.

Although, tau-directed therapy is still in the nascent stages of development, it offers avenues that are still unexplored and need to be looked upon as possible means of therapeutics for AD.
Among the agents developed as tau anti-aggregants, methylthionium chloride, commonly known as methylene blue (MB), developed by TauRx Pharmaceuticals leads the way. It is responsible for interference in the tau–tau binding hence preventing tau aggregation.

A phase II placebo-controlled trial was conducted at three dose levels of 30, 60 and 100 mg/three times a day. The results of the trial produced affirmative results with 80 % slowing in the rate of progression of AD. But, subjects receiving 100 mg dose were discontinued from the trial due to some defects in the chemical formulation that delayed the release of active form of MB.
A better formulation with appreciable bioavailability and tolerability, *Leuco-methylthioninium (TRx 0237)*. It is undergoing Phase III clinical trials in the US and UK on patients ailing with mild to moderate AD. The phase III clinical trials are underway in various protocols in patients with mild to moderate form of AD. These studies are expected to be accomplished by the year 2016 and the outcome of these trials might light up a new dawn in the realm of disease-modifying treatment for AD.
Anti-inflammatory and neuroprotective approaches

Antioxidants

The treatment with antioxidants may cause prevention of propagation of tissue damage but the efficacy of treatment is questionable as there are doubts on its permeability through blood–brain barrier and the suboptimal drug levels are achieved at the target site in the central nervous system.

Results of the studies conducted by Zandi et al. showed that the combination of vitamin E and vitamin C showed decreased prevalence and incidence of AD. Bastianetto et al. carried out an investigation on the efficacy of the various constituents of extract of Gingko biloba against the toxicity caused by NO generators on the hippocampal region. They found out that the flavonoid component of the Gingko extract in a concentration of 25 lg/ml was able to bail out the hippocampal cells from the danger of toxic radicals generated from the sodium nitroprusside. It was also seen that the terpenoid component did not display any prominent anti-Alzheimer activity.
Non-steroidal anti-inflammatory drugs (NSAIDs)

- first-developed GSMs
- down-regulation of pro-inflammatory signals, microglia, and astrocytes and decrease the risk of the disease by lowering Aβ1–42 production

The findings of the Alzheimer’s Disease Anti-Inflammatory Prevention Trial (ADAPT) revealed that the drugs like celecoxib and naproxen do not posses appreciable anti-Alzheimer’s activity and did not improve cognition.

Still, NSAIDs hold the potential for exploration.
Limitations in the development of drug for AD and future perspectives

The failure of prospective disease-modifying therapy in various phases of clinical trials has prompted the scientists from world over to ponder upon the underlying pathophysiology and mechanism of the disease.

Although new mechanisms have made their way to decipher the course and therapy for the disease, still few crucial points have to be kept in mind while developing disease-modifying treatment for AD. First, the mechanisms associated with the disease must be scrupulously and rigorously studied to enhance the underlying cause of the disease. It is of utmost importance to apprehend the relationship between Ab, tau and other related factors to develop a successful disease-modifying therapeutics for AD.