



## Review

## Therapeutics of Alzheimer's disease: Past, present and future

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## ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia worldwide. The etiology is multifactorial, and pathophysiology of the disease is complex. Data indicate an exponential rise in the number of cases of AD, emphasizing the need for developing an effective treatment. AD also imposes tremendous emotional and financial burden to the patient's family and community. The disease has been studied over a century, but acetylcholinesterase inhibitors and memantine are the only drugs currently approved for its management. These drugs provide symptomatic improvement alone but do less to modify the disease process. The extensive insight into the molecular and cellular pathomechanism in AD over the past few decades has provided us significant progress in the understanding of the disease. A number of novel strategies that seek to modify the disease process have been developed. The major developments in this direction are the amyloid and tau based therapeutics, which could hold the key to treatment of AD in the near future. Several putative drugs have been thoroughly investigated in preclinical studies, but many of them have failed to produce results in the clinical scenario; therefore it is only prudent that lessons be learnt from the past mistakes. The current rationales and targets evaluated for therapeutic benefit in AD are reviewed in this article.

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## 1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia, and with a new case occurring every seven seconds globally, the disease itself is becoming a slow pandemic (Ferri et al., 2005). One person for every 85 individuals can be expected to suffer from AD by the year 2050 (Brookmeyer et al., 2007). AD also imposes tremendous emotional and financial burden to the patient's family and community through the provision of care and loss of wages. The disease maybe classified based on the age of onset into early-onset AD and late-onset AD. Early onset AD accounts for approximately 1%–6% of all cases and manifests roughly between 30 and 60 years. Late onset form accounting for around 90% of cases has an age at onset later than 60 years. Etiology of AD is multifactorial with genetic, environmental, behavioral and developmental components playing a role. The greatest risk factor is advancing age; others being a positive family history, head trauma, female gender, previous depression, diabetes mellitus, hyperlipidemia and vascular factors (Kivipelto et al., 2001). The understanding of the pathophysiology of AD is constantly changing; for instance the tangles, a well known pathological hallmark of AD, earlier thought

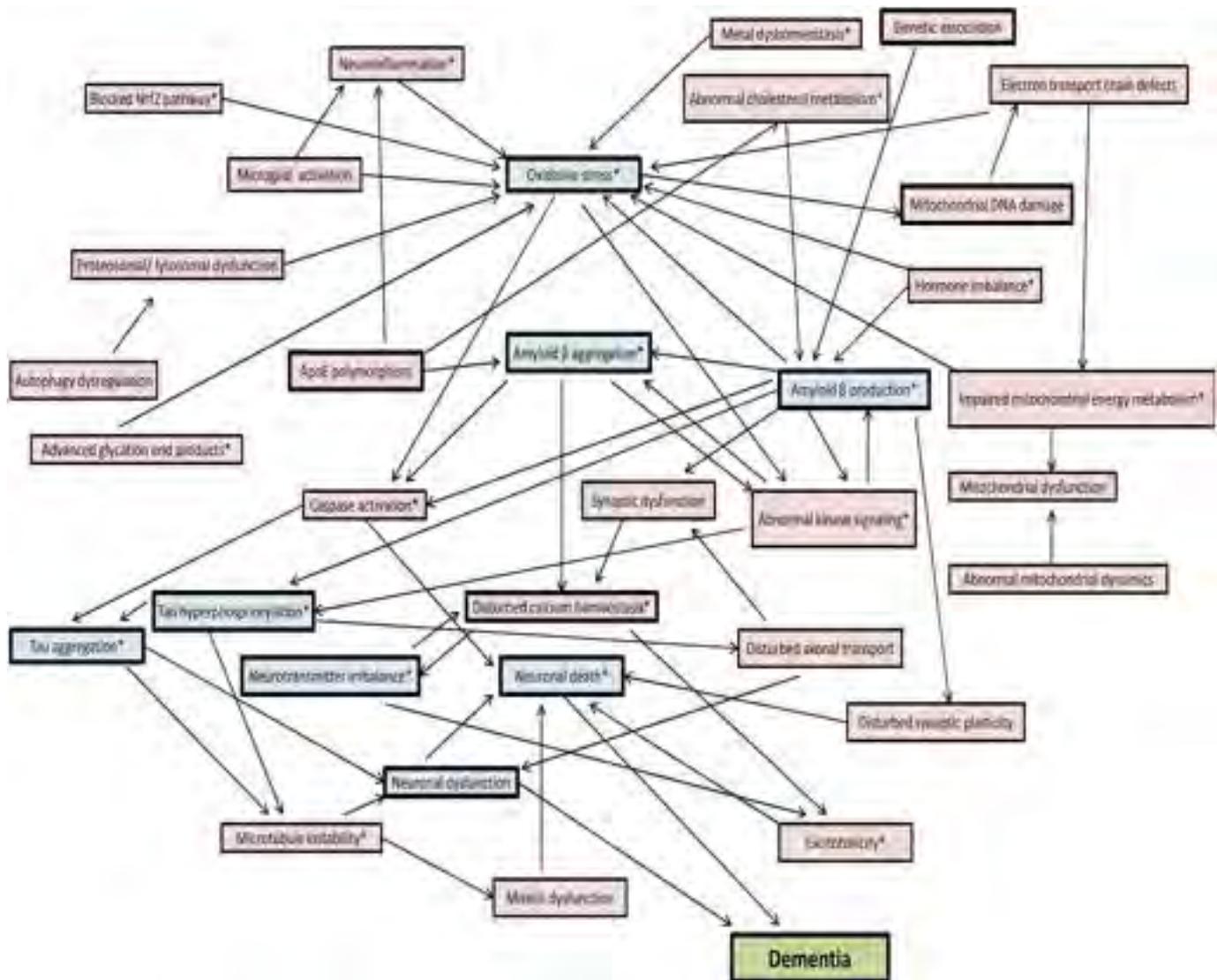
to be responsible for the disease now rather seem to reflect the damage which the neurons have endured over a long time. The notion that amyloid beta peptide (A $\beta$ ) and phosphorylated tau are pathologic molecules is slowly changing, and it seems that they represent a cellular adaptive strategy to oxidative stress. Apart from them, various deranged mechanisms such as chronic oxidative stress, mitochondrial dysfunction, A $\beta$  production, neurofibrillary tangles accumulation, hormone imbalance, inflammation, mitotic dysfunction, calcium mishandling, and genetic components play a role in the disease process. Although the mechanisms are diverse, neuronal death, the inevitable event occurs resulting in AD.

## 2. Therapeutics in AD

Although AD is known for about a century (Ramirez-Bermudez, 2012), four cholinesterase inhibitors and memantine are the only drugs approved by the US Food and Drug Administration for its treatment. These drugs provide symptomatic treatment but do not alter the course of the disease. Hence the modern therapeutic options that target the disease modification part are on a rise. The multiple mechanisms involved in the pathogenesis of AD create considerable difficulty in producing an effective treatment (Fig. 1). This current review attempts to summarize the existing therapeutic

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**Fig. 1.** Pathogenesis of Alzheimer's disease – Web of causation. The figure shows the various mechanisms involved in pathogenesis of Alzheimer's disease. The major mechanisms are in bold boxes. \*Indicates the mechanisms against which therapeutic strategies are targeted.

strategies till date with correlation to the pathophysiologic mechanisms for AD (Table 1).

### 2.1. Modulating neurotransmission

The cholinergic group of neurons is the main neurotransmitter system involved in AD and basal forebrain cholinergic loss is a well recognized pathology. These neurons maintain cortical activity, cerebral blood flow, modulate cognition, learning, task and memory related activities, development of the cerebral cortex and regulation of sleep–wake cycle (Berger-Sweeney, 2003; Schliebs and Arendt, 2006). Considering the many functions of the cholinergic neurons, the symptom complex in AD can at least be partially understood.

The dysfunction of the cholinergic system in AD occurs at various levels including a decreased choline acetyltransferase activity, reduced choline uptake, a decrease in acetylcholine synthesis (Slotkin et al., 1990) and altered levels of acetylcholine receptors (AChRs) (Xu et al., 2012). Glutamate is the primary excitatory neurotransmitter in the hippocampal and neocortical regions of the brain, and they do play a significant role in cognition, learning and

memory process. The post-synaptic membrane has high density of one of its receptors- the N-methyl-D-aspartate (NMDA) receptor. Studies have shown there is an extracellular glutamate excess in AD, contributed both by an increased presynaptic glutamate release and decreased re-uptake which, in turn lead to a tonic activation of NMDA receptors (Revett et al., 2013). The excitotoxicity is 'slow' in contrast to the acute or rapid form that occurs with stroke or epilepsy. Impaired insulin signaling along with mitochondrial dysfunction and receptor abnormalities (Beal, 1992) can predispose to this process when glutamate is excitotoxic even at physiological concentrations (Novelli et al., 1988). Dysfunction in other neurotransmitter systems such as  $\gamma$ -aminobutyric acid (GABA), histamine, and serotonin systems of neurons also lead to AD. The modulation of neurotransmission with drugs continue to remain the best approach to providing symptomatic improvement in patients; of late, mechanistic insights into their disease modifying aspects have also been highlighted.

#### 2.1.1. Cholinesterase system

The four acetylcholinesterase inhibitors (AChEI) approved by the U.S. Food and Drug Administration for the treatment of AD are

**Table 1**  
Therapeutic strategies in Alzheimer's disease.

1. Modulating neurotransmission
<ul style="list-style-type: none"> <li>• Cholinesterase inhibitors</li> <li>• N-methyl D-aspartate receptor antagonism</li> <li>• GABAergic modulation</li> <li>• Serotonin receptor modulation</li> <li>• Histaminergic modulation</li> <li>• Adenosine receptor modulation</li> </ul>
2. Tau based therapies
<ul style="list-style-type: none"> <li>• Tau phosphorylation inhibition</li> <li>• Microtubule stabilization</li> <li>• Blocking Tau oligomerization</li> <li>• Enhancing Tau degradation</li> <li>• Tau based immunotherapy</li> </ul>
3. Amyloid based strategies
<ul style="list-style-type: none"> <li>• Secretase enzymes modulation</li> <li>• Amyloid transport</li> <li>• Preventing amyloid aggregation</li> <li>• Promoting amyloid clearance</li> <li>• Amyloid based immunotherapy</li> </ul>
4. Modulating intracellular signaling cascades
5. Oxidative stress reduction
<ul style="list-style-type: none"> <li>• Exogenous antioxidant supplementation</li> <li>• Augmenting endogenous defense</li> </ul>
6. Mitochondrial targeted therapy
7. Modulation of cellular calcium homeostasis
8. Anti-inflammatory therapy
9. Others
<ul style="list-style-type: none"> <li>• Gonadotropin supplementation</li> <li>• Lipid modifiers – Statins</li> <li>• Growth factor supplementation</li> <li>• Metal chelation</li> <li>• Epigenetic modifiers</li> <li>• Caspase inhibitors</li> <li>• Nitric oxide synthase modulation</li> <li>• Nucleic acid drugs</li> <li>• Multi-target directed ligands</li> </ul>

tacrine, donepezil, rivastigmine, and galantamine, however, tacrine is now rarely used because of its hepatotoxicity (Watkins et al., 1994). AChEI enhance cholinergic neurotransmission through inhibition of acetylcholinesterase (AChE), thus decreasing the breakdown of acetylcholine. It is clear that, when cholinergic transmission occurs, or their receptors become activated there is an increase in the long term potentiation. The cholinergic AChRs are expressed on principal and inhibitory interneurons, both pre- as well as post-synaptically in most regions of hippocampus; thus, boosting acetylcholine levels in the synaptic cleft can have bidirectional influences (Drever et al., 2011). Galantamine also possesses agonist activity at the nicotinic  $\alpha 4\beta 2$  receptor subtype and its clinical benefits are probably due to both the mechanisms (Coyle and Kershaw, 2001). More recently it is known that the muscarinic M1 AChRs are present in intracellular locations, especially in the hippocampal regions (Anisuzzaman et al., 2013). The cell surface M1 AChRs activate the phosphatidylinositol cascade, whereas intracellular M1 AChRs activate the extracellular regulated kinases 1/2 (Anisuzzaman et al., 2013); both the pathways regulate long term potentiation and synaptic plasticity. Cholinergic transmission also plays a role in modulating the mechanisms involved in adult neurogenesis (Bruehl-Jungerman et al., 2011) and studies do suggest that AChEIs alleviates oxidative stress in animal studies and humans (Klugman et al., 2012). Various short term trials with AChEI monotherapy have shown clinically apparent and encouraging improvement in cognitive function, slowed the pace of functional decline or clinical worsening compared with placebo and reduced behavioral symptoms in mild-to-moderate and moderate-to-

severe AD patients; data from meta-analyses also attest to the same fact (Birks, 2006). Efforts to deliver standard drugs efficiently are another area of development; trans-dermal delivery systems for all the three drugs are available but not currently approved. The oral dosing of AChEIs increases the plasma drug levels in a short time interval, which probably accounts for the observed gastrointestinal side effects. The trans-dermal patches can ensure 'peak less' and prolonged delivery with minimal fluctuations in the plasma drug concentrations (Lefevre et al., 2008). Rivastigmine patches (9.5 mg/24 h) produced plasma drug concentrations and results that were comparable with oral capsules (12 mg/day); safety and tolerability profile of the patches were better. The subjects also experienced significantly decreased discomfort with patches (Winblad et al., 2007).

Some novel AChEI molecules have also been developed. Memogain® (GLN-1062; Galantos Pharma) the benzoyl ester of galantamine is a pro-drug that is available as intranasal formulation. The drug has shown excellent efficacy and central nervous system (CNS) bioavailability in animal studies (Maelicke et al., 2010). Huperizine A is a natural alkaloid isolated from the Chinese moss shrub (*Huperzia serrata*) and possesses AChE inhibiting action with modest effects on amyloid precursor protein (APP) metabolism and neuroprotection (Zhang et al., 2008). The drug showed promising safety profile in both phase I and phase II trials. At a dose of 400  $\mu$ g twice daily, the drug was able to improve cognitive outcome by 2.27 points in patients with mild to moderate AD (Rafi et al., 2011). A pro-drug of huperizine, ZT-1 has shown admirable pharmacokinetic profile in a recent phase I study (Jia et al., 2013). Methanesulfonyl fluoride (SNX-001) is an irreversible inhibitor of AChE first reported in 1999 for its therapeutic value in AD (Moss et al., 1999). Preclinical studies demonstrating its benefit in cognition have revived interest in the molecule recently. A phase I trial has studied the extent of AChE inhibition in healthy subjects and has found promising results (Moss et al., 2013). The dual acting AChEI compounds are to be discussed in a different section.

Direct modulation of the cholinergic AChRs is also under considerable evaluation. In AD, the levels of presynaptic M2 AChRs decrease, but those of postsynaptic M1 AChRs remain unchanged. A number of M1 partial agonists like AF102B, AF150(S), AF267B and AF292 and allosteric agonists such as 77-LH-28-1, LY-593093 and Lu AE51090 are available; ML 169 is a recently reported M1 positive allosteric modulator (Reid et al., 2011). The strong side of the M1 agonists seems to be their role in APP processing and thus indirectly on other processes such as tau phosphorylation; studies have shown ablation of M1 AChRs lead to increased amyloid  $\beta$  (A $\beta$ ) generation (Medeiros et al., 2011). AF102B, an M1 partial agonist, significantly lowered CSF A $\beta$  levels in AD patients (Nitsch et al., 2000), where AChEIs showed no effect (Parnetti et al., 2002). AF150(S) and AF267B have also shown promising results in the preclinical setup (Fisher, 2008; Fisher et al., 2002). Another mixed muscarinic/ $\sigma 1$  agonist- ANAVEX 2-73 is currently in phase I/IIa trials. This compound has partial agonistic activity at both muscarinic AChR and  $\sigma 1$  protein (chaperone protein in endoplasmic reticulum activated by unfolded protein response) (Collina et al., 2013). In animal studies ANAVEX 2-73 attenuates A $\beta$  induced memory deficits and toxicity, decreases seeding of A $\beta$ , blocks the activation of glycogen synthase kinase-3 (GSK3 $\beta$ ) and in turn the hyperphosphorylation of tau (Lahmy et al., 2013).

While we slowly begin to understand the therapeutic potential of muscarinic AChRs, the role of nicotinic AChRs in AD is debatable at best. Different neuronal systems express these receptors, and they play diverse functional roles in cognition, memory processes, trophism and neuroprotection (Wallace and Bertrand, 2013). Recent evidences have also uncovered their pathological side and the possible mechanisms by which nicotinic AChRs may contribute

to the pathophysiology of AD (Hernandez and Dineley, 2012; Parri and Dineley, 2010). Thus, their modulation is governed by a subtle balance. The levels of nicotinic receptors may remain unchanged or even upregulated, with progression of the disease process in AD (Ikonovic et al., 2009).

Evidence show that nicotinic AChR agonists produce both beneficial and damaging effects on neuronal function; hence, the net effect is not clear (Fisher, 2012). Studies have shown that  $\alpha 7$  nicotinic agonists attenuate A $\beta$  mediated toxicity (Kihara et al., 2001) but, on the other hand, modify the reactivity and increase phosphorylation state of tau protein (Hellstrom-Lindhahl et al., 2000). How modulating the same receptor decreases one pathology, but increases the other is not clear. More surprisingly, antagonists of  $\alpha 7$  nicotinic AChRs also cause similar effects (Mousavi and Hellstrom-Lindhahl, 2009). A few recent studies highlight the cognitive enhancing potential of cotinine, a metabolite of nicotine; the compound is a positive allosteric modulator of  $\alpha 7$  nicotinic AChRs (Echeverria and Zeitlin, 2012). The properties which make cotinine a better ligand than nicotine would be its low toxicity profile, non addictive nature and good blood brain barrier clearance (Echeverria and Zeitlin, 2012). Apart from its receptor modulation the drug also inhibits A $\beta$  aggregation (Echeverria et al., 2011). The pharmacokinetic and safety profile of cotinine have already been investigated in humans (Benowitz et al., 1983; Bowman and Mc, 1962) but no documentation is available regarding its role in AD. Many of novel ligands for  $\alpha 7$  nicotinic AChR are also currently in development (Toyohara and Hashimoto, 2010). EVP-6124 is a novel selective  $\alpha 7$  partial agonist that improves memory performance in animals (Prickaerts et al., 2012); the compound has successfully completed phase II trials (NCT01073228). MT-4666 is another nicotinic agonist that is currently in phase II trials (NCT01764243). Amongst other novel compounds, ABT-384 (NCT01137526) has completed phase II trials while a trial with ABT-126 is ongoing (NCT01527916).

To summarize, the advantage of M1 agonists over AChEIs could be their potential role as disease modifying agent along with its symptomatic benefits. The role of nicotinic modulators, on the other hand, is not clear. From this group, only AChEIs are currently used in the clinical setting; the direct acting ligands described would require more convincing evidence. Since neuronal dysfunction starts early in the course of disease, the utility of AChEIs is to provide symptomatic relief in that transitional period sustaining the function with the available neurons; with increasing neuronal damage, the therapeutic effectiveness of AChEI slowly diminishes. As to how long the drugs remain valid or how long the patients should be treated with AChEI, the answers vary; reports indicate that benefit may last up to four years (Rogers et al., 2000). The benefit of AChEIs in the behavioral symptoms of AD and their synergistic role in combination therapy with memantine is to be dealt in the following section.

### 2.1.2. *N-methyl D-aspartate antagonism*

Neuronal pathology in AD also extends to the glutamatergic system but at a later stage of the disease. Glutamatergic neurons regulate synaptic plasticity, neuronal growth and differentiation, cognition, learning and memory (Butterfield and Pocernich, 2003). A 'glutamate cycle' occurs between the pre- and post-synaptic neurons, and astrocytes that determines the synaptic concentration of glutamate available for the receptors (Revett et al., 2013). Cycle defects occur at different levels in AD leading to a state of extracellular glutamate accumulation, increased NMDA receptor activation and excitotoxicity (Revett et al., 2013).

A large body of evidence shows mutual interaction between NMDA receptors and A $\beta$  peptides. Studies suggest that NMDA receptors activation lead to A $\beta$  production and vice versa-A $\beta$

oligomers binding and activating NMDA receptors, further substantiating the importance of glutamatergic system in AD (Dinamarca et al., 2012; Revett et al., 2013). Memantine is an uncompetitive NMDA antagonist, has voltage dependency, rapid blocking kinetics, moderate affinity and blocks the channel by trapping it in open conformation (Gilling et al., 2009). Mg<sup>2+</sup> ions block the NMDA channel under resting conditions; when glutamate is available the blockade is relieved, and the NMDA channel is now open for Ca<sup>2+</sup> inflow. In pathological states such as AD, there is a low and persistent state of NMDA activation even at resting periods; in such states, Mg<sup>2+</sup> ions are excluded from the channel, thereby, allowing continuous Ca<sup>2+</sup> flow across the membrane. The moderate affinity and voltage dependency property of memantine allows it to block the persistent NMDA activation and is thus, beneficial in AD. Evidences also indicate memantine mediated blockade is relieved by high glutamate concentrations in the synaptic cleft. Hence, when a physiological impulse arrives the glutamate over-rides the memantine blockade, and physiological transmission can continue without interference (Parsons et al., 2013). Experimental evidences show that memantine treatment improves spatial learning in animal models of AD, protects neurons from A $\beta$  induced toxicity, decreases apoptosis, free radical mediated damage and restored synaptic degeneration (Miguel-Hidalgo et al., 2012). Reportedly memantine also seems to have its antagonizing effect on other receptors such as  $\alpha 7$  and  $\alpha 4\beta 2$  nicotinic AChRs (Buisson and Bertrand, 1998; Maskell et al., 2003), 5-HT<sub>3</sub> (Rammes et al., 2001),  $\alpha 3\beta 2$  (Lee et al., 2012), 5-HT<sub>2A</sub>, dopamine D2 receptors and histaminergic neurons (Motawaj et al., 2011; Nakaya et al., 2011). Hence, the therapeutic benefits of memantine may not be strictly due to its effect on NMDA alone, but except at  $\alpha 7$  nicotinic AChRs there are no solid evidences to show that the effects on other receptors occur at the therapeutically administered concentrations in AD (Rammes et al., 2008).

Currently memantine is the only drug approved for clinical use in moderate to severe AD in USA and Europe; studies show convincing evidence of memantine's value (Hellweg et al., 2012; McShane et al., 2006). Although the effect of memantine is evident in late stages, its role in early AD is unclear. The three main studies that have seen the role of memantine in mild to moderate AD show there are some beneficial effects on cognitive and global functioning status, but it does not impede the progression of disease (Bakchine and Loft, 2008; Peskind et al., 2006; Porsteinsson et al., 2008). A recent meta-analysis also indicates the same (Schneider et al., 2011). Memantine's lack of benefit in the early stages is not well understood yet. The involvement of cholinergic neurons probably occurs early in the disease but, damage to glutamatergic system and excitotoxic degeneration occurs late in the course of disease (Ni et al., 2013). The effect of memantine on other receptor channels might as well play a role here. Memantine also blocks  $\alpha 7$  nicotinic AChRs more potently at therapeutic concentrations (Aracava et al., 2005); this blockade could affect neurotransmission during the early stages of disease when functioning cholinergic neurons are still available. Hence as of now, use of memantine is restricted to the later stages of the disease.

A number of investigators have looked at the possible advantage of its combining memantine with AChEI in AD (Atri et al., 2013; Dantoine et al., 2006; Howard et al., 2012; Lopez et al., 2009; Porsteinsson et al., 2008; Riepe et al., 2007; Tariot et al., 2004). Results of most studies indicate that addition of memantine to AChEI may add to the therapeutic value and improve clinical outcome in subjects. However two recent systematic reviews have concluded that there may be few significant favorable changes from the combination therapy, but it is not currently recommended (Farrimond et al., 2012; Muayqil and Camicioli, 2012). A current trial of memantine and donepezil combination in moderate to

severe stages of AD is ongoing (NCT00866060). A once daily fixed dose combination of memantine and donepezil has also been developed (ADS-8704; Adamas pharmaceuticals); the above compound is currently in phase III trials.

### 2.1.3. GABAergic modulation

GABA is one of the main inhibitory neurotransmitters. Amongst the hippocampal neurons, earliest to be affected are the cholinergic group followed by the glutamatergic neurons; for unknown reasons there is relative sparing of GABAergic neurons (Rissman et al., 2007). Studies also indicate when chronic growth factor deprivation occurs, the GABA transmission changes from inhibitory to excitatory stimulus (Lagostena et al., 2010). However, it is not clear as to which function of GABA is more harming to the cells. GABAergic drugs are currently another class of compounds currently tried for their cognitive enhancing potential (Limon et al., 2011). SGS742 is a GABA<sub>B</sub> antagonist that showed promising results in preclinical and phase I studies. The compound reached phase II trial stage but not beyond. Etazolate, a pharmacological modulator of GABA<sub>A</sub> receptor is also neuroprotective (Marcade et al., 2008). Apart from being a GABA<sub>A</sub> modulator the drug also activates  $\alpha$ -secretase (Marcade et al., 2008) and inhibits phosphodiesterase (PDE)-4 activities (Wang et al., 1997). Etazolate was safe and well tolerated in a recent trial, but the effectiveness and long term benefits are to be determined (Vellas et al., 2011). Inverse agonists for GABA<sub>A</sub> receptor with  $\alpha 5$  subunit specifically also seem to improve cognition in animal models, but studies in humans have yielded conflicting results. One such compound alpha5IA was able to restore the alcohol induced impairment in healthy controls, but there was worsening in learning performance in the elderly subjects (Atack, 2010). Hence the role of GABA modulators in AD is not clearly known.

### 2.1.4. Serotonin receptor modulation

The role of serotonin receptors in AD gained prominence when observation suggested that levels of receptor and the density of 5-HT positive neurons significantly decline in AD brains (Reynolds et al., 1995). The areas of the brain concerned with learning and memory show high concentrations of 5-HT<sub>1A</sub>, 5-HT<sub>4</sub>, 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptors (Cifariello et al., 2008; King et al., 2008). Major anatomical distribution of the individual receptor subtypes differ; the hippocampal formation, entorhinal cortex and raphe nuclei express 5-HT<sub>1A</sub> receptors in (Chalmers and Watson, 1991) at both pre- and post-synaptic locations (Rodriguez et al., 2012). The post-synaptic 5-HT<sub>1A</sub> stimulation inhibits cholinergic transmission, but, on the other hand, the pre-synaptic 5-HT<sub>1A</sub> autoreceptors exert a negative feedback on the serotonergic transmission. The basal ganglia and hippocampus also have a high density of 5-HT<sub>4</sub> (Vilario et al., 2005) and 5-HT<sub>6</sub> receptors (Marazziti et al., 2012). The interaction of the serotonin system in the nervous system gets further complicated because the 5-HT receptors co-localize on glutamatergic, cholinergic and GABAergic neurons, thus, indicating serotonin system is capable of regulating of a variety of other neurotransmitter systems (King et al., 2008).

A number of serotonomimetic compounds (monoamine oxidase inhibitors and selective serotonin reuptake inhibitors) already in clinical use are under consideration in AD as monotherapy or along with AChEI for their cognitive enhancing capacities (Rodriguez et al., 2012). Many novel ligands with agonistic or antagonistic properties targeting different 5-HT receptors are available (5-HT<sub>1A</sub>, 5-HT<sub>4</sub> and 5-HT<sub>6</sub>) (King et al., 2008). A 5-HT<sub>1A</sub> antagonist lecozotan proved to be safe and effective in phase I (Patat et al., 2009) and phase II trials (NCT00151333), but the drug has not been studied beyond that. A number of 5-HT<sub>4</sub> agonistic compounds like PRX-03140, velusetrag, TD-8954, RQ-0000009, SUVN-D1003019 and

SUVN-1004028 have shown cognitive benefits in preclinical studies with potential effects on amyloid processing (Shen et al., 2011). The safety and pharmacokinetic properties of velusetrag are known, and the drug is under use currently for gastrointestinal disorders (Long et al., 2012). SB-742457, a novel 5-HT<sub>6</sub> agonist has also shown positive results in phase II trials as a monotherapy and combination with donepezil (Maher-Edwards et al., 2011, 2010). Interestingly, few 5-HT<sub>6</sub> antagonists like Ro-4368554, SB-258585 and SB-399885 have also shown cognition enhancing properties in animal experiments (Gravius et al., 2011; Hirst et al., 2006); hence, the clinical utility of 5-HT<sub>6</sub> ligands is yet to be understood. Serotonergic modulation also appears to relieve some behavioral manifestations of AD. Inverse agonists of 5-HT<sub>2A</sub> receptors maybe of some help in improving cognitive and non-cognitive processes. Pimavanserin is a novel inverse agonist that successfully reversed psychosis like features in animal models (Price et al., 2012) and in patients with Parkinson's disease (Meltzer et al., 2010). 5-HT<sub>7</sub> is a recently characterized receptor protein and its role in learning, and memory processes are under consideration (Cifariello et al., 2008).

### 2.1.5. Histaminergic modulation

Histamine receptor H3 expression is high in several brain regions, including those involved in sleep-wake regulation and cognitive functions (Motawaj et al., 2010). Activating the receptor inhibits histamine release in the brain but its selective antagonism enhances the release of various neurotransmitters including acetylcholine, GABA, dopamine and nor adrenaline (Chazot, 2010). Intriguingly, the expression of H3 receptor is unaltered despite progress in AD suggesting its modulation could be of therapeutic benefit (Medhurst et al., 2009). Preclinical studies show cognition enhancing properties for novel H3 antagonists, including BF2.649, PF-03654746, GSK189254, MK-0249, JNJ-17216498, and ABT-288 (Brioni et al., 2011). However, results of the phase II trial of MK-0249 show no benefit in subjects with mild to moderate AD (Egan et al., 2012). PF-03654746 has completed a phase I trial, but the results are not available (NCT01028911). ABT-288 was safe and well tolerated in healthy adults (Othman et al., 2013); the compound recently completed its phase II trial (NCT01018875). A small pilot trial with selective H3 antagonist GSK239512 also showed excellent safety profile with positive effects on attention and memory (Nathan et al., 2013). The therapeutic role of these compounds is not clear yet.

### 2.1.6. Adenosine receptor modulation

The neuromodulation role of adenosine has recently come into light, and its role in neurodegenerative disorders is under investigation. Adenosine receptors, especially adenosine2A play pivotal roles in modulation of neuronal function, linking the system to AD related cognitive deficits (Canas et al., 2009). In vivo studies have shown neuroprotective value for SCH58261, an adenosine2A blocker (Dall'igna et al., 2007). Investigation of the utility of cilostazol, an antiplatelet drug and PDE-3 inhibitor for its benefit in dementia is ongoing (NCT01409564).

### 2.1.7. Tackling the neuropsychiatric aspects of AD

The other key aspect of the clinical syndrome of AD is the non cognitive manifestations for which no approved treatments or management guidelines exist. Some treatment related factors that need attention in this regard include the age of the subject, their ability to tolerate psychotropic drugs and its side effects and the possible drug interactions. The common neuropsychiatric symptoms in patients with AD are lack of cooperation/concentration, tremors, irritability, apathy, depression, negativism, sleep disturbances, disinhibition, delusions or hallucinations (Mohs, 2005). Selective serotonin reuptake inhibitors are commonly used as

adjunct drugs to treat the psychotic, apathy and depressive features associated with AD. However a recent report has concluded that sertraline and mirtazapine are not beneficial in AD (Banerjee et al., 2013). Mood stabilizers also do not seem to offer any treatment related benefits in AD (Xiao et al., 2010). The overlap between the neural circuitry involved in dementia and neuropsychiatric aspects allows the drugs modulating one neurotransmission to exert benefit in different domains. There is substantial evidence that the commonly used AChEI drugs—donepezil, rivastigmine and galantamine improve psychiatric and behavioral manifestation along with cognitive enhancement (Pinto et al., 2011). AChEIs as monotherapy as well as in combination with antidepressant or antipsychotics provide a synergistic effect in AD.

Studies also demonstrate the potential value of memantine in improving the behavioral manifestations. At the dose commonly used (20 mg/kg body weight), memantine improves overall functioning status, improves cognitive abilities and activities of daily living, slows down functional decline and decreases worsening of mood and behavior (Hellweg et al., 2012; McShane et al., 2006). A post marketing surveillance study has observed that memantine monotherapy for minimum 6 months improved behavioral outcome in the subjects (Clerici et al., 2012). Memantine also had an added benefit in subjects with agitation, aggression and psychosis (Wilcock et al., 2008). Other drugs that have shown some benefit include methylphenidate and melatonin. Methylphenidate has shown improvement of apathy and depression in AD; however, the findings need to be confirmed from large studies (Padala et al., 2010). Melatonin also has shown its effectiveness in decreasing the sundowning symptoms and sleep disturbances in AD (Cardinali et al., 2010). Currently there is a lack of controlled studies that demonstrate the value of drugs regarding their psychotropic effects in AD; the future merits appropriately designed studies to determine the same.

## 2.2. Tau-based therapies

Neuronal cells commonly express tau protein, where, its purpose is to stabilize the microtubules. By regulating microtubule assembly, tau modulates the functional organization of the neurons, particularly axonal morphology, growth, and polarity (Buee et al., 2000). The protein has several phosphorylation sites, and the microtubule binding property of tau is dependent on the phosphorylation state. The phosphorylated tau binds microtubules with a lesser affinity leading to microtubule instability. In AD, hyperphosphorylated tau accumulates and aggregates into paired helical filaments, loses its microtubule binding and stabilizing role, contributing to neuronal degeneration (Garcia and Cleveland, 2001).

### 2.2.1. Targeting tau phosphorylation

Tau phosphorylation is a key event in AD contributing to microtubule instability; hence, inhibition of kinases to prevent the process is a valid rationale. The main focus has been on glycogen synthase kinase 3 (GSK3), one of the primary enzymes involved in tau phosphorylation. Lithium and valproate have inhibitory actions on GSK3 and when administered they reduce tau pathology in transgenic mice (Engel et al., 2006; Noble et al., 2005). Small scale trials have shown some beneficial effects, but larger, more controlled studies have failed to prove the benefit for both lithium (Hampel et al., 2009) and valproate (Tariot et al., 2009). In addition to an inhibitory effect of caffeine on PDE enzyme, recent studies suggest it also inhibits GSK3 $\beta$ ; caffeine administration in A $\beta$  transgenic animal models has shown decreased A $\beta$  production (Arendash et al., 2009). Various epidemiologic studies also report a decreased incidence of AD in heavy caffeine users (Eskelinen et al., 2009). Tideglusib (NP031112) is an irreversible inhibitor of GSK3 $\beta$  currently

studied for its value in AD and progressive supranuclear palsy. A pilot study in mild to moderate AD with different escalating doses of the drug showed an increasing trend in mini mental state examination (MMSE) and cognitive scales; the drug has recently completed phase IIb trials (NCT01350362). Several small molecule inhibitors of GSK3 like SB216763, CHIR-98014 (Selenica et al., 2007) and SRN-003-556 (Hampel et al., 2009) are currently in pre-clinical studies. SB216763 was able to decrease the amount of phosphorylated tau, but serious adverse effects occurred in control animals (Hu et al., 2009), thus raising caution regarding its use. This result also emphasizes the necessity of a compound that does not affect the basal activity of GSK3. Bezafibrate, a pan-peroxisome proliferator activated receptor agonist has shown its effectiveness in decreasing tau phosphorylation improving behavioral features in P301S mice but the clinical implications are not clear (Dumont et al., 2012). Evidences also suggest a protective role for insulin in AD; preclinical studies show that when administered via intranasal route insulin decreases GSK3  $\beta$  activation and in turn reduces tau phosphorylation (Yang et al., 2013). Clinical evidences demonstrate the potential of intranasal insulin therapy in improving cognitive function (Shemesh et al., 2012) but this effect seems to be strongly dependent on the ApoE $\epsilon$ 4 carrier status and sex of the subject (Claxton et al., 2013; Reger et al., 2008). Numerous clinical trials evaluating the value of insulin in AD are currently ongoing (NCT01767909, NCT01636596, NCT01436045, NCT01595646).

Activation of protein phosphatases to dephosphorylate tau is another strategy under evaluation. The main dephosphorylating enzyme is protein phosphatase 2A; hence activators of the enzyme may hold benefit in AD. Sodium selenite (Ve-015) is a protein phosphatase 2A activator currently in a phase IIa trial in Australia ([www.anzctr.org.au](http://www.anzctr.org.au); ACTRN12611001200976). Studies show the post-translational glycosylation of tau protein with  $\beta$ -N-acetylglucosamine occurs at the same threonine and serine residues, pathologically phosphorylated in AD. Another recent research demonstrates a parallel GSK3 activation with inhibition of N-acetylglucosaminidase (Yu et al., 2012). Hence, maintaining glycosylation is one of the indirect strategies to prevent tau phosphorylation. Thiamet-G is an inhibitor of N-acetylglucosaminidase, tried with some success animal studies (Liu et al., 2004).

### 2.2.2. Microtubule stabilization

Various compounds with microtubule stabilizing effects are in development. The administration of microtubule stabilizer paclitaxel to tau-transgenic mice improves fast axonal transport, microtubule density and motor function (Zhang et al., 2005). However being a potent anticancer drug, paclitaxel raises safety concerns for its use in non-malignant conditions. Epophilone D is another microtubule stabilizing compound known for its blood brain barrier clearance (Andrieux et al., 2006). Low dose chronic epophilone D administration was able to demonstrate significant amelioration in microtubule pathology (Brunden et al., 2010). Two neuropeptides NAP (NAPVSIPQ) and D-SAL (SALLRSIPA) are available that boast microtubule stabilization effects (Gozes, 2011; Gozes et al., 2008). NAP preferentially interacts with neuronal and glial tubulin thus influences microtubule assembly and dynamics with some inhibitory effect on tau phosphorylation at low concentrations (Matsuoka et al., 2008). Intra nasal administration of the peptide has also been tried, and preliminary studies have shown positive results in AD animal models (Matsuoka et al., 2007). BMS-241027 is a small molecule microtubule stabilizer currently in phase I trials in subjects with mild AD (NCT01492374).

### 2.2.3. Preventing tau oligomerization

A compound that prevents tau interaction and neurofibrillary tangle accumulation could be extremely helpful in the treatment of

AD. Drugs such as astemizole, lansoprazole (both benzimidazole derivatives) show a strong affinity to binding tau protein, therefore, indirectly reduce tau–tau interaction (Rojo et al., 2010). Although lansoprazole decreases tau pathology it has a differential impact on amyloid metabolism; lansoprazole treatment in cell and animal models, demonstrate increased amyloid deposition and aggregation probably due to its  $\gamma$ -secretase modulating effect (Badiola et al., 2013). The dye methylene blue (methylthionium chloride) has a range of pharmacologic effects, one of which is its property to prevent tau interactions (Congdon et al., 2012). In addition, methylene blue also has roles on inhibiting amyloid aggregation (Necula et al., 2007), improving electron transport, decreasing oxidative stress, prevent mitochondrial damage (Atamna et al., 2008), regulate autophagy (Congdon et al., 2012) and inhibition of AChE (Pfaffendorf et al., 1997) and hsp70 activity (Jinwal et al., 2009). Rember™ (TauRx therapeutics) was the first generation proprietary molecule of methylene blue tried in AD; the drug successfully stabilized the progression of AD over 50 weeks in human studies (Wischnik et al., 2008). The encouraging led to the development of next generation version of the compound, leuco-methylthionium (LMTX™; TauRx therapeutics). LMTX has currently been advanced into phase III clinical trials (2012). Recently three natural phenolic compounds obtained from olives and derived food products hydroxytyrosol, oleuropein and oleuropein aglycone have also shown effectivity in preventing tau fibrillization in vitro (Daccache et al., 2011).

#### 2.2.4. Enhancing tau degradation

Another appropriate strategy is to increase the breakdown of polymerized tau, thus decreasing its toxicity. Heat shock protein 90 (Hsp 90), a chaperone involved in folding the denatured proteins, seems to play a role in preventing tau degradation (Dickey et al., 2007). Curcumin has a wide range of action, one of which is to inhibit Hsp 90 (Giommarelli et al., 2010). Curcumin treatment alleviates tau pathology in tau transgenic mice by suppressing tangle formation as well as promoting dissolution of already formed tangles (Ma et al., 2013). Various specific inhibitors of Hsp 90 are available currently (reviewed by Zhao et al., 2012), a few of them are clinical trials as an anti-cancer compound. The therapeutic potential of Hsp 90 inhibitors is under consideration in tauopathic and AD animal models. A brain penetrant Hsp 90 inhibitor, EC102 reduced the amount of tau aggregates in the brains of transgenic mice significantly (Luo et al., 2007). The issue of targeting chaperone molecules is the potential interference with their basal activity, which could lead to adverse effects. Although their therapeutic value in malignancies is promising, the future role for these compounds in the field of neurodegeneration is unclear.

#### 2.2.5. Tau immunotherapy

Recently interest in the approaches to promote immunological clearance of tau tangles has increased tremendously (Rosenmann, 2013). Evidence for this principle arose from preliminary studies where animals immunized with wild tau protein epitopes developed CNS infiltrates and encephalitic response (Rosenmann et al., 2006). Later, investigators modified the approach using the pathologically phosphorylated epitopes as immunogens. A study using a cocktail of different pathological epitopes showed a strong reduction in tau pathology in two different animal models without significant adverse effects (Boimel et al., 2010). Passive immunization approach with monoclonal antibodies against phosphorylated tau molecules also show benefit in tau transgenic animal models (Boutajangout et al., 2011; Chai et al., 2011). The treated animals displayed less motor impairment, decrease in phosphorylation of tau and its insoluble aggregates. Monoclonal antibodies against tau oligomers have also been tried with some success in animals (Lasagna-Reeves et al., 2011). The first translational vaccine trial

will use a conjugated vaccine (tau peptide-KLH-conjugate; AAD-vac1, Axon neuroscience) (NCT01850238). Although the concept and preliminary results have been encouraging, considering the present situation of A $\beta$  vaccination trials in humans, the value of tau immunotherapy in patients will only be evident in the future.

### 2.3. Amyloid targeted strategies

Though A $\beta$  fibers are one of the pathological hallmarks of AD, evidences suggest that the peptide has several physiological roles (Atwood et al., 2003). The conditions that turn A $\beta$  into a pathological molecule are not clearly understood but maybe dependent on the concentration of the peptide. When the production of A $\beta$  exceeds the capacity for its clearance they begin to accumulate, increasing the concentration towards toxic levels. A dynamic equilibrium exists between A $\beta$  fibrils-oligomers-monomers, and oligomeric species are more harmful than others (Jan et al., 2011). When A $\beta$  is in abundance, the oligomeric molecules maybe readily available for producing damage. The amyloid based therapeutics target various aspects of APP metabolism (Schenk et al., 2012).

#### 2.3.1. Decreasing A $\beta$ production- secretase modifiers

A $\beta$  peptides originate from the transmembrane protein- APP following secretase processing.  $\alpha$ -Secretase is the principal enzyme acting on APP under physiological conditions followed by  $\gamma$ -secretase. APP undergoes amyloidogenic processing when acted upon by the alternate enzyme  $\beta$ -secretase instead of  $\alpha$ -Secretase. The rationale of modifying secretases stems from the idea that augmenting  $\alpha$ -secretase, converts APP into nontoxic byproducts, whereas inhibiting  $\beta$  and  $\gamma$ - secretases, decreases amyloidogenic APP processing. Ligands binding at the cell surface receptors (commonly muscarinic/GABA agonists) and activation of signaling cascades like protein kinase C regulate the activity of  $\alpha$ -secretase strongly. One of the mechanisms of action of the muscarinic M1 receptor agonists and etazolate is to activate  $\alpha$ -secretase. Recent investigations have suggested that epigallocatechin-gallate, a polyphenol compound from green tea also induces  $\alpha$ -secretase activity and thus non-amyloidogenic APP processing (Smith et al., 2010). The antioxidant benefits of the same compound are also worth mentioning. A phase II trial investigating the drug's benefit in early stages of AD is currently underway (NCT00951834). Bryostatin 1 (Blanchette Rockefeller Neurosciences Institute) is a potent protein kinase C activator and an investigational anti-cancer agent. Results from different invitro and animal studies suggest the therapeutic potential of bryostatin; the drug is currently in phase II clinical trials.

The  $\gamma$ -secretase enzyme performs the processing of multiple class proteins at the basal level besides APP. One crucial molecule is the Notch protein that regulates cell proliferation, development, differentiation, growth, cell communication and cell survival status. Two main classes of drugs that act on the enzyme exist:  $\gamma$ -secretase inhibitors and modulators. The use of inhibitors totally blocks the enzyme and affects its processing of other proteins while  $\gamma$ -secretase modulators have a Notch sparing effect; despite the difference neither class of compounds has shown significant clinical success yet. Some molecules of the nonsteroidal anti-inflammatory drugs (NSAIDs) group have  $\gamma$ -secretase modulating activity. Tarenflurbil, the enantiomer of flurbiprofen modulates the  $\gamma$ -secretase activity and thereby reduce A $\beta$  levels (Eriksen et al., 2003). The phase II trial of the drug showed genuine promise, whereas the phase III trials proved to be a considerable disappointment and so, is no longer used. Subsequent analyses of the study results demonstrated the reasons for tarenflurbil's failure. In the study, CSF levels of tarenflurbil attained were much lower than the predicted concentrations from the preclinical evidence; in addition there was no change in CSF A $\beta$  levels (Galasko et al., 2007). The apparent benefit of

tarenflurbil in phase II trials was, in fact, due to an accelerated cognitive worsening in the placebo arm. The anti-inflammatory actions of tarenflurbil could also be a contributory reason for the observed failure (Imbimbo, 2009).

Semagacestat is another  $\gamma$ -secretase inhibitor that reached clinical setting, but in a large phase III trial the drug produced disappointing results and so abandoned before its completion (Imbimbo et al., 2011). Another specific  $\gamma$ -secretase inhibitor ELND006 showed therapeutic benefit in animal studies and was lead to clinical evaluation, but similar to semagacestat, the drug produced significant adverse effects and the clinical trials met with failure (Hopkins, 2011). The analysis of failure of two specific  $\gamma$ -secretase inhibitors has yielded valuable lessons. It became aware that the  $\gamma$ -secretase enzyme system plays a pivotal role in many signaling pathways mediated by proteins such as p75NTR, Notch, CD46 and about 50 additional substrates. Some of the proteins regulate cell survival, neurogenesis, cell communication, cholesterol metabolism and angiogenesis (Beel and Sanders, 2008). Hence the implications of targeting  $\gamma$ -secretase are not fully understood. The anti-amyloid effects obtained by inhibiting the enzyme have to be weighed against its affected physiological roles; this fact could be one of the major reasons for the failure of the  $\gamma$ -secretase inhibitors. The exact role of these drugs on A $\beta$  peptide dynamics is also not clear. A recent model based metanalysis has estimated that using the  $\gamma$ -secretase inhibitors the A $\beta$  levels drop at the time of dosage but increase during the dosing intervals. The net effect is that A $\beta$  levels increase over a 24 h period, which could provide a partial explanation for the failure of these drugs (Niva et al., 2013).

BMS-708163 (Avagacestat; Bristol-Myers Squibb) is a ' $\gamma$ -secretase modulator' with Notch-sparing effect; the drug had a favorable safety profile in a small phase II trial (Dockens et al., 2012). Two large studies in early as well as mild to moderate AD for a treatment period of 104 weeks are on-going (NCT00810147, NCT00890890). GSI-953 (Begacestat; Wyeth) is another Notch-sparing molecule that targets  $\gamma$ -secretase (Martone et al., 2009). The results from its phase II trial are not available (NCT00547560, NCT00959881). Few  $\gamma$ -secretase modulators like NIC5-15 have completed phase II trial while other drugs-E2212, GSI-1 are in different stages of development.

A variety of molecules targeting  $\beta$ -secretase are available, but only a few have entered clinical trials to date (Ghosh et al., 2012). CTS-21166 (CoMentis, USA) was one of the first molecules to complete phase I trials successfully, but it did not undergo subsequent testing (Hsu, 2010). MK-8931 (Merck, USA) has completed the phase I trial (NCT01496170) now in a phase II/III trial (NCT01739348). LY2886721 (Eli Lilly and company) is the other  $\beta$ -secretase inhibitor that is in phase I/II trial (NCT01561430). GRL-8234 is an experimental  $\beta$ -secretase inhibitor that has shown positive results in preclinical studies; when administered for a long term it demonstrates a reduction in A $\beta$  load in transgenic mice without adverse effects (Chang et al., 2011).

Posiphen<sup>®</sup> (QR Pharma Inc.) is a (+) enantiomer of phenserine, that decreases the levels of APP directly. By interacting with the 5'-untranslated region of APP mRNA, posiphen inhibits ribosomal access and blocks translation; it is thus effectively an APP synthesis inhibitor (Shaw et al., 2001). Posiphen and its principal metabolites also possess sufficient inhibitory effect on interleukin-1 $\beta$ , synthesis of  $\alpha$ -synuclein and AChE activity (Yu et al., 2013). In a small pilot study, posiphen showed favorable reduction in the levels of CSF biomarkers (Maccacchini et al., 2012); the compound is currently in a phase I trial (NCT01072812).

### 2.3.2. Modulating A $\beta$ transport

Apolipoproteins play prominent roles in A $\beta$  metabolism and transport (Fan et al., 2009); though they do not cross the blood

brain barrier, they regulate the movement of A $\beta$  between the central nervous system and periphery (Ladu et al., 2000). Apolipoprotein E $\epsilon$ 4 (ApoE $\epsilon$ 4) increases passage of A $\beta$  from blood to brain (Martel et al., 1997). This transport is receptor mediated, and the low-density lipoprotein receptor-related protein (LRP) plays a central role in the process (Zlokovic, 2004). With age, LRP expression decreases, impairing A $\beta$  efflux contributing to prolonged A $\beta$  stay in the brain (Shibata et al., 2000). Antibodies against LRP reduce A $\beta$  efflux from the brain (Shibata et al., 2000), and peripheral administration of soluble LRP to increase A $\beta$  efflux from brain has also been proposed as a potential treatment strategy in AD (Sagare et al., 2007).

Receptor for advanced glycation end products (RAGE) is a multi-ligand receptor that binds A $\beta$  with high affinity and facilitates the entry of A $\beta$  into CNS; A $\beta$  binds to RAGE at the blood–brain barrier and contribute to increased CNS entry, inflammation and neuronal death (Chen et al., 2007). The expression of RAGE increases in AD (Lue et al., 2001). PF-04494700 was the first oral small molecule antagonist of RAGE tried in humans; the drug had an acceptable safety profile in phase I trials (Sabbagh et al., 2011), but the phase II trial was a failure (NCT00566397). Creating a soluble RAGE receptor analog that would serve as a decoy receptor thus, reducing ligand binding is a valid approach. The infusion of soluble receptor has shown significant benefits in transgenic animals (Arancio et al., 2004). One such soluble RAGE receptor molecule TTP4000 (Trans-tech Pharma) is currently in phase I trials (NCT01548430). FPS-ZM1 is a novel multimodal and specific RAGE receptor developed recently. The studies with the compound has demonstrated significant blood brain barrier clearance, reduced amyloid deposition, and improved cognitive and cerebrovascular parameters in transgenic mice (Deane et al., 2012).

### 2.3.3. Decreasing A $\beta$ aggregation

Tramiprosate is a glycosaminoglycan that binds to monomeric A $\beta$ , preventing its oligomerization and aggregation (Wright, 2006). The drug demonstrated promising profile in phase II studies. A large phase III trial conducted subsequently had intriguing observations. The primary endpoints of the study did not show significant treatment related benefits. However, subsequent secondary analyses of data suggested the probable disease modifying benefits of the drug. Tramiprosate administration produced domain specific cognitive improvement in various aspects of memory, praxis skills and language (Saumier et al., 2009). Treated subjects showed a statistically insignificant but slowing down pattern of cognitive decline when assessed with Alzheimer Disease Assessment Scale–cognitive subscale but not with Clinical Dementia Rating – Sum of Boxes scoring (Aisen et al., 2011). Volumetric magnetic resonance imaging showed a significant reduction in hippocampal atrophy in drug treated subjects (Gauthier et al., 2009). Although the effect of tramiprosate on A $\beta$  appears beneficial, its effect on tau metabolism is unclear. An experimental study has shown that tramiprosate administration leads to unexpected tau aggregation, raising another potential warning statement (Santa-Maria et al., 2007).

ELND005 (Scyllo-inositol) is another compound known for its anti-oligomerization properties. The compound effectively decreased insoluble A $\beta$  and reversed cognitive decline in transgenic mice (DaSilva et al., 2009). A phase II trial evaluated different doses of the compound in mild to moderate AD patients, but only the low dose group completed the trial. Few phase II trials with ELND005 including a 12 week extension study are currently ongoing (NCT01766336, NCT01735630). Colostrinin or proline rich peptide complex was isolated first from ovine colostrum. The protein complex has strong immunoregulatory properties besides which it affects learning, memory and cognitive functioning (Janusz and Zablocka, 2010). Experimental data indicate colostrinin can

prominently inhibit the aggregation of A $\beta$  peptides and dissolve pre-formed fibrils (Janusz et al., 2009). One of the early pilot trials studied the effect of oral colostrinin for 3 weeks and observed positive outcome in subjects with AD (Leszek et al., 2002). A subsequent open label double blinded trial examined the dose effect for 30 weeks where colostrinin was able to increase the cognitive and daily activity of subjects with minimal adverse effects (Bilikiewicz and Gaus, 2004). The compound has not been tested subsequently. A recently characterized inhibitor of A $\beta$  aggregation D737 has shown significant benefits in *Drosophila* model (McKoy et al., 2012). Some novel peptoid compounds with anti-aggregation properties have also been developed (Luo et al., 2013).

The hormone melatonin, discussed under antioxidants also seems to possess anti-A $\beta$  aggregating properties. Administration of melatonin to A $\beta$ -overexpressing transgenic mice decreased senile plaque accumulation (Olcese et al., 2009); however, whether it is a direct effect of melatonin or secondary to its antioxidant and anti-inflammatory actions is not clear. Gelsolin an actin-binding protein is a key regulator of actin filament assembly and disassembly. Intracellularly gelsolin is present in the cytosol and mitochondria and extracellularly in plasma and cerebrospinal fluid (Kwiatkowski et al., 1988). Plasma gelsolin levels decrease in AD and the levels positively correlates with rate of decline in patients (Guntert et al., 2010). Experimental evidence suggests that gelsolin binds A $\beta$ , inhibits its fibrillization, dissolves the preformed A $\beta$  fibrils and accelerates its removal; therefore, it is another possible therapeutic candidate in AD (Chauhan et al., 2008).

#### 2.3.4. Increasing A $\beta$ clearance

Some proteases that degrade the A $\beta$  plaques are plasmin, neprilysin, insulin degrading enzyme, endothelin-converting enzyme, angiotensin-converting enzyme and metalloproteinase 9; a few other proteases also play a minor role (Nalivaeva et al., 2012). The levels of A $\beta$  degrading enzymes decline in AD which may contribute to A $\beta$  accumulation (Yasojima et al., 2001). Tissue plasminogen activator activates plasmin, but plasminogen activator inhibitor 1 blocks this action. Experimental evidence suggests that inhibitors of plasminogen activator inhibitor 1 decrease the plasma and brain A $\beta$  levels in transgenic animals (Jacobsen et al., 2008). Increasing neprilysin levels through viral vector-delivered gene expression has been successful in animal models (Marr et al., 2003). The peptide hormone somatostatin regulates A $\beta$  clearance through activation of neprilysin (Saito et al., 2005). The expression of somatostatin in the brain decreases with age (Gahete et al., 2010); therefore targeting neprilysin with somatostatin or its analogs is an option in AD. Recently small molecule activators of insulin degrading enzyme have also been identified. Although many protease inhibitors are available, the therapeutic benefit of the protease activators in AD is yet to be evaluated (Cabrol et al., 2009). Being a non-specific approach, use of protease inhibitors will require further evaluation. More controlled or targeted delivery approaches may play a valuable role in AD.

#### 2.3.5. Amyloid targeted immunotherapy

Results from animal experiments have shown the beneficial effect of anti-amyloid immunization approaches. AN1792 was the first active vaccine tried in humans. The vaccine used a full length aggregated amyloid peptide (A $\beta$ <sub>1-42</sub>). During the trial about 6% of subjects developed meningoencephalitis hence, was discontinued (Orgogozo et al., 2003). The initial results were discouraging, and CSF biomarkers or their cognitive performances did not show significant differences. Later it became clear that about 60% of patients responded with antibody production and neurophysiological test battery indicated favorable performance in them (Gilman et al., 2005). Volumetric imaging in the vaccine responders at 10–11

months showed an accelerated brain and hippocampal volume loss, but there was no reduction in cognitive scores (Fox et al., 2005). At the end of 4 years, there was a slowing down of functional decline in vaccine responders compared with placebo, but neither group had differences in cortical volume loss pattern (Vellas et al., 2009). Neuropathological examination in 8 vaccine treated subjects showed significant clearance of amyloid plaques (Holmes et al., 2008). Although following vaccination, the subjects showed a slowed cognitive decline and superior plaque clearance it did not stop their progression to severe stages (Holmes et al., 2008).

To avoid the non-specific immune response that might arise due to full length peptides, investigators designed the next generation vaccines against small epitopes. CAD106 has first 6 amino acids as the immunogenic sequence (A $\beta$ <sub>1-6</sub>). The vaccine treatment did not cause adverse effects in a 52 weeks trial; adequate antibody response occurred in more than 75% of subjects with two different dosages (Winblad et al., 2012). The vaccine has recently completed phase II trials (NCT00956410, NCT01097096). ACC-001 is another second generation vaccine currently in phase II trials (NCT01284387, NCT01227564, and NCT00479557). A few novel anti-amyloid vaccines like MER5101, Lu AF20513 have been successful in the pre-clinical studies and some candidate vaccines like ACI-24, Affitope AD-02/AD-03, UB-311 and V-950 are in different phases of development (Davtyan et al., 2013; Galimberti et al., 2013; Liu et al., 2013). More recently hybrid vaccines have come up; an orally administered A $\beta$ -RAGE complex vaccine has shown better results in transgenic mice than A $\beta$  administration alone (Webster et al., 2012).

Bapineuzumab is a humanized anti-A $\beta$  monoclonal antibody directed against its N-terminus. It was the first passive immunization therapeutic tried in AD, but the results from its phase II trial were inconclusive. APOE $\epsilon$ 4 carriers did not show treatment differences, but in non-carriers there was a significant improvement in cognitive and functional end points (Salloway et al., 2009). The investigators predicted that observation could be due to the increased amyloid plaque burden in APOE $\epsilon$ 4 carriers. The phase III trials did not show significant differences in the primary endpoint irrespective of the APOE $\epsilon$ 4 genotype, but they had a high incidence of amyloid related imaging abnormalities (Sperling et al., 2012). A few investigators initiated trials especially in APOE $\epsilon$ 4 carriers, but currently no trials on bapineuzumab are underway (Galimberti et al., 2013). In a pooled analysis of the results of CSF biomarkers from two trials, bapineuzumab arm showed significantly decreased levels of phosphorylated tau compared with placebo. CSF A $\beta$  levels were unchanged, but the total tau levels decreased significantly from baseline in the treated group (Blennow et al., 2012). Follow up neuropathological examination in 3 subjects administered with bapineuzumab has shown some intriguing findings. There was no difference in plaque densities or distribution between immunized and non-immunized subjects, but there was an increase in soluble A $\beta$  deposits with a low A $\beta$ <sub>42</sub>: A $\beta$ <sub>40</sub> ratio suggesting that bapineuzumab had an impact on A $\beta$  dynamics (Roher et al., 2013).

Solanezumab was the second anti-A $\beta$  antibody that entered trials in AD. The phase II trial with solanezumab did not show any treatment related benefits, but it produced a dose dependent increase in plasma and CSF A $\beta$ <sub>42</sub> concentrations (Siemers et al., 2010). Encouraged by the results solanezumab entered phase III trials (EXPEDITION 1 and EXPEDITION 2). Results of co-primary endpoints did not reach significance in both studies, but, pooled data analyses showed a significant reduction in cognitive decline in immunized patients (Tayeb et al., 2013); solanezumab is about to enter another set of phase III trials including the Asymptomatic Alzheimer's disease (A4) trial (Corbyn, 2013). Gantenerumab (Hoffmann-LaRoche) is another monoclonal antibody that has shown promising results in preclinical studies. Gantenerumab

preferentially interacts with aggregated A $\beta$  in the brain without affecting plasma A $\beta$  levels suggesting its systemic specificity (Bohrmann et al., 2012); the effect is dose dependent (Ostrowitzki et al., 2012). Gantenerumab is currently in a phase III trial (NCT01224106). Gantenerumab and solanezumab are together in a phase II/III trial that attempts to assess their potential in individuals at risk for dominantly inherited AD (DIAN TU; NCT01760005). To reduce the risk of Fc $\gamma$  receptor-mediated overactivation of microglia a novel antibody of IgG4 type-crenezumab (MABT5102A; Genetech) is available (Adolfsson et al., 2012). A phase II trial of crenezumab in mild to moderate AD is ongoing (NCT01343966). Alzheimer's Prevention Initiative trial will examine the benefit of crenezumab exclusively in individuals carrying Presenilin1 mutations (Corbyn, 2013). PF-04360365 has completed phase II trials, and results are awaited. A few other passive immunotherapeutics are in various stages of development include GSK933776A, NI-101, PF-05236812, RN6G, SAR-228810, BAN-2401 (Galimberti et al., 2013).

Even healthy volunteers have detectable levels of anti-A $\beta$  antibodies in their plasma, but the antibody titres decrease in AD (Weksler et al., 2002). A 6 month pilot study with 5 patients was one of the first reports of the benefit of IVIG administration in AD. There was no change in MMSE scores but the trial saw a decrease in CSF A $\beta$  levels with a concurrent increase in serum total A $\beta$  levels (Dodel et al., 2004). A subsequent different phase II study carried out IVIG infusion for 15 months with a 3 month interim discontinuation period. The levels of A $\beta$  in CSF decreased during the study period significant improvement in the MMSE score; however, A $\beta$  levels returned to baseline during the discontinuation (Relkin et al., 2009). In a dose finding phase II trial, IVIG (Octagam; Octapharm AG) produced a significant reduction in area under the curve for plasma A $\beta$  for one of its doses; the greatest reduction was in the second week interval, contrasting it from the other studies (Dodel et al., 2013). Baxter Corporation announced the results of their large phase III study recently. The preliminary analysis of data has yielded disappointing results with no significant treatment benefits in the treated group ([http://www. Baxter.com](http://www.Baxter.com)). The subsequent detailed analysis may provide valuable information.

#### 2.4. Targeting intracellular signaling cascades

A $\beta$  fibers activate various intracellular pathways, so drugs that disrupt the abnormal pathways could be useful in AD. cAMP signaling and nitric oxide/cGMP/cGMP-dependent protein kinase/cAMP responsive element-binding protein cascade is prominently linked to A $\beta$  induced synaptic deficits and memory loss associated with AD (Puzzo et al., 2009). In light of this process, pharmacologic inhibition of PDE provides significant benefit in experimental models. Caffeine and etazolate both possess PDE inhibiting activity that could play a role in their pharmacologic effects. Rolipram is a PDE-4 selective inhibitor that effectively reversed memory and cognitive deficits in A $\beta$  treated mice (Cheng et al., 2010); sildenafil, a PDE-5 inhibitor also produced similar results (Puzzo et al., 2009). Cilostazol inhibits PDE-3 activity and its administration protected transgenic mice from A $\beta$  mediated damage, decreased amyloid accumulation and tau phosphorylation (Park et al., 2011); benefit of cilostazol is currently under evaluation in demented subjects (NCT01409564). Some PDE inhibitors that are in preclinical stages of development include AVE-8112, BCA-909, GEBR-7b and THPP-1 (Froestl et al., 2013).

Growing evidence also indicates disturbed lipid signaling pathways in AD; arachidonic acid and phospholipases seem to be key mediators of A $\beta$  induced pathogenesis in animal models of AD. The levels of activated phospholipase A2 group IV isoform increase in the hippocampus of AD transgenic mice as well as patients with

AD (Sanchez-Mejia et al., 2008). Evidences also show that ablation of phospholipase A2 protects rats from cognitive deficits and decreases the levels of total tau in brain (Sanchez-Mejia et al., 2008; Schaeffer et al., 2011). Rilapladib is an oral inhibitor of lipoprotein associated phospholipase A2 that is currently in phase II trials (NCT01428453). Interestingly enough, activation of phospholipase A2 is also suggested as a strategy for cognitive enhancement in AD (Schaeffer et al., 2009). Aberrant phospholipase C signaling also contributes to cytosolic Ca<sup>2+</sup> surge and excitotoxicity. But, the value of its modulation is not clear because, phospholipase C appears to possess a differential role (Shimohama et al., 1998). Recently the role of phospholipase D2 has also been highlighted in AD (Oliveira et al., 2010).

#### 2.5. Tackling oxidative stress

Building oxidative stress is a crucial pathogenetic process in AD (Zhu et al., 2007) hence it becomes necessary to devise strategies that reduce the oxidative burden in cells.

##### 2.5.1. Exogenous antioxidants

Evidence for the protection offered by antioxidants including vitamins (E, C, and carotenoids), phytochemicals and synthetic compounds in AD is inconsistent. Administration of vitamin E in transgenic AD models at early ages reduced lipid peroxidation and plaque burden, but supplementation trials in humans have not shown convincing evidence of their benefit (Farina et al., 2012). Combination of vitamin E with donepezil did not provide additional benefit in patients with AD or mild cognitive impairment (Petersen et al., 2005). A phase III trial combining vitamin E with memantine was completed recently, and the results will answer the many queries that surround the benefit of vitamin E if any (Dysken et al., 2013). A phase III trial of vitamin E and selenium is currently ongoing (NCT00040378). Flavonoids and carotenoids, the other group of ubiquitous antioxidants have also shown neuroprotective effect in experimental setups (Kelsey et al., 2010; Khalili and Hamzeh, 2010). Rutin, a flavonoid compound, protected rats from stress induced damage and neuroinflammation induced by streptozotocin (Javed et al., 2012). Lutein is a natural carotenoid with cytoprotective effect (Vijayapadma et al., 2012); when supplemented in combination with docosahexaenoic acid, verbal fluency, memory scores and rate of learning improved in elderly women (Johnson, 2012).

The spice curcumin has shown several beneficial roles (antioxidant, anti-inflammatory, and amyloid-disaggregating properties) in experimental studies (Lim et al., 2001). Curcumin decreases A $\beta$ -induced inflammation and modestly inhibits  $\beta$ -secretase and AChE (Yang et al., 2005). Animal experiments have shown substantial benefits, but human studies report no significant differences in cognitive function between placebo and curcumin groups (Baum et al., 2008; Ringman et al., 2008). An 18 month study of curcumin in age related cognitive impairment is currently underway (NCT01383161). Other natural antioxidants such as blueberry (Joseph et al., 2003) red grape (Ho et al., 2009) have also been studied in transgenic mice, for their resveratrol content, and the results show reduced plaque burden and improvement in behavioral deficits (Karuppagounder et al., 2009). Epidemiologic studies in humans also show that moderate to mild wine consumption reduces the risk of dementia including AD (Orgogozo et al., 1997; Truelsen et al., 2002). Resveratrol is currently in a phase II trial (NCT01504854).

Melatonin is another potent antioxidant compound with additional pleiotropic effects. Several mechanisms contribute to the disease modifying potential, including inhibition of A $\beta$  generation, aggregation, formation of amyloid fibrils, attenuation of tau

hyperphosphorylation, mitochondrial protection antioxidant and antiapoptotic effects (Wang and Wang, 2006). Human studies show improved cognitive and neuropsychiatric performance including even in a progressed state when treated with melatonin (Cardinali et al., 2010). The utility of melatonin is not without controversy and reports indicate that the administration of melatonin after amyloid plaque deposition has occurred is not beneficial (Quinn et al., 2005) but may offer neuroprotection in the early stages of disease (Gunasingh et al., 2008). Currently a phase II trial with melatonin in prolonged release form is ongoing (NCT00940589). Melatonin receptor agonism has also been tried, but a short phase II trial with a melatonin agonist ramelteon was not able produce any significant treatment related parameters (NCT00325728). Neu-P11 is a novel melatonin agonist that has attenuated neuronal loss and improved memory performance in rats (He et al., 2013).

To summarize the section, in experiments antioxidant compounds show promising results, but their translation to the clinical situation is less successful. With regards to the natural compounds, the epidemiological data consistently show a decreased incidence of AD in the population. This has led to their large scale supplementation of trials, which have almost always yielded negative results. The failure of the natural compounds in human trials could be attributed to one of the many reasons. The other side of many antioxidant molecules is that they behave as pro-oxidants, depending on their concentration and cellular environment (Jones, 2006). This double edged nature of antioxidant compounds is one significant reason for their failure. The heterogeneity in the pharmacokinetic response, in a population, is also to be borne in mind. A study by Lloret et al. (2009) examined the antioxidant redox status in patients treated with vitamin E. Interestingly the subset of patients who failed to respond to vitamin E had lower glutathione levels in blood, compared to responders. The high dose therapy in that subset of non-responders led to rapid cognitive decline. The mechanism behind the non-responsiveness is not clear. Bioavailability and tissue distribution of drugs is also a factor that plays a role. Studies indicate that the bioavailability of vitamin E is different between smokers and nonsmokers so smoking could be a significant confounding factor in determining drug responses (Lodge, 2005). Curcumin's bioavailability is also dependent on various factors such as intestinal metabolism and absorption. Oral dosing fails to raise the serum concentrations of curcumin or its metabolites to detectable levels. The issue of their CNS clearance is, by far, the biggest issue that needs consideration while using them in AD. Having said that, the blood brain barrier clearance and CNS bioavailability following an oral dose of curcumin is a critical factor. Similar could be the case with resveratrol; due to an extensive first pass metabolism, the bioavailable concentration of resveratrol is only about 1% (Walle, 2011). Beyond tissue distribution, the ability of the compounds to penetrate into the mitochondria, the heart of cellular ROS production could be another crucial factor. Epidemiologically what we perceive as a beneficial relationship could be reflective of their cumulative protective role of these compounds. Results of different trials and experiments also point towards antioxidant's value in the early stages of the disease than when sufficient damage has already been done. Considering the long period of latency in AD, appropriate timing of the treatment could also be a significant determinant of a drug's success.

### 2.5.2. Facilitating endogenous antioxidant defense

The primary endogenous antioxidant pathway is the nuclear receptor factor 2 (Nrf2)/antioxidant response element (ARE) cascade. Nrf2 on activation gets translocated from the cytosol into the nucleus where it regulates the expression of several genes. This translocation process is blocked in AD; hence, different compounds that can reestablish the pathway are under consideration (Ramsey

et al., 2007). Facilitation of Nrf2 expression by tertbutylhydroquinone or adenovirus-mediated gene delivery techniques protects cells against A $\beta$  induced toxicity (Kanninen et al., 2008). Similar studies have also been conducted with other inducer compounds like triterpenoid CDDO-methylamide, and the effects have been encouraging (reduced plaque burden, A $\beta$ 42 levels, inflammation, and oxidative stress) (Dumont et al., 2009). Hence drugs inducing the Nrf2/ARE pathway could be a key approach for the treatment of AD. Peroxisome proliferator-activated receptor- $\gamma$  co-activator 1 alpha (PGC-1 $\alpha$ ) is another protein that plays multiple roles in mitochondrial biogenesis, energy metabolism and mitochondrial antioxidants expression. In the human brain tissues, the expression of PGC-1 $\alpha$  decreases with progression of dementia (Qin et al., 2009). PGC-1 $\alpha$  is a crucial transcription cofactor interacting with the nuclear receptor peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) thus regulating the downstream genes. PPAR- $\gamma$  agonists have also been studied as potential therapeutics for AD treatment, and observations have suggested that pioglitazone, activator of PPAR- $\gamma$  improves mitochondrial oxidative metabolism (Skov et al., 2008). In animal models pioglitazone modifies various indices of aging but does not slow down the cognitive decline (Blalock et al., 2010). Pilot studies demonstrate the value of pioglitazone in diabetic AD patients but not in nondiabetics (Geldmacher et al., 2011; Hanyu et al., 2009). The current evidence regarding the benefit of modulating the above pathways is still not sufficient.

### 2.6. Mitochondria specific therapy

Though the traditional antioxidants achieve their way tackling the produced reactive oxygen species (ROS), it is more relevant to control the source of ROS production; hence, mitochondrial drug targeting is tried for various disorders. Coenzyme Q10 (CoQ10) also known as ubiquinone, is a protein shuttling electrons from complex I and complex II in the electron transport chain (ETC). CoQ10 supplementation has potential neuroprotective effects including suppression of ROS production, minimized ROS injury and stabilization of mitochondrial function (Lee et al., 2009). The effect of CoQ10 in preclinical studies has been encouraging, but its effect, neither as monotherapy nor combination has been helpful in human studies. In one of the first phase III trials, CoQ10 did not show therapeutic benefit in Parkinson's disease; therefore, the study was terminated (NCT00740714). Idebenone, a water-soluble analog of ubiquinone has also been tried in humans; although an earlier study demonstrated dose dependent beneficial effects on cognition and disease progression for up to 2 years (Gutzmann and Hadler, 1998), a subsequent study found no significant effect (Thal et al., 2003). The lack of efficacy of the drugs could be due to the fact that both idebenone and CoQ10 require an intact and fully functional ETC and since mitochondria sustains defects in ETC in AD they may be of questionable value (Parker et al., 1994). Methylene blue (discussed earlier) also seems to serve as an alternative electron carrier, bypassing complex I/III blockage thus offering a role in neuroprotection (Wen et al., 2011). An imbalance in mitochondrial dynamics with altered levels of fission and fusion proteins also occurs with AD pathology (Wang et al., 2009); hence an agent that preserves mitochondrial dynamics may play a protective role in AD.

Other mitochondrial antioxidants that are under consideration include acetyl-L-carnitine and R- $\alpha$ -lipoic acid, both of which have demonstrated a reduction in oxidative stress and mitochondrial abnormalities in animals (Siedlak et al., 2009). Lipoic acid also seems to increase acetylcholine production, chelate transition metals, scavenge free radicals, and down-regulate the expression of pro-inflammatory proteins (Maczurek et al., 2008). Lipoic acid in combination with vitamin E and C was compared with CoQ10 or

placebo in a small phase I trial. It was observed that there was a lowering of CSF isoprostane levels in the first group indicating a reduction in oxidative stress, but other groups did not show changes (Galasko et al., 2012). However this beneficial effect on oxidative stress did not reflect in the CSF A $\beta$ , total or phosphorylated tau levels and contrastingly a faster cognitive decline occurred in subjects (Galasko et al., 2012). Lipoic acid and omega-3-fatty acids combination therapy are currently in two phase I/II trials (NCT01780974, NCT01058941).

One promising compound for mitochondrial targeted treatment is the triphenylphosphonium linked ubiquinone derivative, MitoQ (Kelso et al., 2001). MitoQ selectively accumulates in the organelle, continually recycled by mitochondrial enzymes, and it can function even in the absence of an intact ETC, which makes it a potent antioxidant compared to the untargeted ones (Murphy and Smith, 2007). Szeto-Schiller peptide (SS-31) is also a novel mitochondrial targeted ROS scavenger therapy; both MitoQ and SS-31 have shown good results in cell lines (Manczak et al., 2010). However, MitoQ treatment produced disappointing results in a phase II trial in Parkinson's disease patients (Snow et al., 2010). MitoVitE is a potential follow up compound of MitoQ. Selective mitochondrial penetrating cations like SkQR1 and C12R1 have also been identified recently (Chernyak et al., 2013).

Opening of mitochondrial permeability transition pore (mPTP) is a key event in mitochondrial dysfunction, so compounds blocking the process are evaluated in AD. Studies of the antihistamine drug dimebon indicated its ability to block mPTP opening and protect against cellular dysfunction and death (Bachurin et al., 2001). Phase II trial of the drug showed improvement in cognitive scores in the treated group, which led to phase III trials with interest (Doody et al., 2008), but the trials did not show clinical improvement (Jones, 2010). The failure of dimebon was a tremendous disappointment. So what are the reasons for dimebon's failure? Dimebon is a drug with a complex pharmacology and several potential targets. At its working concentration dimebon is capable of inhibiting AChE and also interact with 5-HT<sub>6</sub>, dopamine 1, 5-HT<sub>4</sub> and 5-HT<sub>3</sub> receptor amongst others (Okun et al., 2010). Hence the cognitive outcome would be dictated by the balance between the pro-cognitive (AChE inhibition, 5-HT<sub>4</sub> activation) and anti-cognitive (5-HT<sub>6</sub> stimulation on pyramidal cells and 5-HT<sub>3</sub> stimulation on inhibitory interneurons) effects. The complex interaction of dimebon along with the alteration in the receptor levels that occur with disease progression can in part explain the lack of benefit in the larger studies (Geerts et al., 2012). In addition, polymorphisms in *COMT* Val158Met gene modify the interaction of dimebon with dopamine 1 receptor; hence, genotype variation in the population could contribute modestly to the pharmacodynamic profile. Although some mitochondrial therapeutics exists, their translation into the clinical setting is not successful. A key aspect that would need attention in this regard would be to consider the impact of drugs on the normal functioning tissue mitochondria. Compounds that will selectively targets diseased mitochondria will be extremely helpful in the setting of neurodegenerative diseases.

### 2.7. Targeting cellular Ca<sup>2+</sup> handling

Since perturbed Ca<sup>2+</sup> homeostasis is one of the major mechanisms in AD, it is prudent to evaluate drugs that target different Ca<sup>2+</sup> signaling pathways. Memantine produces modest decreases in Ca<sup>2+</sup> influx thus reducing excitotoxicity (Lipton and Chen, 2004). Pre-clinical evidence suggests that antagonists of NMDA receptor with GluN2B subunit (ifenprodil and Ro25–6981) and ligands of metabotropic mGluR5 receptors (MPEP) protect neurons from A $\beta$  toxicity (Rammes et al., 2011). EVT-101 is one of the few GluN2B antagonists to complete a phase I trial (NCT00526968). Novel

strategies modulating mitochondrial Ca<sup>2+</sup> handling have been reviewed already (Hung et al., 2010). In animal studies both minocycline (Garcia-Martinez et al., 2010) and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) (Sanz-Blasco et al., 2008) show mitochondrial membrane depolarization and reduce Ca<sup>2+</sup> intake inside the mitochondria. Minocycline in addition, has an effect on voltage dependent anion channels (Garcia-Martinez et al., 2010). KB-R7943 is a selective inhibitor of the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger which causes depolarization of isolated brain mitochondria and reduces mitochondrial Ca<sup>2+</sup> uptake (Storozhevych et al., 2010). The A $\beta$  induced disturbances of Ca<sup>2+</sup> homeostasis also seem to be attenuated by Ginkgo biloba extract (EGb761) (Shi et al., 2010), but long term use of the compound did not provide protection from cognitive decline when compared to placebo (Vellas et al., 2012). Another interesting finding was that trifluorocarbonylcyanide phenylhydrazine (FCCP) a strong uncoupler inhibited mitochondrial Ca<sup>2+</sup> surge triggered by A $\beta$ <sub>1–42</sub> oligomers (Sanz-Blasco et al., 2008). Although the findings are encouraging, FCCP is a toxic drug. The direct effect of NSAIDs on mitochondrial membrane potential has also not been well established accordingly. A specific but low potency compound that modulates the uncoupling proteins may have therapeutic benefits. The effect of thyroid hormones, the physiological uncoupler on Ca<sup>2+</sup> homeostasis is also intriguing (Cole et al., 2012). Thyroid hormone supplementation also seem to lessen cognitive deficits in a mouse model of AD (Fu et al., 2010), but its value in humans is yet to be studied. Although during supplementation, a concern of interfering with the thyroid hormone axis does exist, the approach warrants detailed investigation.

### 2.8. Anti-inflammatory therapy

The abundant evidence for neuroinflammation in the disease process had prompted various work groups to try NSAIDs in AD. Benefit of NSAIDs may involve a variety of mechanisms apart from their cyclooxygenase inhibition like maintaining Ca<sup>2+</sup> homeostasis, targeting  $\gamma$ -secretase (Weggen et al., 2003), Rho-GTPases (Fu et al., 2007), and PPAR (Nicolakakis et al., 2008). Through their effect on Rho-GTPases, NSAIDs manage various phenomena related to AD including axon growth (Fu et al., 2007), tau phosphorylation (Sayas et al., 1999), and astrocyte motility (Lichtenstein et al., 2010). Numerous epidemiological studies and clinical trials regarding the benefit of NSAIDs in AD are available (Imbimbo et al., 2010). The epidemiological data point to a reduced incidence of AD in NSAID users (Cornelius et al., 2004; Lindsay et al., 2002), but data from most clinical trials in AD and mild cognitive impairment have either shown neutral or harmful effects (Aisen et al., 2003; Reines et al., 2004). A few studies show that NSAIDs are effective only in the ApoE $\epsilon$ 4 carrier subpopulation (Hayden et al., 2007; Szekely et al., 2008). The disappointing results from clinical trials led to a decrease in pursuance of anti-inflammatory therapy in AD. However a recent study has rekindled the hope of NSAIDs in AD; administration of a COX-1 selective inhibitor, SC-560 in triple transgenic mice has reduced inflammation, neuropathology and improved cognitive performance (Choi et al., 2013). The reasons for the failure of the NSAIDs in AD may be related to the inhibitory effects on microglia. It is well known that ApoE $\epsilon$ 4 allele confers an inflammatory state in the brain when compared with ApoE $\epsilon$ 3 (Vitek et al., 2009). Physiologically, microglial cells seem to play prominent roles in the clearance of A $\beta$  plaques by the process of phagocytosis and also by secreting various proteases (Lee and Landreth, 2010). The evidence for the role of microglia and their inflammatory mediators in modulating neurogenesis is also compelling (Ekdahl et al., 2009). The clearance function declines with age wherein accumulation of plaques continues in spite of increasing microglial numbers (Hickman et al., 2008). Considering the

complex microglial interaction in brain functions, the result of anti-inflammatory treatment is difficult to be predicted.

## 2.9. Other approaches in AD

### 2.9.1. Gonadotropins

Various studies have reported the relationship between AD and the hormone dyshomeostasis secondary to reproductive senescence. The hormones—testosterone, estrogen and progesterone, are neuroprotective, but their levels decrease with aging. Luteinizing hormone (LH), on the other hand, supports the disease process, but the concentrations increase with aging (reviewed in (Barron et al., 2006)). Though the role of the hormones may not be direct or strong, they could significantly contribute to the pathogenesis. The role of hormone replacement therapy (HRT) is still controversial; studies indicate that prior use of HRT decreases the risk of AD in women, but current use is not useful unless used more than 10 years (Zandi et al., 2002). Another recent study shows that low dose estrogen therapy decreases the risk of AD (Yue et al., 2007) the benefit is more in non- $\epsilon 4$  population (Burkhardt et al., 2004). Testosterone supplementation in males improves cognition and quality of life showing protective as well as therapeutic effects (Lu et al., 2006). Since LH and follicle stimulating hormone levels continue to remain elevated in spite of cyclical estrogen and progesterone therapy, modulation of gonadotropin (GnRH) levels might be more valuable than individual hormones themselves. GnRH agonist, leuprolide attenuated cognitive decline and decreased A $\beta$  deposition in AD transgenic mice (Casadesus et al., 2006). In phase II trials of the compound, female patients demonstrated improvement in cognitive function (NCT00076440). A slow pellet release form of leuprolide underwent a phase III trial, but the results are not available (NCT00231946). The role of GnRH antagonists in AD is not known.

### 2.9.2. Lipid modifying therapy

Given the wealth of evidence linking hypercholesterolemia and AD, statins have been extensively studied for their therapeutic benefits. Studies with statins highlight its pleiotropic effects and dose-dependent beneficial effects on cognition, memory and neuroprotection (Li et al., 2006). Statins modify the properties of plasma membrane by diminishing cholesterol levels and modulating the secretase activities thus decreasing amyloidogenic APP processing (Buxbaum et al., 2002). They also seem to alter neuronal activity by cholesterol independent effects such as modifying the protein prenylation of different small GTPases altering their function (Cordle et al., 2005). A possible role for the compounds in cholinergic homeostasis is also suggested; simvastatin inhibits AChE in rats (Cibickova et al., 2007) and prevent the blockade due to AChE inhibitors at  $\alpha 7$ -nicotinic AChRs (Mozayan and Lee, 2007) thus enhancing cholinergic neurotransmission. Statins also protect primary cortical neurons from glutamate toxicity (Bosel et al., 2005). It is seen that low dose statins prevent aberrant neuronal entry into mitosis (Sala et al., 2008), activate anti-apoptotic pathways (Merla et al., 2007) and suppresses inflammation (Cordle and Landreth, 2005), but higher doses of statins have been detrimental and shown to evoke toxic effects (Fonseca et al., 2010).

Evidences consistently show that statins provide neuroprotection and improve disease pathology in animal models, but results have been disappointing in human trials. Controlled release lovastatin administration has shown a dose dependent decrease in serum A $\beta$  levels in non-AD subjects (Friedhoff et al., 2001). However, large trials with high dose statins have failed to demonstrate treatment benefit in patients (2002; Feldman et al., 2010; Shepherd et al., 2002). A small study in AD subjects evaluated the cognitive performance during discontinuation and re-challenge of statins.

Strikingly, there was an increase in MMSE score during drug discontinuation; re-challenge led to cognitive worsening (Padala et al., 2012). The results of a subsequent phase III trial with simvastatin in patients with AD were also disappointing (Sano et al., 2011). A clinical trial of the drug in subjects with mild cognitive impairment is ongoing (NCT00842920).

### 2.9.3. Growth factors

Cholinergic neurons are nerve growth factor (NGF) sensitive and dependent; so neurotrophic factors administration is tried to maintain neurogenesis and cell survival in neurodegenerative disorders. Animal studies show beneficial results when treated with neurotrophic factors (Jonhagen, 2000). Attempt to deliver NGF gene therapy has also been tried in animal and human experiments. The earlier studies delivered gene through implantation of autologous fibroblasts; the method was able to slow down cognitive decline in subjects and PET imaging demonstrated an increase in functional activity of brain (Tuszynski et al., 2005). Virus mediated gene deliveries are also in development. CERE-110 is an adenovirus based NGF gene delivery vector; the stereotactical administration was successful in animal studies, which has prompted, human experiments. Following a successful pilot study, CERE-110 is currently in a phase II trial (NCT00876863). Recently more sophisticated modes of NGF delivery have come up. In the novel encapsulated cell bio-delivery method, an NGF producing human cell line is stereotaxically implanted in the brain (Eriksson-Jonhagen et al., 2012; Wahlberg et al., 2012). The cell line is encapsulated by a semi-permeable membrane such that it allows the influx of nutrients and efflux of NGF in the target regions. A small phase Ib trial in humans showed successful results; the implantation, as well as, retrieval procedures were uneventful, and a year later sustained NGF secretion was still detectable (Wahlberg et al., 2012). A new grade cell line capable of delivering NGF levels 10 times more efficiently has shown promising results in preclinical studies (Fjord-Larsen et al., 2012).

Cerebrolysin<sup>®</sup> (Ever Neuro Pharma) is a porcine derived peptide that possesses neurotropic properties, and has gained attention recently; the peptide has demonstrated clinical efficacy in several randomized trials (Plosker and Gauthier, 2009). Combination therapy of AChEI and cerebrolysin has synergistic effects in mild to moderate AD (Allegrì and Guekht, 2012). The other conditions where use of cerebrolysin is considered are acute ischemic stroke, traumatic brain injury and vascular dementia. Manufacturer sources indicate that cerebrolysin is permitted for use in about 44 countries (including some of the countries in the Commonwealth of Independent States), but, is yet to be approved by the US food and drug administration (Anton Alvarez and Fuentes, 2011). A phase IV trial comparing the value of cerebrolysin over donepezil is currently ongoing in Austria (NCT01822951). The painless form of nerve growth factors is also available; intranasal route of administration has shown successful results in transgenic animals (Capsoni et al., 2012). Numerous small peptide mimetics of tyrosine receptor kinase signaling are in preliminary stages. Small molecule brain derived neurotrophic factor mimetics with specificity towards TrkB have shown considerable effectiveness in improving neuronal survival, inducing differentiation and augmenting synaptic function (Massa et al., 2010). Although preliminary results with different approaches to NGF/growth factor therapy have been encouraging, the issue of aberrant nonspecific neurogenesis needs careful consideration (Fumagalli et al., 2008).

### 2.9.4. Metal chelators

Evidence suggests that metal dyshomeostasis in the brain could be a critical mechanism opening the door to the other

processes of neurodegeneration. However improbable this idea may seem, transition metals participate in the redox reactions and oxidative stress generation in AD (Bondy et al., 1998). The metal chelating properties of A $\beta$  peptides are also known (Hiller and Asmus, 1981); in turn, it could contribute to the pro-oxidant effect of A $\beta$ . While metal chelators like desferrioxamine, ethylenediaminetetraacetic acid can attenuate the effects of A $\beta$ , their rapid degradation, ability to negotiate the blood brain barrier and hydrophilicity are serious concerns (Stone et al., 2011). In transgenic mice, DP-109, a nonspecific experimental chelator compound effectively reduced amyloid burden (Lee et al., 2004). Few analogues of 8-hydroxyquinoline referred to as the metal protein attenuating compounds have shown tremendous potential. The compounds differ from traditional chelators in that they have good blood brain barrier clearance and do not remove metal ions from other tissues, and instead inhibit nonspecific interactions. One of the first generation molecule clioquinol (PBT-1) specifically inhibits zinc and copper ions from binding to A $\beta$ . PBT-2 was a successor molecule of clioquinol. Both the compounds bind copper and zinc avidly, prevent their interaction with A $\beta$ , decrease oligomerization of A $\beta$  and promotes their dissolution; experimental data suggest their beneficial effect on cognition and memory in animals (Adlard et al., 2008; Wang et al., 2012). In phase II trial clioquinol administration decreased CSF A $\beta$  levels in subjects, but did not show treatment related improvements in cognitive scores or MMSE (Ritchie et al., 2003); a subsequent phase III trial and production of the compound were halted. PBT-2 was taken into phase II trials in early 2007 to assess its safety and tolerability. The compound showed admirable overall safety profile. The decrease in CSF A $\beta$  levels and cognitive outcome pattern were similar to clioquinol, but there was a statistically significant improvement in executive function Z scores (Lannfelt et al., 2008). Larger studies would be required to clarify the role of PBT-2 in AD.

Nanoparticles conjugated metal chelators are a recent development, and they show neuroprotection invitro (Liu et al., 2006). Another advancement is the tagging of molecules with a signal moiety, thus ensuring blood brain barrier clearance and target specificity (Scott et al., 2011). Multifunctional 3-hydroxy-4-(1H)-pyridinone pro-ligands are the compounds in which 3-hydroxy-4-pyridinone structure functions as low toxicity metal chelator with antioxidant, antibacterial and analgesic properties while a dye like thioflavin-T detects and binds amyloid deposits in tissues (Scott et al., 2011). Although the idea sounds exciting, more studies are needed to demonstrate their role in AD treatment.

### 2.9.5. Epigenetic modulation

The role of epigenetics in AD did not seem relevant until recently, but now they are thought to provide the much needed reason to the beginning of the pathophysiological events. DNA methylation and histone modifications are the two basic epigenetic modifications. Epigenetic events may provide the supposed connection between gene regulation and environment; evidences suggest that environmental factors [diet, heavy metals, maternal care and intrauterine exposures] may disturb gene regulation during early development and increase susceptibility to developing persistent deficits much later in life (Lahiri et al., 2007, 2008). In such a situation, drugs that alter the DNA methylation and histone acetylation could hold the key to the treatment of AD. The DNA methylation process is complex, and the enzymes and metabolites regulating methylation homeostasis are shown in Fig. 2. The enzymes are dependent on the availability of essential cofactors: folate, vitamins B12 and B6. The disturbance in methylation homeostasis that occurs in AD could in turn be a result of a deficiency of one of the vitamins. This theory has prompted the supplementation of the above vitamins in AD. In

humans there are reports showing a protective effect of B vitamins in AD (Corrada et al., 2005) while some, showing otherwise (Morris et al., 2006; Nelson et al., 2009). Randomized control trials examining the benefit of high dose vitamin supplementation have observed no benefit in improving cognitive decline (Aisen et al., 2008; Galasko et al., 2012). Some novel approaches utilizing combination to create nutrient cocktails have shown benefits in both animal and clinical studies (Ahmed, 2012; Chan et al., 2008; Parachikova et al., 2010). 5-azacytidine treatment of peripheral lymphocyte cultures has shown differential chromosomal sensitivity in AD patients when compared to controls thus indicating the potential of methylation modifiers (Payao et al., 1998).

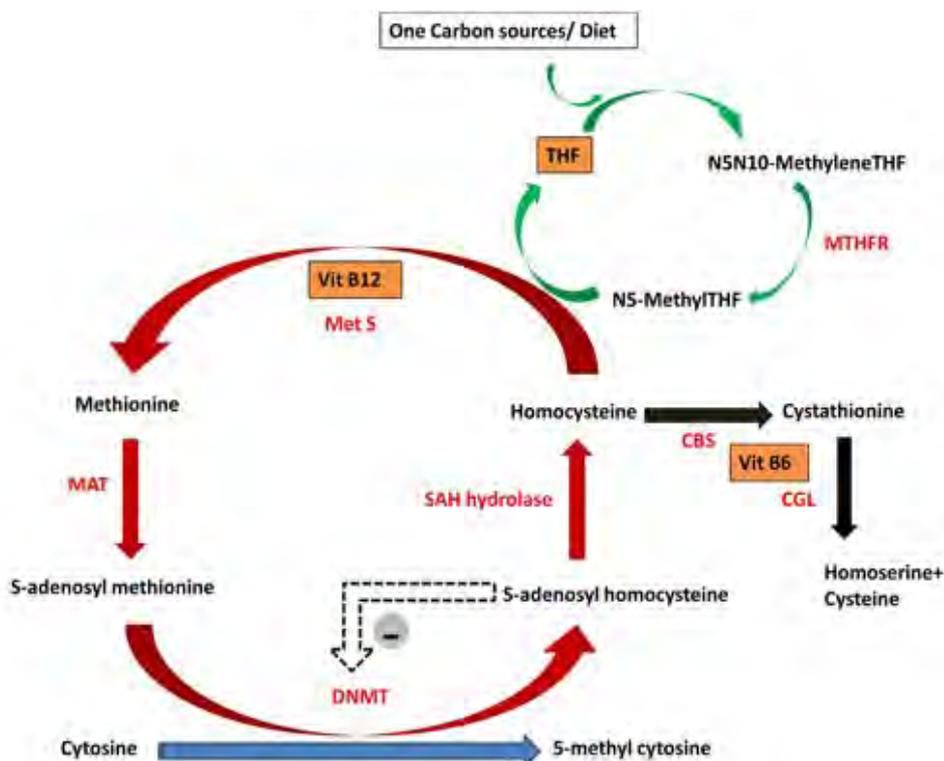
To modify the histone acetylation process in AD, inhibition of both histone acetyl transferase (HAT) and histone deacetylase (HDAC) is under consideration. The antiepileptic drug valproate possesses HDAC inhibiting activity, but its use in humans has not been successful so far. Trials have demonstrated worsening of agitation and aggression, accelerated brain volume loss and cognitive decline in AD patients receiving valproate compared to placebo (Fleisher et al., 2011; Tariot et al., 2011). HAT inhibitors are also currently evaluated because, histone acetylation increases in AD. Curcumin also inhibits HAT activity (Kozikowski et al., 2009; Lim et al., 2001). Although, many epigenetic mechanisms underlie AD pathophysiology, the value of pharmacologic modulation of the above mechanisms is yet to be understood.

### 2.9.6. Caspase inhibition

Caspases, the cysteine family of proteases are critical enzymes that orchestrate the apoptotic pathways. They can be classified briefly as initiator (caspases-2, 8, 9 and 10) and executioner enzymes (caspases-3, 6 and 7). At least 7 caspases (caspases-1, 2, 3, 6, 8, 9, and 12) are implicated in A $\beta$  mediated neuronal death, of which, caspase 6 is the best known (Nikolaev et al., 2009). Inhibition of caspase enzymes as a therapeutic strategy for neurodegenerative disorders is also under consideration. A number of experimental inhibitors for caspases are available, but they are non-specific; recently some selective non-peptide inhibitors have also been developed (Lee et al., 2000; Leyva et al., 2010). Caspase inhibitors, both selective and non-selective have neuroprotective benefits in experimental setups (Ross et al., 2007) but their feasibility as therapeutics is not known yet.

### 2.9.7. Nitric oxide synthase modulators

Nitric oxide (NO) is one of the three gasotransmitters known, and it performs multiple roles in CNS function. NO plays a role in maintaining cognitive function (Chien et al., 2003, 2005), neurotransmitter secretion (Karanth et al., 1993), sleep-wake cycle (Cavas and Navarro, 2006), appetite control (Vozzo et al., 1999) and body temperature homeostasis (Lacerda et al., 2005) and neuroprotection. The physiological functions are controlled by multiple signaling pathways and both genomic and non-genomic effects of NO play a role. The genomic effects are probably mediated by Akt pathway and the cyclic responsive element binding protein (Riccio et al., 2006). NO also seems to protect the neurons from excitotoxicity through its effect on NMDA receptors as well as caspase inhibition (Jaffrey et al., 2001; Mannick et al., 2001). The major concern with NO is its pro-oxidant role at high concentrations, when it can lead to the formation of reactive nitrogen species aggravating cell damage. Nitric oxide synthase (NOS), the enzyme system also presents significant complexity. Studies also suggest that NOS-2 isoform is neuroprotective (Colton et al., 2006) whereas NOS-3 is pro-apoptotic (de la Monte et al., 2007). Thus, modulation of NOS and NO system is complicated, and its therapeutic benefit is debatable as of now.



THF- Tetrahydrofolate, MTHFR- Methylene tetrahydrofolate reductase, Met S- Methionine synthase, MAT- Methionine adenosyl transferase, SAH Hydrolase- S-adenosyl homocysteine hydrolase, DNMT- DNA methyl transferase, CBS- Cystathionine beta synthase, CGL- Cystathionine gamma lyase

Fig. 2. Enzymes involved in DNA methylation system.

### 2.9.8. Nucleic acid drugs

Another relatively new approach is the development of nucleic acid based drugs for treatment of neurodegenerative diseases; some of which include plasmid DNA (pDNA) or antisense oligodeoxynucleotides such as nuclear factor  $\kappa$ -B (NF- $\kappa$ B) decoy based options. They are currently in experimental studies and early phases of clinical trials. One strategy is to provide neurotrophic factors using naked pDNA incorporated with the genes of neurotrophic factors. pDNA can also be used as a DNA vaccine since the molecule is immunogenic thus stimulates the dendritic cells and promotes a T-cell response (Coban et al., 2008). By special delivery approaches, Th2 mediated response can be potentiated specifically. Since this property is ideal for vaccination in AD (which requires a predominant Th2 response) several studies have examined the effectiveness of DNA vaccination and A $\beta$  clearance in animals (Qu et al., 2006, 2004). Targeting NF- $\kappa$ B mediated inflammatory response by creating a decoy also appears to be an attractive strategy. This approach is currently under consideration in cerebrovascular diseases (Yoshimura et al., 2001).

### 2.9.9. Multi-target directed ligands

The complexity of the mechanisms involved in AD has prompted the researchers to develop compounds that could simultaneously interact with several potential targets (multi-target directed ligand design) (Youdim and Buccafusco, 2005). Variety of compounds with dual or multiple target specificities are in development. They interact with different mechanisms, therefore, provide symptomatic and

disease modifying benefits; for instance, compounds with dual AChE and BACE inhibition or AChEI with antioxidant properties (for an excellent review (Bajda et al., 2011)). Ladostigil (TV3326) is one such multifunctional compound in which the carbamate moiety of rivastigmine is transferred on to 6th position of rasagiline (Weinstock et al., 2000). By its blocking AChE, ladostigil can increase cholinergic neurotransmission; with the inhibitory effect on monoamine oxidase-A and B, it improves the extrapyramidal symptoms and provides an anti-depressant effect. It decreases amyloidogenic APP processing. It offers neuroprotective and neurorestorative activities and decreases apoptosis (Youdim and Weinstock, 2001). The compound has shown significant promise in preclinical studies and is currently undergoing two phase II trials in mild cognitive impairment and mild to moderate AD (NCT01354691, NCT01429623). M30 is a next generation compound with similar properties currently in experimental studies (Kupersmidt et al., 2012).

### 3. Conclusion

To summarize, the pathophysiology of AD involves disturbances and imbalances occurring in a variety of mechanisms. It surprises that, in spite of the wealth of knowledge that exists regarding AD, only a handful of options are available currently for its management. The disease process is also complex in its own ways. Symptomatic treatment is the best part of the management currently, however, exciting, and incredible leaps have taken place in developing disease modifying approaches. Recent evidences indicate the disease

modifying potential of the previously thought symptomatic drugs (AChR ligands and memantine) of drugs that their proper usage will improve the clinical outcome in AD. Immunotherapy to stimulate endogenous removal of A $\beta$  and tau is another attractive option. A few of these approaches such as anti-inflammatory therapy, metal chelation, antioxidant supplementation, epigenetic modifications appear non-targeted and instead untimely; hence, the results show more harm than good. Some innovative approaches such as DNA vaccination, NOS modulation, or caspase inhibition are still in their infancy; it might be too early to comment upon them.

Looking back at the failed anti-amyloid and antioxidant drug trials make us think- is the amyloid theory as we know still valid? Have we understood the disease process correctly? Assuming the understanding is right, the failures could represent one or several of the following reasons that have led to the failure of trials: 1. Incomplete understanding of the drug's pharmacokinetics and bioavailability- curcumin and tarenfluril are ample examples whose CNS bioavailability is limited following oral dosage. 2. Unanticipated off-targets- drugs with complex pharmacology may be able to interact with a variety of other receptors and enzymes Eg. Dimebon. In such a case the drug's overall effect would be determined by a balance between the productive and counter mechanisms. The pharmacodynamic implications of the off-target actions can show differential effects on the pathology. Some drugs like tramiprosate have a beneficial effect on amyloid metabolism but aggravate tau pathology. 3. Inappropriate timing- the long latency period of AD adds another dimension in its complexity wherein the principal mechanisms change with the time course and progression of the disease. Antioxidant therapy may be helpful in the early stages of the disease, but not when sufficient damage has already been done. Opposite is the case with memantine- useful in moderate to severe stages, but not in early AD. 4. Inappropriate dosage- low doses of statins are beneficial, but the higher dosages are detrimental. 5. Population heterogeneity- wherein the genotype of the population determines the drug response Eg. Differential response of bapineuzumab in ApoE4 carriers/non-carriers. 6. Incomplete reporting of data from failed trials and diversity in assessment scales that hinder pooled data analyses. 7. Failure to include biomarkers to follow up in the trial. Hence, the question still remains where have we gone wrong? Are the negative results from several clinical trials a failure of the compound or of the experimental design? If the early epigenetic events affect the susceptibility of an individual to AD, how do we stop that? With the abundance of answers available, perhaps it is time we start asking the right questions.

#### Author contributions

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#### Conflict of interest

The authors declare that there are no conflicts of interest.

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