ABSTRACT

Alzheimer’s disease is an age-related central nervous disorder that has created daunting challenges for the treating physicians, the families and the society. Alzheimer’s disease, a leading neurodegenerative disorder worldwide, is a major cause of dementia in the developed and developing countries around the globe. While, there is no definitive cure for Alzheimer’s disease and no treatment is available to reverse or halt its progression. Currently Food Drug Administration approved acetylcholinesterase inhibitors and memantine, a N-methyl-D-aspartate receptor antagonist for the treatment of Alzheimer’s disease. Moreover, new therapeutic approaches, including those more closely targeted to the pathogenesis of the disease, are being developed. This potentially disease-modifying therapeutics includes both beta and gamma secretase inhibitors, cholesterol-lowering drugs, amyloid-beta immunotherapy, non-steroidal anti-inflammatory drugs, hormonal modulation and the use of antioxidants. In this current review we summarize the available evidences on the newer therapeutic approaches for the treatment of Alzheimer’s disease.
1. INTRODUCTION

Alzheimer’s disease (AD) is an age related; particularly the elderly people aged more than 65 years are increasing victims of this disease [1]. In the beginning, AD presents with memory impairment that progressively worsens leading to concomitant declines in other cognitive abilities and behaviors, which result in the complete functional dependency that defines the dementia phase of the illness [2]. AD is the most common cause of dementia. It is the leading contributors to disability among elderly people and imposes an intolerable burden on healthcare systems, society, patients and their families [3]. It is the sixth leading cause of death for all ages and the fifth leading cause of death for those 65 years of age and older in the United States [4]. Recently in 2013 Alzheimer’s disease International has reported that about 44.4 million people worldwide are suffering from AD associated dementia. In addition of this report predicted that the number of dementia patients will increase to an estimated 75.6 million in 2030, and 135.5 million in 2050. Majority of the increase of dementia patients will be from developing countries, and at present 62% of people with dementia are from developing countries and by 2050 this will further rise to 71% [5,6]. Globally it affects more than 115 million people [7].

Till date no drugs are available that can completely cure the disease. Currently available drugs for the treatment of AD include cholinesterase inhibitors such as donepezil, rivastigmine, galantamine, N-methyl-D-aspartate (NMDA) receptor antagonist, memantine and neuroprotective agents [6,8], disease modifying drugs, are still under extensive research [9,10]. Because of potential evidence supporting a neurotoxic role of tau modifications and aggregation in AD, currently research attention has focused to tau as a target for AD therapies [11]. Most recent advances have also been made with radiotracers involving visualization of tau aggregates [12], along with the development of treatment strategies based on inhibitors of tau modification and/or aggregation. Thus the present review provides an up to date insight in the area the pharmacological strategies for AD treatment and recent development in this field.

1.1 Progression of Alzheimer’s Disease

Genetic alterations, polymorphisms, and abnormal immune or inflammatory responses are among the possible risk factors of AD. Factors such as level of education, lack of exercise, traumatic injury, oxidative stress, drugs, hormonal replacement and interactions are among these factors that have been considered as the provider of contributing role to a pathway leading to development of AD [13,14]. Various hypotheses have been put forward regarding the development and progression of AD, but it is simply an age related neuron degeneration and destructions of brain memory. The death of nerve cells causes the memory failure, mood changes and disabled to carry out daily activities. A very important conceptualized hypothesis is amyloid hypothesis and tau hypothesis, Figure 1. The accommodation of senile plaques (SP) and neurofibrillary tangles (NFTs) collectively leads to decline in cognitive function [15]. Plaques are dense in nature and get deposited on protein around the neurons. Senile plaques consist of amyloid-beta (A-beta) produced from amyloid precursor protein (APP).

Tau, is a requisite essential protein in development of normal axonal and neuronal growth. The critical role of NFT in AD pathophysiology is suggested by the correlation between location and density of tau NFT and the symptoms and severity of AD associated dementia [16]. It has been reported that fibrillar A induced tau phosphorylation by the progressive and sustained activation of mitogen-activated protein kinase (MAPK) pathways in mature hippocampal neurons induce induction of Fas ligand that causes death of neuron cells which further leads to dementia [17].

The relationship between Aβ protein aggregation and neurotoxic mechanisms as an additional mechanism in the pathogenesis of AD is represented in Fig. 2. Inflammation associated with trauma or other factors will promote oxidative stress and result in generation of reactive oxygen species, which may cause direct neurotoxicity or lipid damage and aggregation of Aβ protein. Amyloid plaques are made of Aβ peptides and upon breakdown it produces Aβ40 and Aβ42. The amyloid- Aβ42 peptide when gets aggregated and results in the formation of oligomers, protofibrils and fibrils that leads to the generation of AD [18]. Lipid peroxidation products modify the three residues of Aβ42, which increases its membrane affinity and result in acceleration in the conversion of Aβ40 into oligomers and fibrils. These oligomeric Aβ
proteins bind copper ions in the moment they undergo redox cycling. During this process highly reactive oxygen species may be produced by electrons liberated from copper or produced in form of by-products of inflammation. In addition as ApoE4 alleles lack thiol-mediated antioxidant activity that may allow excess oxidative damage in lipoprotein particles, particularly lipid. As advance age itself is linked with reduced tissue levels of antioxidant and accumulated oxidative lipid damage, low levels of adventitial Aβ protein aggregation takes place. These processes promoting further Aβ protein aggregation causing further damage in the system. In the time course of any of these processes, direct neurotoxins may be generated and furthermore Aβ proteins may lead to formation of pores, channels or any other disruptive neurotoxic structures in neuronal membranes.

Moreover, some studies have demonstrated that Aβ oligomers are not toxic unless tau is also present [19]. In the hippocampus area of brain there occurs granulovascular degeneration. Cytokines are also reported to play crucial role in the pathogenesis of AD leading to tissue damage. Oxidative stress of brain cells further damages the normal function of brain [20,21].

The cholinergic deficiency has been related to cognitive decline and behavioral changes of AD. The synthetic enzyme choline acetyltransferase
and the catabolic enzyme acetylcholinesterase are significantly reduced in the cerebral cortex, hippocampus, and amygdala in patients with AD [22]. In addition to these, other determinants such as herpes simplex infection, zinc & copper metals and environmental factors are also reported to be involved in the pathogenesis of AD [23,24].

2. METHODS

All published literature including research papers, clinical trials and reports were searched by using electronic resources such as MEDLINE (PubMed), Cochrane Central Register of Controlled Trials, EMBASE, CINAHL, US Clinical Trial Registry and Google Scholar. The data were retrieved from these resources using various key words such as “clinical trials on Alzheimer’s disease”, “Alzheimer’s disease”, “donepezil in Alzheimer’s disease”, “memantine in Alzheimer’s disease”, metformin in Alzheimer’s disease”, “side effects of Alzheimer’s disease drugs”, “pipeline drugs in clinical trials for Alzheimer’s disease”, “anti-inflammatory drugs in Alzheimer’s disease”, use of zinc and copper in Alzheimer’s disease, oestrogen in Alzheimer’s disease, G-protein coupled receptors and Alzheimer’s disease “vitamin E, vitamin D and vitamin C for Alzheimer’s patients”.

Published literatures over the period of 1990-2016 were considered for this current systematic review. The selection criteria also relied upon the fact that the published literatures must be in English, mainly focused on Alzheimer’s disease and its therapy. No restrictions were made on the type of outcome measures used. The exclusion criteria were made by not considering those articles which were published on or before 1990. Further, the review also excludes literature from case reports, books, notes and letters to the editor. Out of 15729 from PUBMED and 806 from Google scholar were searched and 129 articles were used in this review. All searched research publications and clinical trials data were scrutinized and required information were extracted and summarized in this present review article. The data obtained were reviewed and analyzed depending upon the importance of drug therapy support or failure for the management of Alzheimer’s disease.

3. RESULTS

3.1 Treatment Options

The research has been consistently carried out since 30 years and researcher have made a very good progress but still available drugs are not satisfying the complete treatment for AD. The Alzheimer’s disease is still not having any good treatment option and it’s a reality. This has been become a very big challenge for this modern world of science. As per the clinical data available for clinical trials, 316 clinical trials have been conducted worldwide [5]. If anyone see more details very few are under phase III clinical trials and have got success since last 10 years [25,26]. The National Institute for Health and Care Excellence (NICE) has recommended the important guidelines regarding treating strategy for AD and dementia. It explains that specialist doctor should prescribe drugs with relation to the patient’s cognition, behavior and ability to cope with daily life. These guidelines also explain about proper initiation of cholinesterase inhibitors.

3.2 FDA Approved Drugs

Five drugs are currently approved by the US Food and Drug Administration (FDA) for treating cognitive symptoms of AD. In view of the existing pathophysiology the FDA has approved anticholinesterase agents and NMDA receptor antagonist for the management of AD. A summary of these drugs is presented in Table 1.

3.2.1 Anticholinesterase agents

Tacrine is a very good old agent which has characteristics as a non-competitive, irreversible inhibitor of acetyl- and butyrylcholinesterase. Tacrine was the first anticholinesterase drug that has been approved for the symptomatic treatment of AD [27]. This drug later identified as the hepatotoxic agent which has limited efficacy. Because of this tacrine is no longer used in clinical practice. However, donepezil was identified as an alternative agent. It is a reversible inhibitor of acetylcholinesterase having a long elimination half-life. This drug produces no hepatotoxicity but frequently causes nausea, vomiting and diarrhoea. Donepezil is also accepted as neuroprotective drug [28]. A dose of 10 mg/day of donepezil was suggested to improve cognition among AD patients. Currently pharmacological agents approved by United States Food and Drug Administration (USFDA) for the treatments of AD include donepezil, galantamine and rivastigmine [29]. Galantamine improves arterial function, however galantamine have shown higher mortality rates and bradycardia in AD patients [30]. Another drug rivastigmine is a slow reversible carbamate
inhibitor that blocks cholinesterase activity through binding at the esteratic part of the active site. Unlike donepezil that selectively inhibits acetylcholinesterase, rivastigmine inhibits both butyrylcholinesterase and acetylcholinesterase. It is approved by USFDA for the treatment of mild-to-moderate AD [31]. Early and continued treatment of AD with rivastigmine provides beneficial effects in the rate of decline of cognitive function, activities of daily living, and severity of dementia with daily doses of 6 to 12 mg [32]. Rivastigmine is preferably used transdermally to minimize gastrointestinal side effects in mild to moderate Alzheimer’s disease [33].

### 3.2.2 N-methyl-D-aspartate receptor antagonist

The most suitable drug of this category is memantine. It has been approved for Alzheimer’s disease by USFDA. Many clinical trials have showed a positive response when given in single therapy or in combination with acetylcholinesterase inhibitors. This drug has shown a progressive effect on patients with moderate to severe AD. This drug is helping to modify cognition, function and behaviors of this type of patients. It is also experimentally proved that this drug is neuroprotective and has positive impacts on both neurodegenerative and vascular processes. Their important therapeutic action lies in its uncompetitive binding to the N-methyl-D-aspartate receptor (NMDAR). Moreover, this drug has very low side effects profile [34,35].

### 3.2.3 Side effects

Many studies reported common adverse drug reactions that lead to hospital admission in elderly patients. The most common side effects associated with these drugs for the AD are nausea, vomiting, diarrhea, weight loss and loss of appetite. However, hepatotoxicity is reported to be associated with the use of tacrine in AD patients [41,42,43]. Tacrine is no more used in the therapy of AD. A comparative study reported more frequent adverse events in rivastigmine group than in donepezil group during the titration phase, but similar in the maintenance phase. The authors reported serious adverse events in 31.7% of rivastigmine and 32.5% of donepezil-treated patients [36]. A systematic meta-analysis documented the lowest incidence of adverse events for donepezil and the highest for rivastigmine. The same study reported relative risk of global response to be better with donepezil and rivastigmine compared with galantamine [37]. Among all the early FDA approved drugs rivastigmine has severe side effects. From the literature it has been observed that among acetylcholinesterase inhibitors donepezil has less side effects with compare to other AD drugs. Donepezil is safe for liver impairment and moderate to severe renal impaired patients. A summary of side effects induced by various drugs used for the treatment of AD is presented in Table 1.

### 3.2.4 Drug interactions

Although all available AD’s medications do not produce serious drug interactions that are clinically significant, however, certain medications used concomitantly to treat other medical conditions such as infection, seizure disorders, irregular heartbeats, high blood pressure, anxiety or depression may affect AD. Medications that potentially worsen a person’s mental status includes acid suppressants, antiarrhythmics, antibiotics/anti-infective, anticonvulsants, antidepressants, antihistamines, antihypertensive, anti-parkinsonian agents, antipsychotics, antispasmodics/muscle relaxants and sedative-hypnotics [44,45,46]. Other pharmacological agents such as oxybutynin and tolterodine are used to control urine output in elderly patients and these agents potentially decrease or counteract the effects of the cholinesterase inhibitor medications used to treat AD, making them less effective options [47,48].

### 3.3 Pipeline Drugs in Clinical Trials

Numerous candidate drugs with differing pharmacological mechanisms have been proposed in the recent years and tested in neurobiological models of AD. However, many of those agents showing signs of future success that had been attributed to some of these compounds in animal models failed to prove beneficial effects to humans in early clinical phases. The newer pharmaceutical compounds currently undergoing pre-clinical and clinical phase studies are summarized in Table 2.
### Table 1. Summary of FDA approved drugs for Alzheimer’s disease [36,37]

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanism of action</th>
<th>Indication</th>
<th>Side effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Prevents breakdown of acetylcholine in brain, nicotinic receptor stimulation, mitigation of excitotoxicity, and influencing APP processing.</td>
<td>All stages of Alzheimer’s disease</td>
<td>Nausea, vomiting, diarrhea, weight loss, loss of appetite and increased frequency of bowel movements</td>
<td>[36,37]</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Prevents breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in brain</td>
<td>Mild to moderate Alzheimer’s disease</td>
<td>Nausea, vomiting, diarrhea, weight loss, loss of appetite</td>
<td>[37]</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Inhibits both butyrylcholinesterase and acetylcholineesterase and revents breakdown of acetylcholine and butyrylcholine</td>
<td>Mild to moderate Alzheimer’s disease</td>
<td>Nausea, vomiting, diarrhea, weight loss, loss of appetite, muscle weakness</td>
<td>[36,37]</td>
</tr>
<tr>
<td>Tacrine</td>
<td>Prevents breakdown of acetylcholine in brain</td>
<td>Mild to moderate Alzheimer’s disease</td>
<td>Liver damage, nausea, vomiting, diarrhoea</td>
<td>[38]</td>
</tr>
<tr>
<td>Memantine</td>
<td>N-Methyl-D-aspartate receptor antagonist, Blocks toxic effects associated with glutamate excess and regulates glutamate activation</td>
<td>Moderate to severe Alzheimer’s disease</td>
<td>Dizziness, headache, constipation, confusion</td>
<td>[39,40]</td>
</tr>
</tbody>
</table>

### Table 2. Newer therapy details targeted for disease modification in Alzheimer’s disease

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Therapeutic targets</th>
<th>Current status</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANI 1792</td>
<td>Vaccine-active immunization</td>
<td>Discontinued at phase 1 due to severe meningoencaphalitis</td>
<td>[49,50]</td>
</tr>
<tr>
<td>CAD 106</td>
<td>Vaccine-active immunization</td>
<td>Phase II</td>
<td>[51]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III trial</td>
<td></td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>Beta amyloid monoclonal antibody</td>
<td>Terminated in Phase III</td>
<td>[52,53]</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>Beta amyloid monoclonal antibody</td>
<td>No clinical benefit</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III completed</td>
<td>[54]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no improvement of cognition or functional ability</td>
<td></td>
</tr>
<tr>
<td>Ponezumab</td>
<td>Beta amyloid monoclonal antibody</td>
<td>Stopped at phase II</td>
<td>[55]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No efficacy</td>
<td></td>
</tr>
<tr>
<td>Getenerzumab</td>
<td>Beta amyloid monoclonal antibody</td>
<td>Phase III ongoing</td>
<td>[52,56]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical significant effect was observed</td>
<td></td>
</tr>
<tr>
<td>Crenezumab</td>
<td>Beta amyloid monoclonal antibody</td>
<td>The first fully human antibody</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crenezumab is a passive immunotherapy</td>
<td>[52,57]</td>
</tr>
<tr>
<td>Compounds</td>
<td>Therapeutic targets</td>
<td>Current status</td>
<td>References</td>
</tr>
<tr>
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</tr>
<tr>
<td>Semagacestat</td>
<td>Gamma secretase inhibitors</td>
<td>Failed to slow cognitive decline or improve global functioning in patients with mild to moderate Alzheimer's disease</td>
<td>[55]</td>
</tr>
<tr>
<td>Avagacestat</td>
<td>Gamma secretase inhibitors</td>
<td>Stopped at phase II</td>
<td>No efficacy with risk of skin cancer</td>
</tr>
<tr>
<td>GRL-8234</td>
<td>Beta secretase inhibitor</td>
<td>Ongoing rescues age-related cognitive decline in mice</td>
<td>Due to gastrointestinal and dermatological side effects nonmelanoma skin cancers</td>
</tr>
<tr>
<td>TAK-070</td>
<td>Beta secretase inhibitor</td>
<td>Ongoing</td>
<td>No clinical data available</td>
</tr>
<tr>
<td>CHF5074</td>
<td>Nonsteroid anti-inflammatory drug</td>
<td>Ongoing Phase 2</td>
<td>Phase 1: CH 5074 was reported to be safe and tolerable in these subjects; one notable side effect was mild diarrhea.</td>
</tr>
<tr>
<td>DAPT</td>
<td>Prototypal gamma secretase inhibitors</td>
<td>Ongoing</td>
<td>Preclinical studies</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Anti amyloid aggregator</td>
<td>Ongoing: future agent</td>
<td></td>
</tr>
<tr>
<td>Affitope A D03</td>
<td>Targets modified beta-amyloid peptides</td>
<td>Phase II ongoing</td>
<td></td>
</tr>
<tr>
<td>AAB-003</td>
<td>Passive anti amyloid immunotherapy</td>
<td>Phase I ongoing</td>
<td></td>
</tr>
<tr>
<td>AMBAR</td>
<td>Aluminum replacement</td>
<td>Phase III ongoing</td>
<td></td>
</tr>
<tr>
<td>Tideglusib</td>
<td>Inhibits glycogen synthase kinase-3</td>
<td>Phase 2 completed</td>
<td></td>
</tr>
<tr>
<td>Huperzine A</td>
<td>AChE inhibitor</td>
<td>Phase 2/3; completed</td>
<td>↑cognitive function, daily living activity, global clinical assessment</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Anti-inflammation and antioxidation</td>
<td>Phase 1; ongoing</td>
<td>↑cognitive function</td>
</tr>
<tr>
<td>Compounds</td>
<td>Therapeutic targets</td>
<td>Current status</td>
<td>References</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td>PUFA</td>
<td>Lipoic acid</td>
<td>With other nutrients. Approved drug for arthritis; may modulate immune system; benefit AD patients</td>
<td>[73]</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>PDE inhibitors</td>
<td>Phase 4; completed</td>
<td>[73]</td>
</tr>
<tr>
<td>EVP-6124</td>
<td>AChE inhibitor</td>
<td>Phase 3; ongoing</td>
<td>[73]</td>
</tr>
<tr>
<td>AVP-923</td>
<td>Glutamatergic agents</td>
<td>Phase 2; ongoing</td>
<td>[73]</td>
</tr>
<tr>
<td>Idalopirdine (AE58054)</td>
<td>Serotonergic agents</td>
<td>Phase 3; ongoing</td>
<td>[73]</td>
</tr>
<tr>
<td></td>
<td>5-HT6 receptor antagonist</td>
<td>Positive results in a phase 2 RCT, 278 participants, 6 months; Several phase3 RCTS with donepezil (AChEI)</td>
<td></td>
</tr>
</tbody>
</table>
3.4 Metabolic Correction

It is being convincing that diabetes type 2 is playing very important role to stop the progression of dementia and leading to severe Alzheimer’s disease [74]. In this target of therapy, brain cells are treated with insulin modification therapies to rule out the insulin problem. Clinical trials are still going on to verdict the final benefits of antidiabetic drugs. Study looking for antidiabetic drugs to consider as potential candidate for AD [34]. Liraglutide is an acylated glucagon-like peptide-1 (GLP-1) agonist, is under clinical trial. Scientists considering it as future potent drugs that could be an option to treat AD as it has shown very promising results in pre-clinical study [74]. The known mechanism of liraglutide in AD is that it reduces the amount of amyloid-β (Aβ) and improves cognition capacity of brain. The reported study used 1.8 mg daily dose of liraglutide [20]. It also been expected that other antidiabetic drugs such as rosiglitazone and pioglitazone act as insulin stimulant by decreasing the serum level of glucose. It is also reported that it could promote cholesterol and neuronal Ca^{2+} homeostasis and reduce cerebral inflammation through inhibition of interleukin-6 (IL-6) and tumor necrosis factor (TNF) [21]. Recently new concept has been introduced and intranasal insulin is one of the therapeutic option available in the clinical trial. It has been transported across olfactory and trigeminal perivascular channels and axonal pathways [25]. Because of this insulin has an ability to enter the brain within a short time of period. A randomized, placebo-controlled study explained the effects of intranasal insulin on memory improvement in individuals with AD. The subjects of study were treated with intranasal insulin (20 IU twice daily) that resulted in greater improvement in the memory and attention within a three week period. The subjects have great success, which were with apoe4 gene negative allele [27]. This study report suggested that in patient of AD with diabetes, intranasal insulin may have different effects depending on the apoe4 genotype.

The experimental brain diabetes produced by intracerebral administration of streptozotocin shares many features with AD, including cognitive impairment and disturbances in acetylcholine homeostasis. Experimental brain diabetes is treatable with insulin sensitizer agents, i.e., drugs currently used to treat type 2 diabetes mellitus. Metformin belong to the biguanides that have very good effect in controlling serum blood glucose level which sensitizes the utilization of insulin receptors. Clinical trial studies are investigating the effect of metformin in patients with AD. It is expected that in future this antidiabetic drug could play a very important role to treat memory loss in diabetic patients [28,29].

3.5 Muscarinic Receptor Agonists

M1-type muscarinic acetylcholine receptors have a role in cognitive processing, however, they appear relatively unchanged in the disease process of AD. They have become a potential therapeutic target for improving cognitive function in patients with AD [75,76]. A number of muscarinic agonists have been developed and are under investigation to treat AD. These agents decrease amyloid depositions and reduce oxidative stress induced damage. In a study conducted in mice with small hippocampi, AF150 (S) and AF267B restored cognitive impairments. Further, in aged and cognitively impaired microcebes, prolonged treatment with AF150 (S) restored cognitive and behavioral impairments and reduced tau hyperphosphorylation [76]. Recently few clinical trials are in the hunting process to use second generations of muscarinic agonists as the therapeutic options for AD. Those drugs include milameline and xanomeline. In controlled clinical trials, xanomeline and milameline have shown moderate clinical efficacy, however these agents have produced mild to moderate parasympathomimetic side effects [77,78]. None of these cholinomimetics has been marketed at the present time.

3.6 Glutamate Receptor Antagonists

Glutamate works as excitatory neurotransmitter and it regulates excitatory synapses. The ionotropic N-methyl-D-aspartate (NMDA) receptor plays a crucial role in neuroplasticity and memory formation. It is postulated that excessive activation of the NMDA receptors by glutamate exhibit an important role in the neurodegenerative changes observed in AD [79,80]. Memantine has been available for clinical use in Germany for the treatment of AD for the past 10 years [81]. It has been proved by experimental studies that NMDA antagonist prevent neurotoxicity [82]. Memantine has been proven to be used in improving cognitive dysfunction in patients with mild AD. Benefits with memantine monotherapy in an outpatient study have also been reported. In patients with moderate to severe AD receiving a stable dose
of donepezil, the addition of memantine results in significant improvement in cognitive, functional, and global outcomes compared with placebo [83].

3.7 Anti-inflammatory Drugs

Inflammatory process has a fundamental role in the pathogenesis of AD, evident by elevation of cytokines, protein and activated microglia. A research has reported that prolong use of non-steroidal anti-inflammatory drugs significantly decrease risk of incidence of AD in patients. A number of anti-inflammatory drugs have now been tested for their therapeutic efficacy in AD [84,85]. Prednisolone, a steroidal drug and non-steroidal drugs like diclofenac and indomethacin are good candidate for AD treatment, unfortunately inducing high frequency of side effects. But in contrast to that ibuprofen and sulindac manage to decrease toxicity by reducing antibodies [86]. The most beneficial results was observed with the study of propentofylline. This drug inhibits the action of microglia release inflammatory cytokines [87].

3.8 Chelating Agents

Free plasma copper is the toxic form of copper, which catalyzes amyloid formation thereby generating oxidative stress, free radicals and degeneration of cortical neurons. Age related free copper toxicity is one of the causal factors in pathogenesis of Alzheimer’s disease [88]. Chelating agents are reducing the zinc and copper concentration in the brain of patient with AD. Numerous chelating agents have been investigated for their potential to treat neurodegeneration. A recent review conducted by Budimir reported a series of 8-hydroxyquinoline analogues showed the greatest potential for the treatment of neurodegenerative diseases [89]. Cliquinol and analogs are possible future chelating agents might be useful for the treatment of AD [90,91]. Currently copper and iron chelating or redistribution therapies are being developed and investigated for Alzheimer’s disease but are not yet ready for clinical trials [92]. However, further more research is needed to prove these techniques are safe and can prevent disease.

3.9 Oestrogens

Women have a higher AD incidence than men, pointing that the declining oestrogen levels during menopause may influence pathophysiology of AD. Oestrogen depletion in post-menopausal women represents a significant risk factor for the development of AD and that an oestrogen replacement therapy may decrease this risk and even delay disease progression [93,94]. It has been reported that women who are on oestrogen therapy have shown beneficial effect on cognitive function of brain. The oestrogen and phytoestrogens had shown a very good effect on AD patients who are on hormone replacement therapy. These types of woman have shown improvement in cognitive function of brain [95,96]. However, limited information is available regarding the beneficial effects of oestrogen in AD.

3.10 Antioxidants

Free radicals are neurotoxins as it is initiating neuronal death and increased oxidative stress. Few drugs are suspected to be useful as antioxidants such as vitamin C, vitamin E (α-tocopherol) and free radical scavenger, selegiline. In addition to the free radical scavenging activity of selegiline, inhibition of MAO-B is one of the most accepted mechanism of action for its neuroprotective effect [97]. Further, vitamin E has shown beneficial effects in moderately severe and mild to moderate AD. A study reported benefits of vitamin E among patients with mild to moderate AD. Dosage of 2000 IU/d of alpha tocopherol resulted in slower functional decline. The study findings suggested beneficial effects of alpha tocopherol in mild to moderate AD by slowing functional decline and decreasing burden to the caregiver [98,99]. The treatment of mild cognitive AD with vitamin E is debatable topic as other study reported no benefit in patients with mild cognitive impairment over donepezil therapy. A double-blind, placebo-controlled, randomized, multicenter trial proved that selective monoamine oxidase inhibitor selegiline (10 mg per day), alpha-tocopherol (vitamin E, 2000 IU a day) can be one of the therapeutic options to treat of moderately severe patients of AD [99,100]. Many researchers are struggling to find out the treatment of AD with vitamin C as a supplementary therapy. A study was conducted by Galasko et al. [101] to check the beneficial effects of antioxidant on progression of AD. In seventy-eight randomly selected subjects of the treatment duration for 16 weeks with 800 IU/d of vitamin E plus 500 mg/d of vitamin C plus 900 mg/d of α-lipoic acid; 400 mg of coenzyme Q 3 times/d, the combined effect was studied. The result suggested reduction of oxidative stress in brain. It is
considering using as supportive therapy in elderly people who are having age related AD [102]. However, this treatment raised the caution of faster cognitive decline in AD patients.

### 3.11 Secretase Inhibitors

As per hypothesis that the aggregated antibodies is the cause for AD, so pharmacological agents having properties of preventing or modulating the synthesis of amyloid-β protein might be helpful in the treatment of AD. In view of that research interest was focused for looking drug therapies towards amyloid precursor protein processing. Further, clinical research studies were initiated with semagacestat and tarenflurib (R-enantiomers of flurbiprofen) as secretase inhibitor and modulator, respectively. Unfortunately the results were very inferior to placebo, so this study was not completed and stopped [103,104]. Study on GSI-953 (begacestat), a novel thiophene sulfonamide gamma-secretase inhibitor (GSI) orally active compound in human amyloid precursor protein-overexpressing Tg2576 transgenic mouse, exhibited a robust reduction in brain, plasma, and cerebral spinal fluid Abeta levels, and a reversal of contextual fear-conditioning deficits that is correlated with Abeta load. Also, in healthy human volunteers, oral administration of a single dose of GSI-953 produced dose-dependent changes in plasma Abeta levels, confirming pharmacodynamic activity of GSI-953 in humans [105]. Furthermore, beta secretase 1 (BACE1) inhibitors are a new and promising target for Alzheimer’s disease. Recent study reported that BACE1 inhibition reduced dendritic spine dynamics, reduced neurotransmission, and impaired cognition; however, these disruptive effects were reported as dose dependent [106].

### 3.12 Vitamin D

Receptors for vitamin D have been found in many parts of the brain. Brain is protected by vitamin D from being damaged by plagues and tangles in AD. Various researches reported that vitamin D deficiency may worsen AD and they are somewhat interlinked [107,108,109]. A study results indicated that vitamin D deficiency is associated with a risk of all kind of dementia and AD [110]. Gezen et al. [111] suggested that AD could be the result of a long-term hormonal imbalance in which the critical hormone is vitamin D, a secosteroid that has long been misnamed. A review article concluded that vitamin D clearly has a beneficial role in AD and improves cognitive function in some patients with AD. Calcitriol, 1α,25-dihydroxyvitamin D3, is best used for AD because of its active form of vitamin D(3) metabolite and its receptor in the central nervous system [112]. Study reported combined use of vitamin D3 and docosahexaenoic acid as an emerging novel strategy to enhance direct immune protection of neurons against brain amyloidosis and other brain insults [113]. Furthermore, a recent trial reported combined use of memantine and vitamin D as superior to either memantine or vitamin D alone in halting the cognitive decline amongst patients with AD [114]. Although, vitamin D is a vital for metabolism of bone, calcium absorption and other metabolic processes in the body. Its role in brain function, cognition and the aging process is still unclear. Some studies suggested that vitamin D may be involved in a number of processes related to cognition, but more evidence is needed to better understand this complex relationship.

### 3.13 Immunotherapy for Amyloid

An active and passive immunization option was also tried to reduce the problems in AD patients in various clinical trials but no satisfactory results was observed. A passive immunization therapy was initiated by humanized monoclonal antibodies targeting amyloid-beta peptide (Abeta) oligomers. The clinical trial conducted for bapineuzumab was unsuccessful particularly for cognitive outcomes. The major safety problem of bapineuzumab was that it has induced severe side effect of transient vasogenic edema, in approximately 10% of patients [110,115]. Another drug solanezumab was started involving patients of mild to moderate AD, unfortunately this study results also failed to satisfy the need of AD treatment in its phase trial 3 [54]. Further a study reported that prophylactic administration of 1,4-di-O-methyl-aclyo-inositol to TgCRND8 mice attenuated spatial memory impairments and significantly decreased cerebral amyloid pathology. The authors suggested that abeta aggregation can be targeted at multiple points along the kinetic pathway for the improvement of Alzheimer’s disease associated pathogenesis [116].

### 3.14 Statins

It’s becoming a very famous that statin category drug simvastatin, a inhibitor of HMG-CoA reductase could be a good future candidate to minimize the development of AD. This drug is
acting as anti-amyloid drug. As per FDA recommendation simvastatin is still not active drug for the use of AD [117]. The clinical data obtained was not encouraging that would have warrant the use of simvastatin in clinical practice [118].

3.15 G-protein Coupled Receptors

G protein-coupled receptors (GPCRs) are involved in a number of important neurotransmitter systems in the brain that are disrupted in AD. Emerging evidences into the mechanistic link between GPCRs and AD signifies the potential of this class of receptors as a therapeutic target for AD. Human formyl peptide receptor-like 1(FPRL-1) is a G-protein coupled seven transmembrane receptor which is under studies to use for the treatment of Alzheimer’s disease [119]. In this FPRL1 therapy, it is suggested that this GPCR would mediate the chemotaxis of microglia by abeta42 peptide. In brain neurons FPRL1 has tendency to interact with both neurotoxic Aβ42 and the protective factor humanin (HN). So it is been targeted to utilize the beneficial effect in large interest to reduce neuronal death [120]. The 5-HT6 receptor ligands under GPCR is an another future options that may be a powerful strategy for the treatment of Alzheimer’s disease. Numerous ligands that includes ST1936, GSK215083, SB-271046, Ro-4368554 and SB-258585 has been recently reported that may provide valuable therapeutic options for the treatment of AD. Recently phase II trials of SB-742457 has been completed in mild-to-moderate AD patients [121].

A high-throughput functional genomics screen identified G protein-coupled receptor 3 (GPR3), a constitutively active orphan G protein-coupled receptor, as a modulator of amyloid-beta production. According to research published in the journal Science reported that overexpression of G protein-coupled receptor 3 (GPR3), a constitutively active orphan G protein-coupled receptor, stimulated amyloid-beta production, whereas genetic ablation of GPR3 prevented accumulation of the amyloid-beta peptide in vitro and in an Alzheimer’s disease mouse model [122]. Laboratory mice with Alzheimer’s disease like symptoms showed improvements in learning, memory and social skills when they lacked GPR3.

3.16 Other Options

Epidemiological studies provide important contributions to presenting new bases for future management of AD. Recently a study suggested that risks of developing AD can be decreased by smoking tobacco and it was further suggested that nicotine inhibits neuronal apoptosis which prevents the Aβ25–35-induced neurotoxicity [123], pointing a starting point to new therapeutic approaches. A study reported that aquilaria subintegra leaves can treat AD, probably via acetyl choline inhibition [124]. Extract of milk thistle can inhibit the formation of amyloid by silymarin [125]. Extracted compounds from plants such as Nigella glandulifera Freyn et Sint with anti-inflammatory properties could provide a complementary therapy [126].

Newer approaches are under investigation and some have already shown promising results in the treatments of AD patients. The immunotherapies that increase Aβ accumulation in preclinical models [127], categorised as metabolic-based therapies [128] are representing example. Another example described by Xia and Liu for the treatment of AD is metal chelation suggested as metal binding with Aβ [129].

4. CONCLUSION

Many clinical trials have been conducted and some are still in progression. A limited clinical trials has provided effective and productive results. Some hypoglycemic agents such as metformin and liraglutide have been proved beneficial in AD mainly by decreasing the risk of cognitive impairment. Till date there is no confirmed result for the selection of drug of choice for AD. However, immunotherapy with solanezumab towards amyloid beta have shown good results in preclinical studies, but they failed to show effective therapeutic outcome in clinical trials. Simvastatin showed a positive results but it can be used as preventive therapy for AD. The current effective drug in market for AD is donepezil which is anticholinesterase inhibitors. Since GPR3 is highly expressed in areas of the normal human brain implicated in Alzheimer’s disease and is elevated in the sporadic Alzheimer’s disease. Hence, GPR3 represents a promising therapeutic target for the treatment of Alzheimer’s disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.
References


48. Anon. Medication use and the elderly. CMAJ. 1993;149:1152A.


96. Helmuth L. Protecting the brain while killing pain? Presented at the International Conference on Alzheimer’s Disease and Related Disorders, Stockholm; 2002.


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