

Alzheimer Disease: Various Therapeutic Interventions and Alternative under Clinical Trial

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ABSTRACT- Alzheimer Disease (AD) is an incurable progressive neurodegenerative disorder. It is the most common cause of dementia and is increasing worldwide. Various mechanism of pathogenesis of AD is given and is still under study. Despite of its etiology, the disease is characterized by presence of senile plaques which is deposition of Amyloid Beta protein and other is intracellular neurofibrillary tangles. Several other factors like Hypertension, diabetes, obesity and inflammation, hormonal imbalance are associated with increased risk of AD. This article summarizes various interventions which have impact on slowing the progression of disease therefore any intervention which delays the onset of moderate to severe symptoms will have significant effect on patient and their families. Also it includes various drugs and agents which are currently under clinical trial studies. These agents mainly act upon Beta Amyloid, cholinergic system, various vaccines, antibodies, γ and β Secretase inhibitors and modulators, Agent affecting phosphorylation and blocking of tau protein along with agents which have indirect effect on neurotransmission like serotonergic 5HT₆, Histaminergic H₃, modulation of acetylcholine response of α -7 nicotinic acetylcholine receptors. Development of new drugs is very time consuming process and had very less chance of success. The drug which passes the phase 2 clinical trials with positive results generally fails in phase 3 trial because of serious adverse effect and lack of drug safety profile.

Key-Words: Alzheimer, Intervention, β -Amyloid, Cholinergic

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INTRODUCTION

Alzheimer's disease is condition in which there is an irreversible neurodegeneration of brain and protein^(1,2). It is most common form of dementia with progressive neurodegeneration and impairment in cognition accompanied by abnormal behavior and personality changes. With increase in age, chances of the incidences increase⁽³⁾. The disease progression is divided into three stages mild, moderate and severe as determined by global cognitive test scores.⁽⁴⁾

The pathogenesis of AD is complex and still unclear. Regardless of its etiology, it is generally accepted that, the disease is histopathologically characterized by presence of extracellular neuritic (senile) plaques and intracellular neurofibrillary tangles.

Due to Accumulation of amyloid B protein (AB), the senile plaque is formed while the neurofibrillary tangles are made of hyper phosphorylated tau protein⁽⁵⁾. The role of these proteins in pathophysiology of AD and its relationship with cognitive symptom is not clear and still under study. For instance, the amyloid β (A β) plaques presences for identification of AD as distinct disorder, does not clearly correlate with AD symptom⁽⁶⁾ and can be found in healthy elderly person with sign of no cognitive impairment⁽⁷⁾. The complexity of AD indicates that several other factors are involved in its pathogenesis.⁽⁸⁾ These factors include genetic makeup that is the incidence of AD in the family of patient, cerebrovascular disease, traumatic brain injury, Depression, Hormonal imbalance, Inflammation, Hyperlipidemia (obesity), Hypertension and Diabetes. Consumption of high Fat Diet has known to cause increase risk of number of medical condition including obesity and diabetes which are associated with increased risk of Alzheimer disease and other form of cognitive impairment⁽⁹⁻¹¹⁾.

Unfortunately none of therapies are present which completely stop the progression of disease and there is no treatment available which intervenes the progressive deterioration of cognitive and memory functions⁽¹²⁾. This

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article summarizes various intervention which slows the progression of disease and the latest advances in anti-AD Drug candidates which are currently undergoing clinical trials (1,13-15)

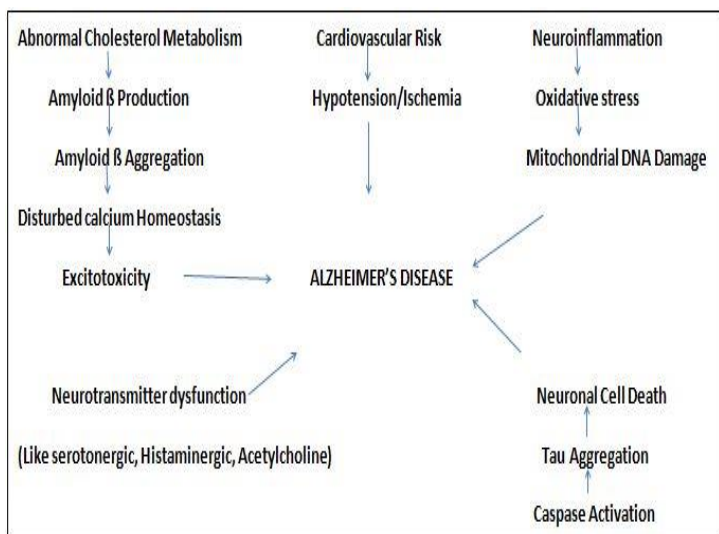


Fig. 1: Mechanism of Alzheimer disease²

Table 1: Therapeutic strategies involve in Alzheimer's disease³

1. Modulation Of Neurotransmitters	<ul style="list-style-type: none"> • Cholinesterase Inhibitors • GABAergic Modulation • Serotonin Receptor • Histaminergic modulation
2. Tau Based Therapies Include	<ul style="list-style-type: none"> • Tau Phosphorylation Inhibition • Enhancing Tau degradation • Tau based Immunotherapy
3. Amyloid based strategies	<ul style="list-style-type: none"> • Amyloid Transport • Secretase Enzyme Modulation • Promoting Amyloid Clearance • Amyloid Based Immunotherapy
4. Oxidative stress reduction	<ul style="list-style-type: none"> • Antioxidant Supplementation • Promoting endogenous defense
5. Modulation of cellular calcium Homeostasis	
6. Others	<ul style="list-style-type: none"> • Caspase Inhibitors • Nitric Oxide synthase Modulation • Nucleic acid Drugs • Multi Target Direct Ligand

Cholinergic Theory

Multiple neurons are damaged in Alzheimer disease. Most profound damage are in cholinergic system, that is large number of neuron located at the base of forebrain in the nucleus basalis of Meynert, a brain area believed to be involved in thought integration. The discovery of cholinergic cell loss led to the development of cholinergic hypothesis linked to pathophysiology of Alzheimer disease.

The cholinergic hypothesis targeted cholinergic cell loss as the main source of cognitive and memory impairment in Alzheimer disease. (16)

Oxidative stress in Alzheimer disease

Oxidative stress is characterized by an imbalance between production of reactive oxygen species and antioxidant defense. With increase in level of ROS, neurodegeneration occur. Another source of reactive oxygen species is amyloid beta peptide itself in presence of metal ions. Therefore oxidative stress is an integral factor in neurodegenerative disease. (16)

Pharmacological treatment For AD

Currently, the treatment Available for AD patient include Acetylcholine esterase inhibitors (AChEIs) and N-Methyl-D-Aspartate (NMDA) receptor antagonist provide at best palliative symptomatic relief of symptoms.

Mechanism of Action of AChEIs

Acetylcholine is the main synaptic and diffuse neurotransmitter of the cholinergic system, a system of complex network connecting limbic and cortical regions involved in control of attention and memory (16). Various cholinergic activity markers such as acetylcholine synthesizing enzyme choline acetyl transferase (ChAT) and receptor binding are decreased in brain of AD patient and have direct effect on cognitive decline (17). AChEIs inhibit the degradation of acetylcholine by acetylcholine esterase thus steady the rate of cognitive decline. Various AChEIs like donepezil, galantamine and rivastigmine are prescribed to AD patient for cognitive aid.

Mechanism of NMDA Antagonist

NMDA Receptor are mainly present in numerous amount at hippocampus and are known for their role in memory formation and learning high plasticity via glutamate neurotransmitter allows the person for long term potentiation. The NMDA are having high permeability to Ca²⁺ ions but to prevent calcium toxicity, this channel is voltage dependently blocked by magnesium ion thus important for inhibiting neurotoxicity by limiting the high level of Ca²⁺ influx into post synaptic neuron. Memantine is non-Competitive NMDA Receptor antagonist and able to prevent Ca²⁺ influx while allowing sufficient ca²⁺ necessary for synaptic transmission. During convergence of temporal or spatial activation of glutamatergic synapses which occur during learning and memory, the Memantine NMDA receptor channel antagonism is released (18) and used as monotherapy in moderate to severe AD or along with AChEIs.

Effect of Treatment

An effect of AChEIs treatment on cognitive performance in AD patient has been studied. Double blind placebo controlled studies with Donepezil (5-10mg/kg) found effective in improving cognitive performance in mild-moderate AD (19-20), showing some effect for moderate-severe patient with dose of 23mg/d (21). Small et (22)., (2005) used MMSE to evaluate the effect of oral rivastigmine(8.9 mg/d) treatment for five years, who found decline rate of 8.9 point in treated patient compared to

nearly fourteen point in model of untreated patient. In this study, 22.4% of treated patient dropped out due to adverse effect commonly gastric distress. Transdermal patch of rivastigmine reduces these side effects⁽²³⁾ and is clinically effective⁽²⁴⁾. Also patch may allow patient to receive and maintain the therapeutic dose due to higher retention and compliance⁽²⁵⁾. Galantamine (18-24mg/d) is well tolerated and provide more protection against cognitive decline when compared with placebo in mild to moderate patient⁽²⁶⁾. These medications tend to lose their effect once the disease progress beyond the moderate stages and hence these drugs are not licensed for severe AD. AChEIs treatment only target to slow the natural progression of disease⁽²⁷⁾.

Memantine have no benefit over placebo for those with mild AD^(28,29) and thus prescribed in combination with continuing AChEIs treatment. Memantine treatment along with AChEIs treatment provided significant benefit in cognitive and psychiatric symptom compared to the patient receiving a placebo after six month⁽³⁰⁾. Also combination treatment was found effective to reduce the risk of nursing home admission^(31,32).

The only limitation with this medication is that they are only able to provide symptomatic relief and in some cases offer no protection at all. Also the full mechanism behind this medication and the effect they have on the brain are not fully understood. For instance, the effect of AChEIs on cholinergic system is well established but their influence on the brain inflammatory system via nicotinic acetylcholine receptors is only recently becoming appreciated⁽³³⁾. Increase in Antioxidant level with AChEIs treatment⁽³⁴⁾ and protection from A β Mediated toxicity⁽³⁵⁾ have shown by using animal studies. AChEIs treatment has no effect on blood antioxidant⁽³⁶⁾ or proinflammatory biomarkers levels after one year of treatment⁽³⁷⁾.

Cardiovascular Risk Factor and Antihypertensive Intervention

The result from large population studies suggest that hypertension (HT) in mild life is a risk factor for late life development of AD⁽³⁸⁾. Mild hypotension in elderly is associated with lower incidence of AD^(39,40) and other type of dementia⁽⁴¹⁾. Panel member of Eight Joint National Committee in 2014, produced report which recommends that hypertension in the elderly (greater than 60 years) is treated with systolic blood pressure ≤ 150 and diastolic blood pressure < 90 ., as more aggressive treatment to goal SBP >140 and whereas for those over 75 years cardiovascular risk was not affected until SBP >150 Suggesting that cardiovascular risk associated with BP shifts with advancing age^(42,43). BP of 135/80 mmHg is associated with best cognitive performance in healthy adults over 65 years.⁽⁴⁴⁾

Antihypertensive Medication

Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor 1 blocker are antihypertensive medication which has effect on Renin-Angiotensin system (RAS). AChEIs which penetrate the brain have protective effect on global cognitive test scores in AD patient⁽⁴⁵⁾ as compared to non-brain penetrating AChEIs despite successful BP control, leading to suggestion that this medication is able to have influence on cognitive independent of its vasoactive effects. ACEIS and AT1RB

increase the level of angiotensin 4 in brain⁽⁴⁶⁻⁴⁷⁾ and have been found to be effective in improving learning and memory in animal model⁽⁴⁸⁾. The exact mechanism behind this are not yet clear, however angiotensin 4 have role in increasing cellular uptake of glucose.

HT and antihypertensive medication may also affect AD associated neuropathology. Level of A β plaques and NFTs in post mortem brain tissue in AD patient is measured⁽⁵⁰⁾. Less plaque in HT patient taking HT medication are observed as compared to patient who did not take HT medication. The effect of HT should not be considered alone in dementia. Several other characteristics are involved that include obesity, insulin resistance and low grade chronic inflammation in addition to HT⁽⁵¹⁾. Furthermore no data exist from the study of phase three clinical trials to support the use of antihypertensive medication in management of AD.

Anti-inflammatory Based Intervention

Both peripheral^(52,53) and central⁽⁵⁴⁾ immune activity is involved in AD patient. Microglia has been observed to be activated by A β In vitro⁽⁵⁵⁾ suggesting inflammation may be triggered by AD pathology. But there is no evidence of positive effect of NSAIDS and other anti-inflammatory treatment and don not appear to be useful as treatment to slow down progression of illness.

Diet

Diet have double edged sword like effect on the development and progression of AD. Diet rich in trans saturated fats, processed sugar and low in poly unsaturated fat and other essential nutrients contribute to ill healthy by affecting multiple organs and system.

Obesity has been identified as major risk factor for AD⁽⁵⁶⁻⁵⁹⁾. The western diet having high level of red meat and saturated fats have been associated with increasing level of AD⁽⁶⁰⁾. The Mediterranean diet (MeDi) on other hand has been associated with less risk of AD⁽⁶¹⁾. In early stages of disease, the effect of MeDi diet in slowing progression of AD is investigated by⁽⁶²⁾. Thus by modifying the diet and control on various factors which indirectly affect the Obesity leads to slowing the progression of AD.

Epigallocatechin -3 gallate and luteolin mainly found in green tea were the two most important mitochondrial restorative compound which decrease the level of MMP (Mitochondrial membrane potential), reactive oxygen species, and ATP level to 50-80 % in mitochondrial isolated from hippocampus, cortex and striatum. The result from the study suggested that Epigallocatechin-3- gallate and luteolin like flavanoids are used as multi-potent therapeutic agent in future.⁽⁹⁹⁾

Various Therapeutic Interventions for Alzheimer which are currently in clinical trials

Immunotherapy focused on β amyloid

This include both passive immunization which consist of an injection of pre- prepared antibodies and an active immunization where immune system is stimulated to produce its own antibodies through administration of a vaccine⁽⁶³⁾.

Prepared and administered antibodies can be precisely directed against APP, monomeric A β , soluble A β oligomers, insoluble A β fibrils as well as against A β carrier protein and

transport channels are very important because of our lack of precise knowledge as to which form of A β Are involved in pathogenesis of AD.

Active Immunization

It involves administration of a vaccine containing antigens. This process has both advantages and disadvantages^(63,64). The potential drawback is the diversity of response. The immune system of elderly patient may produce autoimmune system side effect instead of producing appropriate antibodies.

The very first active vaccine against A β tested in human designated as AN-1792, Contained full length pre-aggregated amyloid peptide (A β 1-42)^(13,65). Because of severe side effect including aseptic meningoencephalitis in 6% of vaccinated patient with AD^(65,66), the phase 2 trial was terminated in January of 2000⁽¹³⁾. Immunological response to vaccine was also weak as compared to placebo-treated control group. In post mortem examination of brain of vaccinated patient, there is decrease level of insoluble amyloid plaques⁽⁶³⁾. This lead to an important data for further clinical trials. The CAD106 Vaccine contains an A β ₁₋₆ Fragment as potential immunogenic sequence attached to a carrier formed from the coat protein of bacteriophage Q β as an adjuvant⁽¹³⁾. It did not lead to adverse effect observed in case of AN-1792 in phase 2 trial and 75% of patient responded with antibody production in adequate level⁽⁶⁷⁾. But the study did not confirm clinical efficacy in term of difference between treated group and control group. Phase 2 trials results are yet to be published done in December 2012⁽⁶⁸⁾. The next vaccine designated as ACC-001 Contain six amino acid sequences A β ₁₋₆ connected to a carrier protein by use of surface active saponin adjuvant QS-21. Phase 2 trials were terminated in 2014 due to serious adverse effect associated with strong autoimmune response^(68,69). The other vaccine who reached phase 2 trials include Affitope AD-02(A β ₁₋₆) and V-950^(1,14,63,68).

Passive Immunization

It is most widely developed approach in clinical trials in which the administered antibodies are exogenous and are delivered from a source other than patient's own immune system. They are usually including humanized murine monoclonal antibody or donor- derived human polyclonal antibodies. The advantage of this approach is rapid clearance of antibody in case of side effects because of administration of known amount of specific antibody.

The first humanized monoclonal antibody was Bapineuzumab used against the A β N- Terminus A β ₁₋₅ which binds more strongly to deposit amyloid plaques than to soluble A β monomer. Bapineuzumab advances to next phase although the result of phase 2 trial were not unequivocal but in phase 3 trials, double bind placebo controlled parallel group did not confirm drug's efficacy while showing its adverse effect^(13,68) which include vasogenic edema and intracerebral microhemorrhage detected by magnetic resonance imaging as amyloid related imaging abnormalities(ARIA).

Better outcomes were seen in case of solanezumab, a humanized monoclonal antibody. It is specific to the mid domain of the A β peptide (A β ₁₆₋₂₄) and binds selectively to monomeric soluble toxic species of A β . Phase 3 trials

involving over 2000 patient from 16 countries with, mild to moderate AD revealed reduction in cognitive decline by 34% but only for patient with mild type of disease^(13,66,70).

Gantenerumab is conformational antibody and is able to specifically bind to aggregated A β In the brain. It possess two binding sited, one which interfere with N- terminus of region of A β While other binds to the mid domain of A β peptide⁽¹⁴⁾. Currently Gantenerumab is in phase 2/3 trials and last until 2016.

Genezumab is novel human IgG4 monoclonal antibody which binds to A β oligomers fibrils and plaques and inhibiting its aggregation and promoting disaggregation. Currently it is in phase 2 trial with mild to moderate AD patient.⁽¹⁴⁾

Intravenous Immunoglobulin (IVIG)

It is the mixture of polyclonal antibodies prepared from blood plasma of thousands of healthy young volunteers⁽⁶³⁾. IVIG has strong affinity for neurotoxic oligomers and A β Fibrils and display potent immune modulating and inflammatory effect. But lack of positive result in phase 3 trial conducted in nov 2012 in US resulted in termination of study^(14,68).

Decreasing A β Production-Secretase Inhibitors

It generally includes two classes.

γ -Secretase Inhibitors and modulators

Role of β and γ Secretase is considered as target in search for new AD treatment strategy because of role in formation of various aggregate of amyloid protein⁽⁷¹⁾. This enzyme is composed of Presenilin 1, Nicastrin, Anterior pharynx defective-1(APH-1) and Presenilin 1 enhancer-2 (PEN-2)⁽⁷²⁾. γ - Secretase complex is involved in proteolysis of more than 90 other intramembranous signaling proteins⁽⁷³⁾.

Semagacestat is the first drug which is non-selective γ -Secretase inhibitors and failed in two large phase 3 studies with more than 2600 patient from 31 countries^(72,74). The reason behind failure of non-selective inhibitors was because of omnidirectional role of Presenilin1, a catalytic subunit of γ - Secretase⁽⁷⁵⁾ The most important adverse effect associated with γ - Secretase include hematological disorders, gastrointestinal symptom, skin reaction and hair color change⁽⁷⁶⁾. These entiresymptom are mainly caused by impaired Notch Transduction due to complete inhibition of the enzyme.

Second generation γ -secretase inhibitors avoid influence on Notch protein Transformation result in improving their safety profile⁽⁷⁷⁾. The first γ -Secretase modulator to undergo clinical trial was Avagacestat (BMS-708163)⁽⁶⁸⁾. Other γ - Secretase modulator that is Begacestat (GSI-953) stopped in phase 1 trial.

β - Secretase Inhibitors

Another target interfering with amyloid formation pathway is β Secretase which belong to group of aspartyl proteases. Apart from involvement in amyloidogenic metabolism of APP, it play important role in metabolism of other protein including neuregulin 1(NGR 1) responsible for myelination of neuron⁽⁷⁸⁾.

The most promising inhibitor is MK-8931, which successfully passed safety profile involving 88 healthy volunteer in 2012⁽⁶⁸⁾. Phase 1b study in 32 patients

confirmed the safety and efficacy of MK-8931⁽⁷⁹⁾. Phase 2/3 trial with 2000 and 1500 patient is currently underway⁽⁶⁸⁾.

Another β - Secretase inhibitor LY2886721 Passed phase 1 trial but phase 2 studies with 130 patients exhibiting mild AD was discontinued in June 2013 due to abnormal liver biochemical test⁽⁷⁹⁻⁸⁰⁾.

Immunotherapy Directed Against Tau protein

Recent Research has shown that the antibodies against pathological tau protein which are able to cross blood brain barrier are transferred into neuron with participation of Fc receptor and via endosomal/liposomal system, it bind to pathological tau protein⁽⁸¹⁾. AADvac 1 is the first vaccine and is currently undergoing phase 1 clinical trial.

Blocking Phosphorylation of tau protein

Protein kinases are class of enzymes involved in tau phosphorylation and most important of them is glycogen synthase kinase 3 beta (GSK-3 β) and has been reported that neurotoxic A β promotes GSK-3 β activity thus GSK-3 β inhibitors are potent drug targets.

Tideglusib (NPO31112, NP-12) is an irreversible GSK-3 β inhibitor and shown to reverse amyloid load in brain tissue, prevent cell loss and reduce spatial memory deficit in preclinical studies^(1,69). In preliminary study patient exhibited slightly improved cognitive function measured using Mini Mental State Examination and cognitive scales in mild to moderate AD cases⁽⁸²⁻⁸³⁾.

Intranasal insulin may decrease the activity of GSK-3 β And lead to inhibition of tau phosphorylation thus have role in treatment of AD⁽⁸⁴⁾. Phase 3 clinical trial are currently undergoing for Humulin R in patient with mild type of AD.

Other mechanism

Serotonin is a neurotransmitter which indirectly affects the neurodegenerative process. 5-HT₆ Serotonin receptors present in brain are mainly responsible for memory and cognitive function⁽⁸⁵⁾. Blocking of 5HT₆ Receptors result in increased level of acetylcholine in synaptic cleft lead to improve in cholinergic transmission and hence enhancing memory and cognitive functions. It is known that cholinergic activity generally deteriorates due to degeneration of cholinergic neurons in case of Alzheimer disease. Therefore the compound which affects the 5HT₆ Receptors are potential therapeutic targets for symptomatic treatment of AD.⁽⁸⁶⁾

Idalopirdine (Lu AE58054) is a selective 5HT₆receptor antagonist which successfully passed a phase 1 study in healthy volunteers exhibiting good safety profile⁽⁸⁷⁻⁸⁸⁾. From the result of preclinical studies, it has been suggested that the use of 5HT₆ antagonist along with cholinesterase inhibitor may increase beneficial effect on cognition.⁽⁸⁹⁾ Phase 2 study was carried out among 278 patient out of which 133 received placebo and 145 received the drug with mild form of AD, taking donepezil 10 mg daily for at least four month^(87,90) indicate improvement in cognitive function measured using ADAS-cog subscale with few side effects.

Histamine H₃ receptor antagonists

Histamine H₃ receptors both auto and heteroreceptors are present in large amount in structure of brain-mainly

prefrontal cortex, hippocampus and hypothalamus and are responsible for memory and cognitive processes⁽⁹¹⁾. The H₃ receptor is a presynaptic receptor and blocking of which leads to increase release of acetylcholine, dopamine, GABA, noradrenaline and histamine in synaptic cleft. H₃ receptor antagonist may indirectly improve cholinergic neurotransmission⁽⁹²⁾. ABT-288 is a competitive selective H₃ receptor antagonist which demonstrated a good safety profile and tolerability in phase 1 studies involving healthy volunteers⁽⁹³⁻⁹⁴⁾ and recently completed phase 2 clinical trial involving 242 patients with mild to moderate AD⁽⁹⁵⁾. GSK239512 is another H₃ antagonist which is also currently undergoing phase 2 trial on patient with mild to moderate AD (NCT01009255)^(68,96).

Enhancement of acetylcholine response of α -7 nicotinic acetylcholine receptors

Encenicline (EVP-6124, MT-4666) is partial α -7 nicotinic acetylcholine receptor selective agonist which has been evaluated for treatment of AD and cognitive deficits in Schizophrenia. It act as co agonist with acetylcholine and being selective α 7-nAChR agonist may enhance cognition without causing side effects relating to over activation of other nAChR subunits or muscarinic acetylcholine receptors⁽⁹⁷⁾. Phase 2 trial have confirmed the positive result of drug safety and efficacy by the ADS-cog-13 sub-scale.

SUMMARY

Interesting Therapeutic approaches including NMDA receptor antagonism, modulation of calcium homeostasis, reducing the oxidative stress that is antioxidant effect, statin therapy and potential therapeutic approaches which mainly target on anti A β agents such as vaccines, antibodies and inhibitors and modulators of γ and β Secretase, agent blocking the phosphorylation of tau protein as well as agent which affect the neurotransmitter release (like serotonergic 5HT₆ and histaminergic H₃). It is known that development of newtherapeutic agent is very time consuming and complex process with 95% chances of failure. Most of the drug which passes the phase 2 trial studies generally fails in phase 3 trial because of the lack of therapeutic potential, some serious adverse effects and unknown drug safety profile. Number of drugs is currently under clinical trial studies but none of them are approved for use in AD treatment thus this article presents the future direction for seeking novel, safe and effective treatment for AD.

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