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Review Article

Recent advancement in drugs of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD), a multifaceted neurological ailment that progresses over time, is the most common cause of dementia in older people. Intracellular neurofibrillary tangles and extracellular amyloidal protein deposits contribute to senile plaques on a pathological level. AD symptoms vary depending on the stage of the disease. Depending on the severity of cognitive impairment, AD is classified as preclinical or presymptomatic, mild, or dementia-stage. In addition, the condition is influenced by a number of risk factors, including advancing age, hereditary factors, head injuries, vascular diseases, infections, and environmental variables. There are currently only two types of licenced medications to treat AD: inhibitors of the cholinesterase enzyme such as donepezil, rivastigmine, galantamine and antagonists of N-methyl d-aspartate (NMDA) such as memantine, both of which are only effective in treating the symptoms of the disease and do not cure or prevent it.

Keywords: Alzheimer disease, Neuro-degeneration, Tau-protein, β-amyloid protein, Presymptomatic, Clinical trials

INTRODUCTION

Alzheimer's disease (AD) was described for the first time in 1906 by the German psychiatrist, Dr. Alois Alzheimer. He performing histopathologic study of brain of his patient auguste D. who was suffering from dementia. He revealed the presence of two types of lesions in the brain senile plaque and neurofibrillary tanglen. Alois Alzheimer, reported *"A peculiar severe disease of the cerebral cortex"*. AD is an irreversible, progressive and neurodegenerative brain disorder that affects person's ability to work, memory loss, thinking skills and other important mental functions. Young adults rarely experience AD. Above the age of 65 years people have there is a 10% chance to develop a disease and over the age of 80 years of people have 50% chance to have this disease. Irreversible loss of cognitive functions may be caused by cerebral disorder such as AD and some of them extraneural systemic disease or other factors like physiologic abnormality in the pulmonary, circulatory, renal or hepatic system and intoxication, infections, nutritional disorders, such as vitamin D or vitamin B12 deficiency and oxygen deprivation the brain.[1]

It is characterized with the aid of the improvement of amyloid plaques and neurofibrillary tangles; the lack of connections among nerve cells, or neurons, within the brain; and the death of these nerve cells.[2] According to new research, depression and anxiety are connected to an earlier start of AD. The age of beginning of AD is around 2 years sooner in individuals with depression and 3 years earlier in people with anxiety compared to those without these illnesses, according to the researchers. Furthermore, having more than one psychiatric illness accelerates the onset of AD.[3] In new approach estrogens loss associated with menopause may explain why women are much more prone than males to develop Alzheimer disease. Menopausal status was the key factor contributing to greater beta amyloid (A) levels, worse glucose metabolism, and reduced grey matter volume (GMV) and white matter volume (WMV) in women in a study with over 120 individuals.[4]

According to WHO, currently dementia is the 7th leading cause of death out of all disease. ADmay contribute to 60-70% 0f cases. Worldwide, around 55 million people have dementia; the older people population is increasing almost in every country. The expectation is that in 2030 there will be 78 million and 139 million in 2050.[5]

ETIOLOGY

The underlying etiology of AD pathological alterations (A, NFTs, and synaptic loss) is yet unknown. Several ideas have been offered as causes for AD, but two are thought to be the most important. Increased age, hereditary factors, head injuries, vascular illnesses, infections, and environmental variables have all been identified as risk factors for AD.[6]

SIGN AND SYMPTOMS

Mild AD includes the following symptoms: Loss of memory, Uncertainty regarding the location of familiar landmarks, compromised judgment, which frequently leads to poor decisions, Absence of spontaneity and initiative and changes in mood and personality; increased anxiety.

Moderate AD includes the following symptoms: Memory loss and confusion are becoming more common, friends and family members are difficult to recognize, language difficulties; difficulties reading, writing, and working with numbers, inability to pick up new skills or deal with novel or unexpected events, irritability, hallucinations, delusions, suspiciousness or paranoia, perceptual-motor difficulties: for example, difficulty getting out of a chair or setting the table. Severe AD includes the following symptoms: Restlessness, agitation, anxiety, tearfulness, and roaming, particularly late in the day or late at night, repetitive remarks or movements; muscular twitches on occasion, seizures, skin infections, and swallowing difficulties, groaning, moaning, or grunting are all examples of groaning, sleeping time has increased and inability to control bladder and bowel movements.

Patients with end-stage AD may spend much of their time in bed, if not all of it. Other infections, most often aspiration pneumonia, are frequently the cause of death.[7]

DIAGNOSTIC CRITERIA

The following methods can be used to diagnose AD: (a) examination of the patient: the above-mentioned indications are typically used to make a clinical diagnosis of AD during the early stages of the disease; (b) lumbar puncture: tau and phosphorylated tau levels in the cerebrospinal fluid are frequently elevated in Alzheimer's disease, although amyloid levels are typically low; nonetheless, routine testing of CSF tau and amyloid is not advised at this time, except in research settings; (c) imaging research: Imaging scans are especially useful for excluding potentially treatable causes of gradual cognitive impairment, such as chronic subdural hematoma or normal-pressure hydrocephalus. Furthermore, volumetric hippocampal studies and 2-(18F) fluoro-2-Deoxy-D-glucose positron emission tomography (FDG-PET) with or without amyloid imaging have been used to detect and distinguish dementia etiologies.[8]

STAGES OF AD[9-11]

The clinical stages of AD can be divided into: (a) the pre-clinical stage of AD is characterized by mild memory loss and early degenerative alterations in the cortex and hippocampus are typical early signs and symptoms of the disease; (b) the mild or early stage of AD, in which patients experience difficulties in their everyday lives due to a loss of focus and memory, disorientation of location and time, a change in mood, and the onset of depression; (c) moderate AD is a stage of AD in which the disease has extended to sections of the brain's cortex, causing memory loss, difficulty recognizing relatives and friends; and (d) severe AD, also known as late-stage AD, is characterized by the spread of the disease to the entire cortex area, as well as a severe accumulation of neuritic plaques and neurofibrillary tangles, causes progressive functional and cognitive impairment and eventually leads to death.

NEUROPATHOLOGY

AD can be caused by the formation of abnormal deposits of protein in the brain. These are called plaques and tangles, and they are formed by two proteins: amyloid and tau.

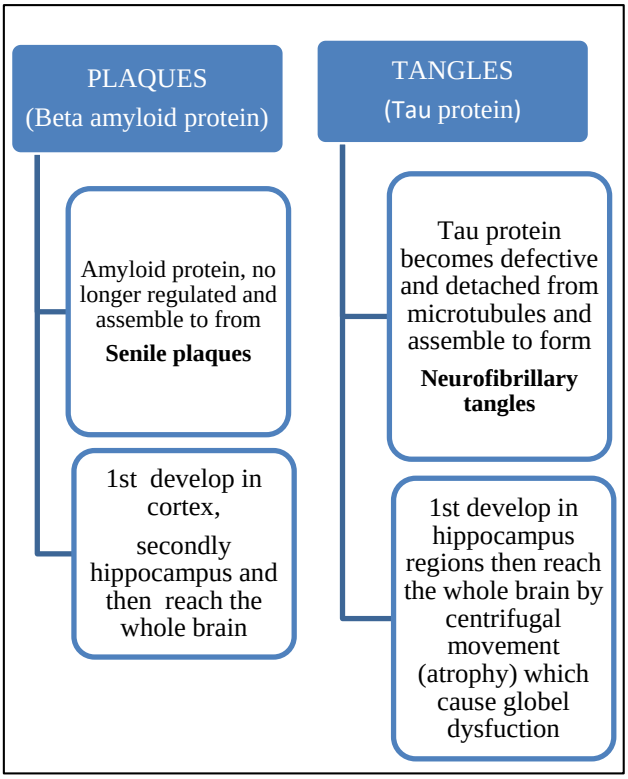

Figure 1: Pathology of Alzheimer disease.

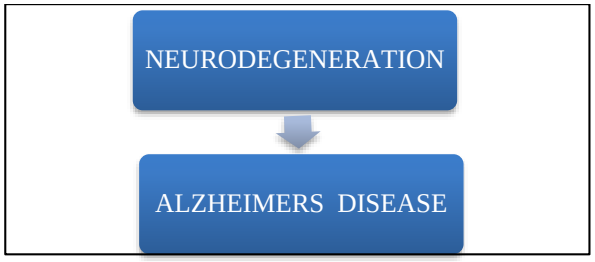

Figure 2: Pathology of Alzheimer disease.

SENILE PLAQUES (SP)[12-14]

Neuritic deposits of beta-amyloid protein (A) known as senile plaques come in variety of morphological shapes. Production of A deposits from the transmembrane amyloid precursor protein is carried out by proteolytic cleavage enzymes. Because Aβ is involved in neurotoxicity and neuronal function, buildup of thicker plaques in the brain can cause cognitive deficits.

NEUROFIBRILLARY TANGLES (NFTs)[12-14]

NFT are aberrant tau filaments that can be twisted around each other to create paired helical filaments (PHF) and accumulate in neuralperikaryal cytoplasm, axons, and dendrites, resulting in a loss of cytoskeletal microtubules and tubulin-associated proteins. Hyperphosphorylated tau protein is a major constituent of NFTs in the brains of AD patients.

SYNAPTIC LOSS[12-14]

AD is most commonly seen in the early stages of the disease. Memory impairment is caused by synaptic damage in the neocortex and limbic system. Synaptic proteins include neurogranin, a postsynaptic neuronal protein, visinin-like protein-1 (VILIP-1), and synaptotagmin-1 serve as biomarkers for detecting synaptic loss and severity.

TREATMENT

The major treatment for AD includes cholinesterase inhibitors (ChEls), N-methyl-D-aspartate (NMDA) blockers, BACE (β-site amyloid precursor protein cleaving enzyme 1) inhibitors, and microglial activation inhibitors.

Cholinesterase inhibition

It is also known as acetyl cholinesterase inhibitors, ChEls block the breakdown of acetylcholine. Food and drug administration (FDA) approved three ChEls are as follows in Table 1.

This are used to inhibit acetylcholine dehydration in the synapses, which cause continous accumulation of Ach activation of cholinergic receptors.

Donepezil is slow but completely absorbed from the intestine, reaching peak plasma concentrations in 3 to 4 hours and steady- state concentration in 15 to 21 days at daily administration. Although 96% bound to plasma proteins, it has little interaction with alternative drugs and therefore the 5 mg dose are often given safely to patients with mild to moderate liver and kidney disease. Donepezil has been proven to be beneficial in mild, moderate, and severe stages of AD.[15] Rivastigmine is a slowly reversible inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), the inhibition of enzymes could result in stronger biological effects, and greater and longer lasting clinical benefits.[16]

Galantamine: Modulates the nicotinic acetylcholine receptor, which increases acetylcholine from surviving presynaptic nerve terminals. The levels of glutamate and serotonin may rise. The peak plasma time is 1 hour and 18% bound to plasma protein.[17]

Table 1: Pharmacological characteristics of cholinesterase inhibitors.

Generic name	Brand name	Dose	Meals	Metabolism
Donepezil	Aricept	5 mg OD to be increased to 10 mg OD after one week	No effect of food	Substrate of CYP2D6 and 3A4 glucuronidation
Rivastigmine	Exelon	1.5 mg OD to 1.5 mg OD every week to 6 mg BD	Take with food	Cholinesterase-mediated hydrolysis
Galantamine	Razadyne	4-12 mg BD	Take with food	Substrate of CYP2D6 and 3A4 glucuronidation

NMDA antagonist

Memantine is a partial antagonist of N-methyl-D-aspartate receptor (NMDAR), supported for moderate to serious AD under brand name namenda, axura and akantinol, and may have potential in reducing extra neurological circumstances, like vascular dementia and Parkinson's disease. The over-initiation of NMDA glutamate cause neurotoxicity- as a partial NMDAR antagonist, obstructs the NMDA glutamate receptor to standardize the glumatergic system and ameliorate cognitive and memory loss.[18]

Mechanism of action

Non-competitive, low to moderate affinity NMDA receptor antagonist that preferentially binds to NMDAR-gated cation channels and blocks the receptor only under

condition of overstimulation, without affecting normal neurotransmission.

Adverse effect

Vomiting, dyspnea, confusion, hypertension, headache, constipation, dizziness, cerebrovascular accident are adverse effects.[19]

Table 2: NMDA antagonist for Alzheimer's disease.

Generic name	Brand name	Dose	Metabolism
Memantine	Namenda	5 mg OD to be increased by 5 mg/d every week to 20 mg/d	3 polar metabolites (minimally active)

BACE inhibitions

β-site amyloid precursor protein cleaving enzyme inhibitors, blocking off primary enzymatic step of Aβ formation. The amyloid hypothesis of AD states that the accumulation of oligomers of β- amyloid and soluble aggregates in the brain is the main pathological event of the disease. In AD patients, BACE1 inhibitors markedly lower plasma and CSF levels of Aβ and reduce plaques in the brain, but without cognitive, clinical, or functional benefit.[20] The APECS and AMARANTH studies showed that the beta- secretase inhibitors (BACEs), verubecestat and lanabecestat, failed to slow cognitive and fuctional decline in people with early or prodromal Alzheimer's disease. Verubecestat confirmed worsening at the CCS-3D total score, episodic memory, and attention/processing speed domains. Lanabecestat confirmed worsening at the RBANS total score, immediate memory.[21]

Microglial activation inhibitors

Activated microglia with macrophage- like features invade and surround β-amyloid plaques in Alzheimer disease, probably contributing to the turnover of β- amyloid, however they also can secrete pro inflammatory elements that can be concerned within side the pathogenesis of AD.[22]

Treatment to reduce the underlying procedure of Alzheimer disease

Aducanumab is the primary disease-enhancing therapy accepted via the FDA to treat AD. The medicinal drug allows to lessen amyloid depoits inside the mind and may assist sluggish the development of Alzheimer's. Aducanumab became authorized through the FDA's Accelerated Approval Program. This method calls for an extra examine after approval to verify the predicted medical advantage. If the observe-up trial fails to verify clinical gain, the FDA may withdraw approval of the drug.[23]

NEW TECHNOLOGIES FOR AD

The gut-brain axis theory in adis supported by genetic evidence

A recent study suggests that the genes that cause irritable bowel syndrome flare-ups may also play a role in future brain health. AD and gastrointestinal tract (GIT) diseases have been linked genetically, according to research (AD). All the GIT illnesses, with the exception of irritable bowel syndrome, were found to be associated with AD among individuals studied. It appears from the study that abnormal cholesterol was a risk factor for both AD and gastrointestinal diseases. Although these findings suggest a correlation, the researchers warn that a causal link cannot be proven between these two groups of illnesses. The data support the gut-brain axis theory, but they don't demonstrate a causal relationship between GI issues and AD or vice versa. [24]

Drug distribution through the blood-brain barrier for the treatment of AD

AD treatment is complicated by two issues, both of which relate to the blood-brain barrier (BBB). First off, since 100% of biologic pharmaceuticals and 98% of small molecule drugs cannot cross the BBB, BBB drug delivery technology is required in the development of AD medications. Second, the development of BBB drug delivery technology by the pharmaceutical industry would allow for the creation of novel AD treatments that can truly enter the brain parenchyma from blood. Less than 1% of all AD medication development initiatives in 2020 will employ BBB drug delivery methods. The development of new medications that target these many AD sites in combination with BBB drug delivery technology may result in the development of new and potent therapies for this severe condition.[25]

The mechanics of small molecule transport across biological membranes, such as the BBB, is described before a review of medications in clinical trials for AD. After systemic administration, biologic medicines are big molecules with little BBB penetration, large molecule drugs such as biologics, therapeutic antibodies, decoy receptors, and neurotrophins do not cross the intact BBB. Because the BBB is intact in AD, it is not surprising that such agents fail repeatedly in clinical trials. Another issue is that it is not common practice to measure BBB drug transit, and the methods that are employed are susceptible to artifacts, as well be covered below.

Blood brain barrier prevention techniques

The CNS medication developer may use a variety of BBB avoidance techniques to enroll patients in clinical trials without using a BBB drug delivery method.[26] The FDA has

not approved any novel AD medications as a result of the BBB avoidance techniques outlined below.

Drug transport in the BBB is measured by drug distribution in CSF

When a medicine is shown to spread into cerebrospinal fluid (CSF), it is considered to have crossed the BBB (CSF). Drugs, however, can reach the CSF but not pass through the BBB. This is due to the two barriers that exist in the brain. These are the choroid plexus, which creates the blood-CSF barrier, and the brain capillary endothelial wall, which creates the BBB.[27] The blood-CSF barrier at the choroid plexus separates blood from CSF, whereas the BBB at the brain capillary separates blood from brain interstitial fluid (ISF) within brain parenchyma. Drug delivery through the choroid plexus epithelial barrier determines drug transport into the CSF, whereas drug delivery via the brain capillary endothelial barrier, which makes up the BBB, determines drug transport into the ISF. Because it is considered that CSF and brain ISF are in equilibrium behind the BBB, the distribution of drugs into CSF is employed as a proxy for measuring drug penetration into the ISF of brain parenchyma. These cellular barriers have varied patterns of transporter expression, in addition to the choroid plexus' leakier solute transport when compared to the brain capillary endothelium.[27]

The blood-CSF barrier is formed by the choroid plexus, which does not express P-glycoprotein, which is strongly expressed at the capillary endothelium of the BBB. As a result, there is an increased uptake of the p-glycoprotein substrate drug into brain tissue when a p-glycoprotein inhibitor is also administered.[28]

Measurement of drug uptake in the brain

The role of brain blood volume since there is a linear relationship between drug dose and amount found in the brain, a substance is said to cross the BBB. But this medication might only enter the brain plasma volume, bypassing the BBB entirely. By measuring the brain/plasma ratio, which is a volume of distribution (VD) with the units of µl/g brain, it is possible to establish that therapeutic antibodies are transported into the brain. The brain blood volume, which ranges from 10 to 20 µl/g, should be used to compare this VD.[29]

Low and high injection doses (ID) of therapeutic antibodies for AD have been given to mice models, and the higher ID results in increased brain antibody concentrations.[30,31] However, given that the antibody concentration in blood is higher at the high ID, this is the anticipated outcome if the antibody is restricted to the brain blood volume due to a lack of BBB transit. The therapeutic antibody is not actually transported across the BBB; rather, the brain/plasma ratio of the antibody is 1-2 µl/g, which is indicative of inadequate washout of the antibody from the brain blood volume.[30,31]

Drug-induced BBB disruption

Acuranumab, a therapeutic anti-Abeta antibody, has been shown to diminish brain amyloid plaque at increasing IDs, supporting its hypothesis that it penetrates the brain ARIA-E, or amyloid-related imaging abnormalities of edoema, are also brought on by aducanumab at greater IDs, albeit.[30] One type of vasogenic edoema called ARIA-E is connected to BBB disruption.[32] ARIA-E and plaque reduction have a linear connection, according to the published clinical trial results on aducanumab.[30,33] ARIA-E and plaque reduction caused by antibodies are correlated, which shows that the antibody reaches the brain by a process that disrupts the BBB.

Transitory BBB disruption

Temporary disruption of the BBB, disrupting endothelial tight junctions, the ultrasound/microbubble method increases paracellular transport, which opens the BBB to both small and big molecules, and transcellular transport, which enhances vesicular transport.[34,35] In addition to improving drug delivery to the brain, BBBD results in increased brain uptake of plasma proteins such albumin, which is toxic to neurons.

Small molecular drugs for Alzheimer's disease

Despite a worldwide effort by the pharmaceutical industry to discover small molecule inhibitors of Abeta peptide production or oligomerization, no small molecule medication has been FDA approved for AD since 2003.[36] The issue with the small molecule method to CNS drug development, in particular receptor-based HTS drug discovery, is that the medications almost always have a MW>400 Da and/or generate >7 hydrogen bonds, and these characteristics result in minimal BBB transit.

The pharmaceutical industry has invested heavily in the development of biologics for AD, primarily therapeutic antibodies, due to the difficulty in creating small molecule drugs for AD.[37,38] For the detection and treatment of Alzheimer's disease: existing and future challenges in nanomedicine-based technologies and novel biomarkers.[39] PROTAC technology for the treatment of AD.[40]

Clinical trials of new drugs for AD

Numerous international pharmaceutical companies have tried numerous times to develop an amyloid clearing medication based on the amyloid hypothesis, but without success. Consequently, it's possible that the amyloid theory isn't entirely plausible. 2019 may mark a turning point because fewer anti-amyloid experiments were conducted. The development of new pharmacotherapies requires a thorough understanding of the role played by amyloid beta and other AD-related variables. Researchers have created and are currently testing a number of potential interventions aimed at various targets, including anti-amyloid and anti-tau, neurotransmitter modification, anti-

neuroinflammation and neuroprotection, cognitive enhancement, and interventions to relieve behavioural psychological symptoms.

There are eight medicines that target amyloid that are in nine phase 3 trials as of 2019. In two of these, individuals with preclinical AD were enrolled; one trial required a positive amyloid PET, while the other required a genetic mutation or significant hereditary risks. With one trial for prodromal and mild AD and two for mild to moderate stages of AD-related dementia, patients with prodromal AD and positive biomarkers were enrolled in four trials. Positive amyloid PET or CSF biomarker test results indicating early AD were required for inclusion in these trials. Using the National Institute on Aging's and the Alzheimer's Association's (NIA-AA) criterion of moderate cognitive impairment (MCI), these findings included decreased CSF A-42 and increased CSF tau. The number of anti-amyloid phase 3 medication trials decreased in 2019 as compared to 2017 and 2018, and anti-amyloid trials have also been expanded to include AD's prodromal or even preclinical stages.

The use of AD surrogate biomarkers as supplementary outcome indicators is common. The most frequently used outcome biomarkers in clinical studies have been amyloid PET, volumetric MRI, CSF amyloid, and CSF tau. The AD Composite Score (ADCOMS), which combines results on items from the AD Assessment Scale-cognitive subscale (ADAS-cog), clinical dementia rating (CDR) score, and Mini-Mental Status Examination (MMSE), has been a helpful indicator of cognitive outcome in studies involving early-stage AD with minimal cognitive deficits.[41,42] The amyloid hypothesis has also been contested, and in 2019, there were much fewer phase 3 anti-amyloid trials. There are many different targets for phase 1 and phase 2 trials, and current trends indicate increased focus on neuroprotection and anti-neuroinflammation in these phases, respectively. To effectively halt the progression of chronic progressive illnesses, two or more medications are typically needed. Prospectively, it could make sense to do clinical trials using 'dirty medications' that operate on a variety of targets, including those related to amyloid and tau, neurotransmitter alteration, anti-neuroinflammatory and neuroprotective effects, and cognitive improvement.[43]

Table 3: Since 2016, phase 3 anti-amyloid treatment trials have failed.

Year	Drug	Mechanism of action	Participants	Main reasons for failure	Remarks
2016	Solanezumab	Monoclonal antibody	Mild AD	Lack of efficacy	
	Solanezumab	Monoclonal antibody	Prodromal AD	Strategic	
	Verubecestat	BACE inhibitor	Mild to moderate AD	Lack of efficacy	
2018	Verubecestat	BACE inhibitor	Prodromal AD	Lack of efficacy	Worsens cognition
	Atabecestat	BACE inhibitor	Preclinical AD	Toxicity	Worsens cognition
	Lanabecestat	BACE inhibitor	Early AD	Lack of efficacy	Worsens cognition
	Lanabecestat	BACE inhibitor	Mild AD	Lack of efficacy	Worsens cognition
2019	Aducanumab	Monoclonal antibody	Early AD	Lack of efficacy	
	CNP520	BACE inhibitor	Preclinical AD	Lack of efficacy	Worsens cognition

Table 4: Currently running phase 3 trials on anti-amyloid therapy AD in 2019.

Agent	Mechanism of action	Target type and therapeutic purpose	Status
Plasma exchange with albumin 1 immunoglobulin	Plasma exchange	Removed amyloid	Completed
ALZT-OP1a+ ALZT-OP1b	Mast cell stabilizer, anti-inflammatory	Amyloid-related and antineuroinflammatory	Active, not recruiting
ANAVEX2-73	Anti-tau, anti-amyloid	Anti-tau, anti-amyloid, and antineuroinflammatory	Recruiting
Crenezumab	Monoclonal antibody directed at oligomers	Remove amyloid	Completed
E2609 (elenbecestat)	BACE inhibitor	Remove amyloid production	Active, not recruiting
Gantenerumab	Monoclonal antibody	Remove amyloid	Active, not recruiting
Gantenerumab and solanezumab	Monoclonal antibody	Remove amyloid/reduce amyloid production	Recruiting
GV-971 (sodium oligomannurarate)	Aβ aggregation inhibitor	Amyloid-related	Completed

Continued.

Agent	Mechanism of action	Target type and therapeutic purpose	Status
Solanezumab	Monoclonal antibody	Remove amyloid and prevent aggregation	Active, not recruiting

Table 5: Currently running phase 3 trials on nonanti-amyloid therapy in AD in 2019.

Agent	Mechanism of action	Target type and therapeutic purpose	Status
AC-1204	Induction of ketosis	Metabolic; symptomatic cognitive enchancer	completed
AGB101 (levetiracetam)	SV2A modulator	Amyloid-related and neuroprotective; disease-modifying therapy	Recruiting
Aripiprazole	Partial agonist at dopamine D2 and 5- HT 1A receptors	Neurotransmitter based; symptomatic cognitive enhancer	Terminated
AXS-05	Sigma-1 receptor agonist; NMDA receptor antagonist and dopamine norepinephrine reuptake inhibitor	Neurotransmitter based; BPSD (agitation)	Recruiting
Azeliragon	Microglial activation inhibitor, antagonist of the receptor for advanced glycation end products	Amyloid-related and antineuroinflammatory; disease-modifying therapy	Terminated
Coconut oil	Reduction in ADP-ribosylation factor 1 protein expression	Anti-amyloid, antineuroinflammatory anti-oxidative, and neuroprotective; symptomatic cognitive enhancer	Terminated
COR388	Bacterial protease inhibitor	Antineuroinflammatory; disease-modifying therapy	Recruiting
Gabapentin enacarbil	Glutamate\receptor-independent mechanisms	Neurotransmitter based and neuroprotective; symptomatic cognitive enhancer	Recruiting
Escitalopram	Serotonin reuptake inhibitor	Neurotransmitter based; BPSD (agitation)	Recruiting
Ginkgo biloba	Antioxidant and anti-amyloid aggregation	Antioxidant and anti-amyloid; symptomatic cognitive enhancer	Recruiting
Icosapent ethyl (IPE)	Omega-3 fatty acids protect neurons from disease	Neuroprotective; disease-modifying therapy	Recruiting
Idalopirdine	5-HT6 receptor antagonist	Neurotransmitter based; symptomatic cognitive enhancer	Completed
Mirtazapine	Alpha-1 antagonist	Neurotransmitter based; BPSD (agitation)	Recruiting
Nabilone	Agonists at cannabinoid receptors 1 and 2 (CB1/2)	Neurotransmitter based; BPSD (agitation)	Completed

CONCLUSION

From the above review study we concluded that what are the various consequences related to the AD and the measure taken to control the various stages of this disease. The various standards are seen which can control the various stages by drugs and the therapies which can manage the disease in good manner.

AD is an irreversible, progressive and neurodegenerative brain disorder that affects person's ability to work, memory loss, thinking skills and other important mental function. Worldwide, around 55 million people have dementia; the older people population is increasing almost in every country. The expectation is that in 2030 there will be 78 million and 139 million in 2050. On other hand, large molecule drugs such as biologics, therapeutic antibodies, decoy receptors, and neurotrophins do not cross the intact BBB. Because the BBB is intact in AD, it is not surprising that such agents fail repeatedly in clinical trials. In this novel strategy, BBB drug delivery technology is created concurrently with CNS drug development for AD.

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