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# ALZHEIMERS'S DISEASE AND FAILURE OF IT'S CLINICAL TRIALS

Neurology

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## ABSTRACT

Alzheimer's Disease is a progressive illness ,causing memory loss and cognitive decline in several domains.Commonly occurs at the age above60.Patients eventually die from complications like infection,dehydration and malnutrition.Current medications like cholinesterase inhibitors may slowthe progression but unfortunately there has been no curative treatment till now.So there is an urgent need to develop new promising treatment approaches.Following review is regarding the Alzheimer's disease and its therapies that are under research and reasons for the unsuccessful clinical trials.

## KEYWORDS

### INTRODUCTION

One of the most common causes of dementia in elderly is Alzheimers disease, usually affecting people in their 60s.Its a chronic and a progressive irreversible neurodegenerative disease that causes significant morbidity among patients.This disease is slowly becoming a public health concern due to the repeated failures of its treatment approaches. Alzheimer's disease is one of the many diseases that will make the patient dependent on others for their basic living and causes much suffering. Even after so many years of clinical research by the neuroscientists there is no absolute cure for Alzheimers's disease though there are some drugs that help to alleviate the symptoms . According to a 2018 census, 5.7 million Americans are suffering from Alzheimer's dementia,with mostly patients above the age of 65 and is known to be a 6th leading cause of death in USA.And because of the increase in the life expectancy people having AD is also on rise.Characteristic clinical feature of AD is memory dysfunction and cognitive decline e.g forgetting about recent conversations or events,misplacing items,forgetting about the names of objects and places,trouble thinking of the right word,poor judgement and difficulty in making the decisions , mood and personality changes.

### Etilogy

AD is believed to get started from entorhinal complex of hippocampus. Both genetic and environmental factors have been associated with the disease.Age is the single most important risk factor for AD,with majority of the patients that are above 65 and older. Family history of AD also increases the chances of having Alzheimer's. People having a parent ,brother,sister or a first degree relative suffering from Alzheimer's have increased chances to develop the disease. Gene APOE e4 has also been associated with increase risk of Alzheimer's by 2-3 folds though presence of APOE e4 in a person does not always mean that the person will get the disease for sure.In contrast APOE e2 has been linked with decreased risk .Familial AD has an early onset and predominantly autosomal dominant,with mutations in Presenilin1, Presenilin 2 and APP. Others risk factors associated with dementia are Hypertension, Diabetes,Smoking,High cholesterol levels, Traumatic brain injury. Whereas High Education, Social and cognitive engagement,Increase Physical activity all decreases the risk for dementia.

### Pathophysiology

The underlying **pathophysiology** of AD has been linked to many hypothesis but Amyloid cascade and Tau hypothesis are more recent than the others. The others are cholinergic and the glutaminergic theories.The hallmark for AD are extracellular amyloid plaques and intracellular neurofibrillary tangles,first identified by Alois Alzheimer.Along with this,neuronal damage and neuroinflammation can also be seen in the AD brain . Beta Amyloid plaques are derived from the cleavage of APP( Amyloid precursor protein). There are usually three secretases alpha,beta,gamma that help to cleave APP. Most of the times the APP is cleaved by alpha and beta causing no products to accumulate however if APP is cleaved by alpha and gamma , Beta amyloid 40 and B amyloid 42 are formed .Beta amyloid 42 will then cause aggregation of amyloid plaques.Location of APP is on chromosome 21,and as Down syndrome patients have an extra number of gene that makes them exhibit the symptoms of AD earlier than the other patients. Another hallmark for AD is Neurofibrillary tangles, these tangles are formed from tau protein,It is believed that amyloid plaques trigger the formation of neurofibrillary tangles.Tau helps in stabilising the microtubules in neurons. Microtubules transport substances to different parts of the neurons.In AD brain, tau hyperphosphorylation cause tau aggregates that eventually form neurofibrillary tangles.Eventually destroying the cell's cytoskeletal system, neuronal transport system and neuronal dysfunction. Cerebrovascular diseases such as subcortical infarcts are also linked to dementia and neuro degenerative diseases like AD.

**Signs and Symptoms** AD patients have variable signs and symptoms. Typically there are 4 stages in AD. Preclinical,Mild,Moderate and Severe.In **preclinical stage** its usually hard to diagnose AD. In **Mild stage** there is only minor memory loss and mild cognitive impairments, AD is usually diagnosed at this stage.In this stage people usually forgets recent events and conversations, have difficulty recalling words/names/places, have difficulty in learning new concepts, ask questions repetitively, confusion and disorientation, personality and mood changes, difficulty making their decisions etc. Patients in this stage are usually independent and require assistence with only complicated tasks. In **Moderate stage** patient needs assistance for daily activities,its known as the longest stage in AD. Most of the symptoms are similar to those of the mild stage but more severe in intensity e.g. person forgetting about his/her personal details, begin wandering,increased disorientation and confusion, experiencing delusions and hallucinations,impulsive behaviour, problems in speaking,continued mood swings,disturbed sleep.In **severe AD** the patient becomes completely dependent on the caregivers, In this stage the patient cannot recognise his or her own family, has loss of bowel and bladder control,difficulty swallowing, loss of speech. As patient is bed bound the risk of getting infections increases.Eventually the person enters into a vegetative state.

### Diagnosis

Most of the times,AD can be diagnosed by taking a Good history and a Neurological examination.Medical History must be taken from the patient's family or a reliable informant who is capable to tell about the patient's condition because patient itself might not be aware of the disease. A thorough medical history,family history,psychiatry history for Geriatric depression or anxiety,any history of substance use is important to rule out other differentials. A complete physical exam and neurological exam including Mental Status Examination(MSE) and Mini Mental Status Exam(MMSE) are important. Mental Status Examination consists of a clinical assessment to describe a patient's mental state. Other than this, laboratory studies like CBC, Thyroid profile,VitaminB12,Homocysteine and Folic acid levels,RPR,HIV testing,Urinalysis and urine culture should be done. Neuro imaging studies like Head CT Scan and Brain MRI should be done to rule out stroke or any other white matter disease.In AD brain,MRI will show cerebral atrophy,narrowing of gyri,widening of sulci,thinning of cortex,prominent atrophy of hippocampus and dilatation of left ventricles mainly the temporal horns.CSF testing shows elevated proteins,can be done but does not provide much relevant information.Cell biomarkers like hyperphosphorylated tau and beta amyloid plaques can be tested,but till now they are not the the gold

standards,more study is going on these tests.Patient with family history of early onset Alzheimer's can get Genetic testing done.Confirmatory diagnosis is autopsy.

**Current Therapeutic Strategies Available For Ad**

Even after decades of research not much has been found that can stop or reverse the progression of this disease.Drugs currently used for AD provide only symptomatic relief and delay the symptoms of AD.FDA approved drugs used in AD are donepezil,rivastigmine,galantine and memantine.These drugs act on brain neurotransmitters.

**CHOLINESTERASE INHIBITORS**

Cholinergic hypothesis that was stated in late 1970's and early 1980's believe that symptoms in AD are due to cholinergic deficit mostly in hippocampus and neocortex. Acetylcholine is an essential chemical in brain that helps in cognition,learning and memory.Cholinesterase inhibitors are a class of drugs that inhibits the acetylcholinesterase enzyme from breaking down acetylcholine ( a neurotransmitter in brain) therefore increasing both the levels and the duration of acetylcholine in the cholinergic synapses. This class of drugs is usually the 1st line treatment for mild to moderate AD.The three drugs that are approved to treat AD are donepezil,rivastigmine and galantamine. Tacrine is a also an anti cholinesterase but its discontinued in USA due to hepatotoxicity. Donepezil can be used in all the stages of AD.Its a reversible, non competitive cholinesterase inhibitor.It improves the memory,awareness and ability to function.Its preferred because of once daily dosing. Rivastigmine is a carbamate pseudo irreversible inhibitor of ACEI ,It is also known to slightly improve cognitive function, can be taken orally or by transdermal route with lesser side effects .Galantamine is a specific competitive reversible ACEI and also enhances the action of Acetylcholine on nicotinic receptors. Galantamine has also shown some improvement on cognition and overall global functioning in AD.Basically its similar to donepezil and rivastigmine in its efficiency and efficacy.Side Effects of ACEI are mainly gastrointestinal side effects like nausea,vomiting, diarrhoea, muscle cramps. Donepezil can cause insomnia.Its believed that donepezil also act on other stages that are involved in the pathogenesis of AD by reducing inflammatory cytokines.Galantamine is be used cautiously in patients with renal and liver disease.

However ACEI have shown no effects on progression or slowing of the disease, it just keeps the patient in a manageable state and makes the patient a bit independent in performing their daily activities therefore reducing the burden on caregivers.

**N Methyl D Aspartate receptor antagonist**

This class contains Memantine,used for moderate to severe AD.Memantine is a NMDA antagonist,believed to be a neuroprotective agent in Alzheimer's disease.Glutamate is a chemical in brain that acts on ion gated NMDA channels and is important for normal functioning of brain like learning and memory.However overstimulation of these NMDA receptors by glutamate can cause toxicity and damage of the neurons.Memantine is an uncompetitive antagonist at glutaminergic NMDA receptors,it does not act on the normal transmission of NMDAR as its required for normal functioning however if chronic overstimulation of receptors occurs it will block the pathological transmission by inhibiting the calcium influx.Memantine can be combined with other ACEI to achieve better cognitive function.Side effects of memantine include diarrhoea, constipation, dizziness, somnolence and headache. However researchers believe that memantine had shown much improvement in AD brain at preclinical level studies,its not that promising and effective for curing AD when used at clinical level.

**PRECLINICAL LEVEL STUDY OF DRUGS**

In world every year 7.7 million cases are diagnosed with dementia out of which 70% are due to AD .As this progressive dementia puts a huge burden on patient,caregivers and the society and poses a public health concern, and with the current regimen of drugs not very successful in curing the disease it demands an urgent need to develop new approaches for the drug development.There is lack of AD drugs in the market because of the ineffective advanced clinical trials,though there are many drugs that have successfully cleared the preclinical phases. Following review is regarding the therapies that are under the research.

**STEM CELL THERAPY FOR AD**

It is believed that stem cells have a great potential for treating AD progression.Stem cells are the undifferentiated cells that have the calibre to become specialised cell types.In animal models, pathologies of AD brain are created that includes injecting beta amyloid plaques ,inducing brain injury and neuronal loss.As we know current treatment of AD only provides symptomatic approach there is a strong hope from the stem cell therapy,as it is believed that transplanted stem cells replace neurons that have degenerated, this regeneration is particularly mediated through BDNF and also stem cells release neurotrophic factors that improve the synaptic transmission and synaptic density.Stem cells were shown to improve the cognition,learning and memory in the injured experimental mice.Researchers also state that stem cells release cytokines that have neuroprotective role in AD. However the adverse outcomes of this therapy can be the risk of developing tumours on transplanting these stem cells,so its important to do more research regarding the clinical efficacy of this therapy.And to investigate clearly the molecular mechanism of the stem cells and its contribution.

**DRUGS TARGETTING NEUROINFLAMMATION**

Researchers state that there is a correlation of neuroinflammation and AD.Reactive gliosis has been demonstrated in AD brain.Inflammation is a defense mechanism by which the body recognises the damaged tissue or the pathogens and begin the healing process.It is body's normal immune response. Glial cells in the CNS maintains homeostasis and provides nutrients and protection to the neurons and its various subtypes are astrocytes,microglia,oligodendrocytes and ependymal cells. Astrocytes provides biochemical support,provide tissue repair at the times of inflammation and damage,support endothelial cells in forming blood brain barrier.Oligodendrocytes form myelin sheath over the axons in CNS.Microglia plays an important role in removing the debris in damaged and injured parts of brain,acts like a tissue macrophage. Whenever there is any brain insult these cells come into play and help in repair. These cells usually have a neuroprotective role however if there is uncontrolled and chronic activation of these cells, risks outweigh the benefits causing neuroinflammation by releasing cytokines and pro inflammatory mediators known as reactive gliosis causing pathological damage.In AD astrocytes and microglia acquire a reactive phenotype and change their morphology,these cells also have receptors for pro inflammatory mediators. Microglia are able to identify beta amyloid oligomers, neurofibrils, APP through these receptors.Few examples of these receptors are toll like receptors (TLR), CD14 coreceptor,CD 36, integrins etc. When these receptors on microglia bind to beta amyloid, there is release of inflammatory cytokines like interleukins, interferons, tumour necrosis factor, chemokines, prostaglandins, thromboxane,NO, reactive oxygen species etc All these sequences cause neuroinflammation and contribute in homeostatic imbalance, dysfunction in blood brain barrier,synaptic and neuromuscular unit impairments. Recently drugs that act against neuroinflammation are being searched , drugs that can block the receptors present on glial cells or block the release of various cytokines that can stop the whole sequence of inflammation.Non steroidal inflammatory drugs like indomethacin have shown some improvement in cognition in the enrolled participants however majority of the clinical trials have failed. Researchers stated that naproxen has been shown to have some positive results by decreasing tau and beta amyloid plaques. Vaccination against tau and beta amyloid has also been tried but despite of having successful preclinical trials,,clinical trials have failed due to some serious side effects.One thing that makes it very difficult to make successful clinical trials is the lack of animal models that will imitate AD brain.Inflammation is a cascade involving many mediators so identifying a specific target to work on is difficult.

**FOCUSED ULTRASOUND AND ALZHEIMER'S DISEASE**

Recently, use of focused ultrasound waves in the treatment of AD has gained a lot of attention.In AD FUS is used to temporarily open the blood brain barrier that will help the drugs to reach the localised CNS area.Blood brain barrier consists of tightly packed cells that maintains a strict control on the passage of molecules into the CNS but this property of BBB can potentially be a problem when you want to deliver therapeutic agents to the CNS for example in the treatment of neurodegenerative diseases or brain tumours.The ultrasound was combined with injecting of micro bubbles intravenously.This whole process is MRI guided for more target specific approach. Microbubbles with the help of low power ultrasound oscillate in the blood vessels,expand and contract and temporarily open up the blood brain barrier.The frequency of 0.2 - 1.5 MHz is suitable in humans but in animal models much higher frequencies have been used.Advantages of FUS are, its a non invasive and a safe technique that opens the BBB

temporarily for approximately 6 hours ,after this time period BBB goes back to its normal functional state without any damage .By the use of MRI we are able to have a more focused approach in the delivery of drugs. However FUS has shown beneficial results in animal models without the disease,more experimentation has to be done because it might be possible that it acts differently in diseased models and in human trials.Studies show that even if focused ultrasound is used alone to open the BBB it can help to reduce the senile plaques because its believed that passage of immunoglobulins (IgM and IgG), microglia and astrocytes increases through BBB and thus causing clearance of the plaques.Neurogenesis has also been linked.However the limitations for using this strategy are that using MRI guided focused ultrasound requires an expert approach.Moreover its yet not clear if we can reuse the therapy for drug delivery for long term treatments like that of Alzheimer's disease.

**Tau targeting drugs**

Tau proteins in the neurons stabilises the microtubules.In AD there is abnormal hyperphosphorylation of tau proteins that will form paired helical filaments . These filaments are not soluble unlike tau,and make neurofibrillary tangles.These tangles accumulate in the neurons destroying the whole normal anatomy and physiology of cytoskeleton. Other pathological features in AD brain are Hirano bodies,neuronal protein inclusions and abnormal ADF/cofilin.Many trials of AD are against the beta amyloid plaques not much has been said regarding tau hyperphosphorylation.In this review,we are going to discuss about tau targeting drugs that act against hyperphosphorylated tau,cytoskeleton destabilization and its aberrations. Located on chromosome 17, tau is a microtubule associated protein (MAP) required for arranging of microtubules and has six isoforms as a result of alternative splicing. Hyperphosphorylation of tau is believed to be due to dysregulation between tau kinases and phosphatases.Few examples of tau kinases that have been associated with AD are as follows Glycogen synthase kinase 3beta cyclin dependent protein kinase CAMP dependent protein kinase Stress activated protein kinases JNK and p38 Mitogen activated protein kinases ERK1 and ERK2 Researchers state that if they inhibit kinases involved in AD they can act on the underlying pathology of tau aggregation. JNK has an association with beta amyloid plaques and memory loss in AD.So JNK inhibitors like SP600125 has been tested on preclinical stages on animal models like APP and presenilin 1 mutated mouse model.Improvement in cognition and decrease in neuronal damage has been reported.Cyclin dependent protein kinase 5 ( Cdk5) has also been linked with AD. Cdk5 is involved in many normal neuronal processes like its neurotransmission, migration, growth and survival etc. However pathological activation and imbalance of Cdk5 can be dangerous to neurons because they will eventually cause hyperphosphorylated tau and cell death.Cdk5 inhibitors like ROSCOVITINE and FLAVOPIRIDOL hav good potential,but are still in the trial phases. GSK3 inhibitors like TIDEGLUSIB has completed phaseII trial. Phosphatase agonists like PP2A agonist has also a good potential to work against tau aberrations. Tau aggregation inhibitors like methylene blue derivatives TRx 237 has also been promising. Microtubule stabilising agents like Paclitaxel,Epothilone D have failed the clinical trials. Paclitaxel also used in the treatment of various cancers have been associated with various adverse effects. Taxane derivative like TPI 287 is still in the clinical trial phase. Immunotherapies active and passive are also been considered against tau for cognition improvement.

**Failure Of Clinical Trials In Alzheimer's Disease**

AD was diagnosed several decades from now but even today unfortunately we don't have a definitive cure to this disease.Now the question is why there are so less past successful clinical trials? Hundreds of therapies have been tried but none has ever achieved the desired result. There can be several reasons that needs to be addressed that might cause hinderance to the successful human studies. -Recently studied drugs like Monoclonal antibodies that mainly work on amyloid plaques, have failed because its believed by the researchers that may be the drugs are acting on an incorrect substrate.Maybe the MABS are working on the wrong site or the other reason stated is the recruited sample of population might already be in the advanced stage of the disease and at that stage treatment might not be beneficial. -Long term studies for the clinical trials need subjects that will stick to the research. However loosing subjects in the long process,errors while recruiting the subjects, long term double blinded studies,confounding variables to name a few are complications while doing research. -Animal Models are extensively used in research for studying the progression of the disease and for the trials of new therapeutic agents. In preclinical trials of AD,animal models are genetically modified to have presenilin 1/APP mutations which lead to disturbed amyloid pathway causing accumulation of beta amyloid plaques.One reason that human studies have failed despite having successful preclinical trials can be because animal models cannot mimic human brain completely.They lack the complete pathology of AD brain like tau accumulation, neuroinflammation and severe memory loss as compared to humans. -Other explanation why human trials are repeatedly failing can be because BBB in humans and some animal models are different, therapeutic agents might not be able to penetrate the human BBB and treat AD. Its important to ensure that drugs properly reach the CNS to gain the therapeutic effect.Molecules should ideally be less than 500 daltons. Researchers state that plasma/CSF ratios can be measured to determine the brain entry. -Its important to explore the maximum tolerated doses in the trials. -Appropriate sample size is important to have efficient research and to evaluate the clinical differences between the groups. -Failure to see any decline in the placebo group in the study is also considered to be a failed trial, because the study might not have enrolled AD patients in the placebo group. -For a clinical trial, enrolled participants must exhibit biomarkers of the disease for example tau hyperphosphorylation,amyloid plaques. Trials exhibiting subjects with only AD symptoms without any pathological features is not very accurate for the study. -Determining target engagement for the verification of drug target interactions earlier in the study before advancing it to phase III for example in phase II trial will increase the likelihood of having positive outcomes. -Assessing mutiple potential biomarkers in the studies e.g. tau hyperphosphorylation, amyloid plaques,inflammatory and oxidative stress markers, brain changes in AD to determine the clinical effects of the treatment. -Clinical trials demands recruitment of thousands of subjects so the global variations, language differences,variations in genes and nutrition all make changes in the collected AD data.

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