Review Article

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RISK FACTORS AND CURRENT STRATEGIES TO OVERCOME ALZHEIMER'S DISEASE: A REVIEW

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ABSTRACT

Alzheimer's disease is currently the biggest health care issue in developing countries. There is still no effective therapy that can slow the progression of disease. This is the most common cause of dementia among people aged 65 and older. It affects 10% of people over 65 years of age and 50% over 85 years of age. This phase of neurodegenerative disease is marked by two distinctive pathologies: β -amyloid plaque deposition and hyperphosphorylated tau neurofibrillary tangles. Pathology and Possible Risk factors have been extensively included in this review. It also reviewed about currently available drugs with their drawbacks. Treatment is primarily focused on symptomatic treatment, while there are ongoing studies aimed at reducing the development and overall disease burden within the brain. Here, we are discussing recent developments in our perception of Alzheimer's disease clinical assessment and treatment, with updates on clinical trials still taking place. It also includes some protective measures to overcome by Alzheimer's.

Keywords: Alzheimer's disease, Dementia, β -Amyloid, Hyperphosphorylated Tau, β -secretase

INTRODUCTION

Alzheimer's disease is one of the fatal neurodegenerative diseases and the direct cause of dementia.¹ More than 50 million people around the world are currently affected by Alzheimer, including Alzheimer's disease, affecting people 65 years of age or older. It is estimated that by 2030 it will be increased to 74.7 million.² About 2.1 million Alzheimer's patients having age of 85 years or older were reported in year 2017.³

Alzheimer's disease is complex neuropathological disorder and is characterized by accumulation of extracellular amyloid plaques, intracellular neurofibrillary tangles, and neuronal cell death.⁴ Aging is considered as the principal risk factor for sporadic Alzheimer's disease i.e. Alzheimer's disease development. Other potential risk factors including hypertension, dyslipidemia, metabolic syndrome and diabetes have also been identified.⁵

Amyloid plaques consist of amyloid- β (A β), an amyloid- β protein precursor (A β PP) cleavage material. Some complex pathology can occur sequentially, but many are present in the person with Alzheimer's disease at the same time in the brain.⁶

The other signature protein aggregate in Alzheimer's disease, neurofibrillary tangles, consists of hyperphosphorylated tau protein. Tau promotes the stabilization of microtubules under normal conditions; when hyperphosphorylated, tau accumulates in paired helical filaments into "tangles".⁷

The loss of basal forebrain cholinergic neurons is suspected to establish cholinergic deficits that lead to Alzheimer's disease to short-term memory loss in Alzheimer's disease.⁸ "Inflammation" has proposed to be one of the main contributing factors in development of Alzheimer's disease. Findings in line with this principle include high concentrations of pro-inflammatory cytokines expressed in Alzheimer's disease by activated microglial cells and reactive astrocytes. Around 1% or less of a small percentage of Alzheimer's cases are affected by unique mutations in one of three genes: the protein gene amyloid

precursor, the protein gene presenilin 1 or the protein gene presenilin 2.⁹

Its most significant pathogenic factor in Alzheimer's disease is the gradual accumulation of fibrillary A β in the mitochondria.¹⁰ Interruption of oxidative phosphorylation, increase production of reactive oxygen species (ROS) and caspase dependent regulation of cell death mechanisms.¹¹

Despite massive Alzheimer's disease advancements in research related to apoptotic processes, there is no effective therapeutic strategy to stop or slow this cycle over expression of cyclin B1 in primary neurons.¹²

The Histopathological and experimental data supporting the influence of oxidations on Alzheimer's disease (oxidative-stress-hypothesis) pathogenesis is that Alzheimer's disease is increasing. So far, the following major findings have been included:

1. Elevation in the Amount of oxidized nucleic acid, protein, and lipid concentrations.
2. Compared to other disease pathological manifestations, early introduction of these modifications.
3. Elevated concentrations of metal ions from otherwise less harmful cellular oxidants that would catalyze free radical generation.
4. Specifically, age-associated oxidative cross links involving proteins and sugars, resulting in Alzheimer's disease advanced glycation end products (AGEs) being created.
5. The experimental activation by amyloid β peptides (A β) of cellular oxidative stress.
6. The important recapitulation in transgenic animal models of the cellular effects of A β .¹³

Therefore, this review throws light on various Risk factors and the possible therapeutic avenues for Alzheimer's disease.

Epidemiology

Alzheimer's disease is remarked as the "global public health priority" by World Health Organization in 2012 and 2015. In 2015, the number of people affected by Alzheimer's disease and other dementias worldwide was estimated as 47 million, which is expected to reach 75 million by 2030 and 131 million by 2050.¹⁴

Cases of dementia are measured at 4.9 million in Asia (49% of the total), 2.5 million in Europe (25%), 1.7 million in America (18%), and 0.8 million in Africa (8%).

The numbers represent a drastic increase in Asia, America, and Africa, while there was a decrease in the new cases in Europe. Within Asia, countries like India, Japan, and China are predicted to in Alzheimer's disease prevalence.¹⁵

Pathology of Alzheimer's disease

Alzheimer's disease is characterized by the substantial synaptic loss and neuronal cell death in the brain regions is mainly responsible for cognitive function, especially in the medial temporal lobe, cerebral cortex, hippocampus, entorhinal cortex and ventral striatum.

The Histopathological examination of the cerebrum of patients with Dementia incorporate amyloid fibrillary stores around the dividers of veins related with various kinds of feeble plaques, gathering of irregular fibers of tau protein, with ensuing neurofibrillary tangles (NFTs) arrangements, misfortune of neuronal and synaptic, just as glial enactment and aggravation.¹⁶

Inside this, two fundamental speculations have been formed to explain the etiology of the disease. As per the amyloid cascade theory, the neurodegeneration starts with the Amyloid precursor protein proteolytic cleavage (Application) and results in the generation, conglomeration and deposition of β -amyloid ($A\beta$) plaques and senile plaques.

As for the concept of cholinergic, any impairment in the cholinergic system is enough to cause a memory deficit. The brains of Alzheimer's disease Patients showed maximum degeneration by cholinergic neurons and choline acetyltransferase and acetyl cholinesterase enzymes in Alzheimer's disease decreased their function in the cerebral cortex. The enzyme phospholipase A2 (PLA2) contributes to the release of arachidonic acid from the membranes of phospholipids, which is essential to the synthesis of the inflammatory response's main mediators.

Since phosphatidylcholine is one of the substrates of PLA2, the activity of this enzyme may lead Alzheimer's disease to lower abolition of phosphatidylcholine cat.¹⁷

Risk factors

Age

Age, one of the non-modifiable risk factors, is the greatest causative factor for forming Alzheimer's disease. Dementia is most often seen in older Alzheimer's disease patients; 65 years of age and older. Nearly 5 % of people over the age of 65 and 74 have Alzheimer's disease. The number rises to 50 percent for those over 85 years of age. It should be important to remember that Alzheimer's disease is not a common part of aging, and it is not enough to cause Alzheimer's disease alone in older age.

Various studies indicate that aging, including in the brain, can affect the self-repair mechanisms of the body and many of the cardiovascular risk factors increase with age, such as high blood pressure, heart disease, and high cholesterol.

Family history

There is no need for a person to inherit the disorder or have an Alzheimer's family history. Individuals with an Alzheimer's parent, brother or sister, however, are more likely to develop the disease than those without a first-degree of relatives with Alzheimer's.

Those who have more than one first degree relative to Alzheimer's are at a somewhat greater risk. Factors related to genetic inheritance (genetics) and common environment and predisposing factors (e.g. exposure to nutritious food and daily exercise habits) can play a role as diseases occur in families.

The elevated risk of getting an Alzheimer's genetic history is still not elucidated by how the person has inherited the risk gene APOE- $\epsilon 4$.

Genetic mutations

Different mutations in one of three genes affect a Small proportion of people of Alzheimer's cases are predicted to be 1% or less: the amyloid precursor protein gene, the presenilin 1 protein gene, or the presenilin 2 protein gene.

A gene mutation is an unusual change in the format of chemical combinations forming the gene. Genes with any of these unique mutations were termed "deterministic genes," which means that one of the genes' inheritance virtually guarantees an Alzheimer's disease patient's development of Alzheimer's disease.

In these individuals, signs of dementia tend to develop around 65 years and older but can be as early as 30 years in age, while the vast majority of the people with Alzheimer's disease begin late at 65 years of age or older.

Apolipoprotein E (APOE)- $\epsilon 4$ allele gene

This APOE gene is the trigger for a protein that holds cholesterol in the blood. Anyone inherits one type of the APOE gene from each parent $\epsilon 2$, $\epsilon 3$, or $\epsilon 4$. It is known that having the form of $\epsilon 3$ does not increase/decrease the Alzheimer's incidence though $\epsilon 2$ could decrease the incidence. Nevertheless, the presence of $\epsilon 4$ increases the risk of developing and developing Alzheimer's disease at a younger age. Most who inherit two genes of $\epsilon 4$ are always at greater risk than those with one gene of $\epsilon 4$. Researchers noted to be between 40 and 65 percent of those living with Alzheimer's have Alzheimer's disease one or two copies of the APOE- $\epsilon 4$ gene.

Amyloid Hypothesis

In this context, the deposition of Amyloid precursor protein (APP) is one of the main risk factors. Amyloid precursor protein is generally required for neuronal cell growth, but the Post-translational alteration takes place via two mechanisms, α - or β -site enzyme cleavage. In both cases, the C terminal fragment is created between the Trans membrane region, membrane treated and further processed.

γ -secretase is the byproduct of α -secretase and the product produces an evidently free from toxic protein fragment, although sequential β site cleavage enzyme produces the APP (BACE) and

the amino acid fibrillogenic amyloid beta ($A\beta$) cleavage is 38–43.¹⁷

The most susceptible amino acid for aggregation is $A\beta_{42}$, located in center of the neuritic plaques and it is toxic to synapses when aggregated into oligomers and the main pathological element in Alzheimer's disease is considered by the neurons.¹⁸

More than 150 mutations have now been identified resulting in this family Alzheimer's disease, which all include all three genes that are completely involved in the creation of $A\beta$.

The highest percentage of disease-treating agent for Alzheimer's disease is APP production and $A\beta$ through reducing the development of $A\beta$ toxic type; removing $A\beta$ from the brain by movement of degrading Alzheimer's disease action, transportation or immunotherapy; or preventing harmful effects of $A\beta$.¹⁹

Figure 1: Alzheimer's disease pathological cascade
 A β : Amyloid beta, APP: Amyloid precursor protein, P-tau: Phosphorylated tau protein.

Tau and Neurofibrillary tangles NFTs

NFTs are the products of paired helical hyperphosphorylated filaments derived from Tau protein (MAPtau or tau) associated with microtubules and condensed into cytoskeleton inclusions.²⁰ Tau phosphorylation is important for its function, but hyperphosphorylated tau is no longer in contact with microtubules, in ste Alzheimer's disease of binding it is aggregates into paired helical filaments.²¹

This le Alzheimer's disease is to a general micro tubular instability and axonal transport disruption that ultimately le Alzheimer's disease s to Neuronal damage and death of cells. The elevated levels of phosphorylated or complete tau throughout the CSF are clear indicators of neurodegenerative diseases; it is alre Alzheimer's disease y explained in (Figure 1) how this APP, NFTs and other factors causing Alzheimer's disease.²²

Several basic scientific models suggest that that the aggregation of tau proteins in neurodegenerative models can reduce $A\beta$ -dependent cognitive decline or $A\beta$ -dependent impairment.²³

Cholinergic Hypothesis

Cholinergic Hypothesis is one the most important risk factor for Alzheimer's disease. Recent studies suggesting that damage or abnormalities in this pathway is a control causing factor for Alzheimer's disease. The cholinergic theory states that the loss of

cholinergic development in the central nervous system substantially progresses to Alzheimer's disease vanced age and cognitive decline in Alzheimer's disease.²⁴

Moreover, the cholinergic role of memory and learning in the brain was first identified more than 30 years ago after the cholinergic antagonist especially antimuscarinics agents were found to impair memory.

Some of the studies reported that the activity of acetyl cholinesterase (AChE) and choline acetyl transferase (ChAT) levels are more in Alzheimer's disease patients explained in (Figure 2).²⁵

Acetyl cholinesterase is an enzyme responsible for degrading Alzheimer's disease action of acetyl choline in the synaptic cleft, reduced level of acetyl choline is directly responsible for Alzheimer's disease. There is extensive evidence that the nerve growth factor (NGF) in the basal forebrain supports cholinergic neurons and is deficient in NGF le Alzheimer's disease ing to atrophy and possibly cell death. In + contrast, aged cholinergic neurons are less likely to release acetylcholine after potassium stimulation than they were able to synthesize the transmitter.

This selective weakness of neurons comprising basal forebrain cholinergic pathways should therefore be taken into consideration in the theories concerning the proximal cause of Alzheimer's disease.²⁶

Figure 2: Acetyl cholinesterase role in Pathophysiology of Alzheimer's disease

Oxidative Stress

Oxidative stress is a crucial factor in Alzheimer's Pathophysiology. Oxidative stress occurred by generation of free radicals. Free radicals in Alzheimer's disease are the chemical species containing unpaired electron and those are formed during the pathophysiological processes. Even though reactive oxygen species (ROS) play a significant role in physiological concentrations including regulation of the cell cycle, phagocytosis, and enzyme activation in several cell signaling pathways. Excessive ROS production results in a variety of harmful effects including damage to DNA, lipids, and proteins.²⁷

Mechanisms for the pathogenesis of Alzheimer's disease are the role of mitochondrial dysfunction and enhanced apoptosis with low antioxidant status. Many studies have shown that the role of superoxide anion, hydroxyl radical in Alzheimer's disease, hydrogen peroxide and nitric oxide in oxidative stress mediates Alzheimer's disease neurodegeneration.²⁸

Microglia cell activation attributable to synaptic lesions generates excessive superoxide radical in Alzheimer's disease. Greater metabolic requirements and the post-mitotic nature of neurons and glial cells frequently make themselves highly vulnerable to oxidative stress. The low rate of brain regeneration and insufficient antioxidants capacity throughout the brain further increases oxidative stress.³⁰ mitochondrial autophagy is a key source of ROS output.³¹

Diagnosis of Alzheimer's disease

Alzheimer's disease diagnostic criteria are currently based on clinical and psychometric evaluation. There is no single Diagnosis test for Alzheimer's dementia. To help make a diagnosis, physicians use a variety of techniques and equipment.

The followings are included:

- To provide a detailed medical and family history, including records of psychological and cognitive and behavioral changes
- Ask family members to provide feedback on improvements in Thinking skills and attitudes, cognitive training, and physical and neurological testing.

- Carry out patient blood tests and neuroimaging to rule out any other potential causes of dementia symptoms such as cancer or certain vitamin deficiency sciences.
- Provide brain scans to assess if the patient has higher levels of amyloid plaques, an Alzheimer's sign in certain contexts; average levels may suggest that Alzheimer's is not the cause of Dementia.

Some diagnostic tools should also be developed to help measure the effectiveness of new therapies. Neuroimaging and particularly magnetic resonance imaging (MRI) have been shown to be an indicator of early detection of Alzheimer's disease, especially in individuals medically diagnosed as mild cognitive impairment (aMCI) that is a precursor to Alzheimer's disease in most patients.³²

Cerebrospinal fluid analysis can reveal high levels of abnormal components in the cerebrospinal fluid such as β -amyloid, Tau protein, and Tau protein phosphorylated. It may take several days or weeks for a patient to complete the necessary tests and exams, and for the doctor to analyze the data and make a diagnosis.

Pharmacological treatment

This seems to be necessary for the new treatment for Alzheimer's disease. However, trials have already shown that Alzheimer's disease symptoms have significant contributions to treatment and it is well known that the use of inhibitors of acetyl cholinesterase (AChE) has already shown symptomatic effectiveness and decreased progression of disease.³³

Acetyl cholinesterase inhibitors for Alzheimer's are a symptomatic therapy (examples are Tacrine, rivastigmine, donepezil and galantamine). These compounds prevent neurotransmitter acetylcholine degradation in Alzheimer's disease (enzymes acetyl cholinesterase and Butyrylcholinesterase) and improve the activity of acetylcholine on nicotinic and muscarinic receptor activation in the brain.³⁴

Rivastigmine is commonly used for the treatment of Alzheimer's, being able to block the enzymes acetyl cholinesterase and Butyrylcholinesterase, being highly effective in raising acetylcholine cerebral levels. Moreover, this medication produced many Alzheimer's disease side effects on choline

(such as Alzheimer's disease verse effects of the gastrointestinal system) when the dosage was suddenly increased.³⁵

One selective acetyl cholinesterase inhibitor, donepezil, was studied for one year experimentally and after prolonged therapy and reported a 38% reduction in functional deterioration in patients with Alzheimer's disease compared to placebo.³⁶

Tacrine is an inhibitor of the first generation and was the first reversible inhibitor of acetyl cholinesterase used for the treatment of Alzheimer's disease. This drug has, however, been of severe toxicity and is no currently used in clinical practice. Tacrine h Alzheimer's disease shown hepatotoxicity experimentally, le Alzheimer's disease ing to increased hepatic transaminases, resulting in drug-induced hepatitis in many patients and le Alzheimer's disease s to cessation of medication regrettably, around 90% of drug induced hepatitis cases of Alzheimer's disease occurred within the first twelve weeks of Tacrine therapy.³⁷

Studies have recently highlighted the synthesis of Tacrine congeners, which were much more efficient and selective than those of the original drug.³⁸

Galantamine has also been an anti-cholinesterase used for the Alzheimer's disease therapy. The drug can suppress acetyl cholinesterase and modulate allosteric nicotinic receptors as well. In fact, there's is evidence that galantamine increases brain perfusion and metabolism of cerebral glucose (which would be associated with a gain in cognitive stabilization in the clinical setting).³⁹

Besides the improvements during treatment, these enzyme inhibitors of acetyl cholinesterase that trigger an increase in the output of this enzyme after pharmacological treatment has been discontinued.⁴⁰

Memantine is a commonly used NMDA receptor antagonist for mild to extreme Alzheimer's disease treatment. The medication is thought to work by blocking NMDA channels reversibly. Memantine supplementation substantially enhances different aspects of the disorder such as behavior, everyday living behaviors, and global function. There is considerable evidence, however, that the use of prevents neurodegeneration progression in Alzheimer's disease patients.⁴¹

The use of poly phenolic antioxidants to reverse age related deficits and a cognitive and motor decline in Alzheimer's disease patients is also of concern. However, studies using these nitro phenols ' microinjections have also shown that these compounds have been able to prevent amyloid deposition in rat brains.⁴²

Alzheimer's disease advanced targets to treat Alzheimer's disease

Potential Alzheimer's disease care research involves targeting etiological pathologies: Neurofibrillary (p-tau) and senile (A β) tangles. It remains, however, a question as to which phenomenon is one the suitable target for slowing or stopping neurological deterioration and how soon care should be initiated.⁴³

Clinical studies continue to recruit symptomless individuals with genetic susceptibility or biomarkers suggesting increased risk of Alzheimer's disease, with results predicted early over the next era.

With a more collaboration among investigators, private and public funding, and monitoring of at-risk populations, a greater indicator of successful clinical studies can be produced.

Anti-amyloids

According to the amyloid progression hypothesis, harmful plaques tend to be the disease's earliest sign, a statement supported by A β data up to 20 years before symptoms begin.⁴⁴

Researchers found that this abnormal amyloid plaque causes tau protein phosphorylation, which further extends to surrounding neurons perhaps infectiously by micro tubular transportation, contributing to neuronal collapse.⁴⁵

Monoclonal antibodies (passive immunotherapy) are one class of drugs produced using this data. Another way of treatment includes an antibody injection targeting excessive A β and making it easier to extract it from the brain. To remove these plaques from the brains of people with Alzheimer's disease; initially, two of these monoclonal antibodies were produced.⁴⁶

Neither drug increased cognitive performance in Le Alzheimer's disease ing specialists in patients with mild to moderate illness to conclude that only after taken in these drugs can be effective in the early stages of MCI and mild dementia.

Studies comparing similar drugs are continuing in this class with either the intention of enhancing or maintaining cognition attributable to Alzheimer's disease in patients with MCI.

Another approach to the A β plaque burden in the brain is to inhibit the enzymes that produce the A β peptide from its parent, the amyloid precursor protein (APP). A number of drugs are currently being developed to target β -site APP cleaving enzyme 1 (BACE1), which is deemed essential for the production of A β peptides.⁴⁷

Although earlier studies of BACE1 inhibitors have not provided meaningful results in humans, the new agent verubecestat does have more than 40 times reduced A β levels in the brains of rodents and primates and showed a good safety profile in early human studies.⁴⁸

One therapy is currently under investigation for elderly patients with clear biomarkers or Alzheimer's disease family history, known as early studies, for its effect on memory and learning performance. Although no current studies are ongoing using this method in humans, many experts believe that combination therapy using A β removal methods can potentially le Alzheimer's disease to success in Alzheimer's disease care.⁴⁹

Anti-tau drugs

Although phosphorylated tau tends to be the ultimate pathology and seems to be probably to be the direct cause of Alzheimer's disease symptoms, medications are also developing to lighten the burden of this protein.⁵⁰ Several different tau vaccinations showed both efficacy and safety in animal models and an anti-tau drug showed a good safety profile in a recent small study and even triggered a human immune positive response.⁵¹ Many other early stage drug trials targeting the tau protein are currently in progress, although the findings have yet to be published, Along with this some which are in clinical studies phase are shown in Table 1.⁵²

β -secretase inhibition (BACE 1 inhibitor)

Cleavage of APP by BACE would be the First phase in the production of APP proteolytics, allowing it to be the ideal spot for all post-translation products to intervene to prevent development in the casc Alzheimer's disease e.

In sporadic Alzheimer's disease, the forms of Alzheimer's disease, BACE activity is increased.⁵³ BACE knockouts have restricted phenotypic changes in excess of reduced A β levels proposing that there can be minimal side effect profiles of potent inhibitors.

It has been hard to develop agents capable of inhibiting BACE's multisite behavior on its APP substratum. Initially, effective

inhibition needed large molecules (> 500 kDa) that could not cross BBB.⁵⁴

Nevertheless, recently developed higher lipophilic nature, less orally active agents with exposure to the CNS, and these agents are actually being used in human clinical trials.⁵⁵

Table 1: The therapies and objectives under study are outlined

The Target	Drug candidate	Study phase	Expected date of Completion	Out comes
Amyloid- β	c Alzheimer's disease 106	2	May 2024	
	CNP520	2	May 2024	
	LY3002813*	2	December	
	Solanezumab	3	Terminated May 2017	Not successful effective
	GSK933776	2	Finished	Not successful
Phosphorylated tau	UB-311	1	Finished	Safe for phase 2
	IONIS-MAPTRx	1, 2	February 2020	
	ABBV-8E12	2	June 2021	
	RO7105705	2	September 2022	
BACE1	Elenbecestat	3	December 2020	
	LY3202626*	2	December 2020	
	Verubecestat	3	March 2021	
	LY450139	3	Finished	Not successful
RAGE	Azeliragon	3	Terminated January 2019	Not successful

Butyrylcholinesterase (BuChE)

Butyrylcholinesterase (BuChE) is a hydrolase that hydrolyses choline esters. Degeneration of the cholinergic system of the basal forebrain is a sign of Alzheimer's disease. Studies have found that in the neurodegenerative disease, as in Alzheimer's disease, the biochemical properties of BuChE have changed.⁵⁶

Because of the loss of Ach and AchE neurons expressed in the high amount responsible for the reduction of neurotransmitters and their enzymes. In the cortical region, BuChE increases during Alzheimer's disease, which is responsible for the formation of neuritic plaques and neurofibrillary tangles.

Agonism and antagonism of the GABA receptor

Although nerve cells with exciting neurotransmission were destroyed in Alzheimer's disease, inhibitory mechanisms, including GABA neurotransmission, may go uncontrolled as well as cause cognitive problems.⁵⁷ However, this system's stabilizing agents will modify the exciting tone and may excitotoxicity. For mild cognitive impairment, one selective GABA B receptor antagonist was clinically investigated but consequently, the usefulness of Alzheimer's disease was not demonstrated.⁵⁸

Conversely, reverse agonists GABA A receptor benzodiazepine binding (believed to enhance synaptic inhibition by reducing chloride ion flux) can improve cognition. A Phase II clinical study of etazolate, an analog of the GABA A receptor, recently completed registration. As an Alzheimer's disease treatment based more on its affinity to A β than any GABAergic properties, the synthetic GABA analogue 3-amino-1-propanesulfonic acid was actively pursued.⁵⁹

Serotonergic modulation

Of the 14 main serotonin receptor subtypes (5-hydroxytryptamine [5-HT]), others, namely 5-HT_{1A}, 5-HT₄, and 5-HT₆, are substantially depicted in memory and learning areas and decline in Alzheimer's disease.⁶⁰

Serotonin receptor levels (5HTRs) can also change the very mild disease which further involves these receptors in the Alzheimer's

disease related cognitive impairment. In other dementias, 5-HTRs may also be modified.⁶¹

The 5HTRs' function is complicated, including the control of a variety of other neurotransmitter systems such as ACh, dopamine, GABA and glutamate.⁶² Across animal models, both selective agonists and 5-HTR antagonists have beneficial cognitive effects across line with this description. A selective 5-HT_{1A} receptor antagonist has entered Phase I human research as a treatment for Alzheimer's disease.⁶³

Combination therapy

Combination studies are distinct from Alzheimer's disease additional studies; latter are the typically utilized for new treatments in Alzheimer's disease while two drugs are tested alone, in combination, and in comparison, with placebo, usually in a 2x2 trial design in combination therapy studies. Treatment combinations might be pharmacodynamics or pharmacokinetic. Pharmacodynamic combinations are structured to have various effects on the disease whereas pharmacokinetic combinations for affects the absorption, distribution metabolism or elimination of a drug.

Pharmacodynamic combinations for Alzheimer's disease care might include symptomatic medicines that fix the behavioral and cognitive manifestations of Alzheimer's disease without modifying the underlying biology of the disease or disease-modifying therapies (DMT) that alter the course of the disease by Alzheimer's disease dressing the core biology of Alzheimer's disease in to nerve cell death.⁶⁴

The high incidence of inflammatory modifications in Alzheimer's disease indicates that co-Alzheimer's disease ministering anti-inflammatory and amyloid or tau-directed therapies needs evaluation. Masitinib, a potent tyrosine kinase antagonist, antagonizes the activity of mast cells and potentially regulates pro inflammatory mediators, possibly targeting neuroinflammatory pathways that are thought to play a role in Alzheimer's disease pathogenesis.⁶⁵

There are currently two DMTs in Phase III studies that resolve two goals and are acceptable combination therapies. ALZT-OPT1

a combination of cromolyn (anti amyloid) and ibuprofen (anti-inflammatory agent) identifies early Alzheimer's disease patients who either receive or do not receive standard care agents.

For patients with mild to moderate Alzheimer's disease, rasagiline, a potent MAO inhibitor is also present in a phase II trial. Rasagiline has been shown to be neuroprotective, anti-apoptotic dependent on Bcl2, protein kinase C and the proteasome-ubiquitin complex.⁶⁶

Vaccination

Full length vaccination A β peptide reduces the burden of amyloid and prevents learning and memory loss in Alzheimer's disease animal models. Recent animal model research suggests that vaccination will reduce the burden of amyloid and the severity of NFT. Due to a 6% occurrence of T-cell mediated meningoencephalitis, a clinical trial of A β vaccination (AN1792) in 300 moderate Alzheimer's disease patients was halted.⁶⁷

However, a major research focus remains the clinical development of Alzheimer's disease immunotherapy; including successful vaccines. Full length vaccinations are under progress, as are peptide fragment vaccines.⁶⁸

Passive immunization aims to provide the vaccination's abasement and possible therapeutic benefit by avoiding the T-cell mediated response.

Likewise, microglial activation occurs in response to vaccination and passive immunization in transgenic Alzheimer's disease models.⁶⁹ Clinical research also includes a variety of antibody therapies, including two monoclonal antibody therapies in Phase III trials Bapineuzumab and Solanezumab.

A new area of clinical research is the therapeutic use of naturally occurring auto antibodies in the form of intravenous immunoglobulin (IVIg) as treatment for Alzheimer's disease. In a sample of eight Alzheimer's disease patients, IVIg therapy raised plasma and decreased A β CSF levels.⁷⁰

Neuroprotection

In the context of disease specific pathology, neuroprotective approaches aim to maintain cell health. These include medications that reduce inflammation or other Alzheimer's disease pathobiology downstream markers.

Epidemiological studies, for example, have indicated disease prevention properties for NSAIDs and statins.^{71,72}

The anti-inflammatory effects of NSAIDs and the lowering cholesterol properties of Statins may be both helpful in the prevention or treatment of Alzheimer's disease. Nevertheless, both agent groups can also minimize A β .⁷³

Mitochondrial dysfunction plays a defined role in cell death in Alzheimer's disease; soluble Ab reaches the mitochondria which results in dysfunction of the mitochondrial membrane, Ca²⁺ entry, lower energy output and oxidative stress that can eventually lead Alzheimer's disease to neuronal death.⁷⁴

Agents that stable the mitochondrial membrane, inhibit mutation of mitochondrial DNA, eliminate reactive oxygen species, or enhance mitochondrial function that prevent age-related cellular changes and counteract neurodegenerative diseases, like Alzheimer's disease. Dimebon (Dimebolin, latrepirdine) is a non-selective antihistamine that was previously approved in Russia

and is now being formulated for Alzheimer's disease and Huntington's disease.⁷⁵

Future strategies to treat Alzheimer's disease

Alzheimer's disease is a complex multifactorial disease that may need equally complex treatment strategies. Early detection of illness, alternative medications and lifestyle choices are all likely to contribute to the effective are Alzheimer's disease ication of the disease.⁷⁶ to understand the immediate future in the production of Alzheimer's disease drugs, it is important to assess the current state of the industry.

Considering the urgent need and strong focus on developing new therapy classes for Alzheimer's disease, there is a potential for rapid translation into clinical research of basic science findings. It is almost certain that the next 5 years will bring new findings that will increase our goal range in Alzheimer's disease. A significant number of agents are now in the final phase of clinical development and we are likely to be able to confirm effectiveness for one or more agents capable of at least slowing the progression of disease in the next five years.

Alzheimer's disease clinical trials may include biomarkers so that accurate timing of interventions can be elucidated in the design of the study, as well as patient subgroups for intervention can be established and outcome measures tracked. At the early stages of the disease, current efforts have been moved to prevention of Alzheimer's disease.⁷⁷

Multi targeted drug development and drug repositioning in Alzheimer's disease are other major focus areas.⁷⁸ In Alzheimer's disease dition, duration of the disease should also be considered by the clinician while treating an Alzheimer's disease patient for a better drug development.

CONCLUSION

Alzheimer's is rapidly increasing in the population of the world. Alzheimer's disease management remains a major challenge for current drug discovery due to the unclearly understood mechanism of Pathophysiology and target recognition. There are just a few approaches and drugs for treating the disease. In this study, we concentrated on several established targets that are involved directly and indirectly in the generation of beta amyloid and neurofibrillary tangle in Alzheimer's disease as well as other molecules.

Here we discussed about Possible Diagnosis, Availability of drugs and their limitations, Current novel approaches to treat Alzheimer's disease along with their status in clinical trials are discussed.

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