INTRODUCTION
Alzheimer’s disease has been considered as one of the most vulnerable neurological disorder observed in old age which was first explained by Alois Alzheimer in 1906. Alzheimer’s disease which blankly known is that it is the condition of the human being in which they forget to do even the daily routine matters. A rich knowledge on AD will be inestimable to take part in this distress. Alois observed that a strange substance showed weird alterations in neurofibrils. They are non-uniform sediment of β-amyloid on the brain, found in areas, that mainly includes the hippocampus, amygdale and the cerebral cortex. In medical words it is a common type of dementia occurring in older people practically due to ageing. The several evident molecular and cellular events that follows Alzheimer’s disease includes β-amyloid deposition, tau protein hyperphosphorylation and neurofibrillar tangles formation, nicotinic acetylcholine receptors (nAChRs) expression reducing, cholinergic markers and certain risk factor genes and mutation presences. Acetyl cholinesterase (AChE) succeeded in being a reliable therapeutic target for Alzheimer’s indicative progress. For the treatment of the myasthenia gravis the inhibition property of acetyl cholinesterase was a proven efficacy, as a result the inhibition property was given the consideration of achievable therapeutic target. Blood and neural synapse are the two regions were the AChE is primarily present. The two acetyl cholinesterase used for the improvement of the cholinergic neuro transmission and cognitive functions comprise donepezil and rivastigmine. These cholinesterase inhibitors including galantamine were introduced a long year back and was on the research field for the treatment application of the Alzheimer’s disease from the beginning of 20th century also. They proved to be the complete answer for the treatment of the Alzheimer’s disease. In more than 50 countries donepezil was considered as a leading treatment for Alzheimer’s disease in the beginning. It came under the second generation of the AChE inhibitors. Most of the studies proved that the donepezil is a reliable drug over many other adverse drug reactions. NMDA (N-methyl-D-aspartate) receptors antagonist memantine have also been taken into research for the treatment of the Alzheimer’s disease. They help in the improvement of the cognitive functions of the affected patients. Other therapies aiming hyperphosphorylated tau and novel targets such as mitochondrial function enachments, serotonin receptors, advanced glycation end products and nerve growth factor controlling receptors and a vast strategies researches and implementation are going on. Nicotinic receptors and researches using α-secretase have grown up as a strategy of treatment for the Alzheimer’s disease. Since nano technology is an emerging field in the present years recent studies have revealed that nano technology plays a vital role in the early detection and management of the Alzheimer’s disease which provides a successful diagnosis of the disease and opens a path for more treatment possibilities. In United Nations a survey conducted showed that by 2050 about 300 millions of people will be crossing the age of 80 years are believed to be affected by this neurodegenerative disease. Below is a bar chart that emits a comparison between 5 states of America with Americans age 65 and older that have been affected and believed to be affected by Alzheimer’s disease.

Chart 1: Representation showing the ratio of American people affected in 2000-2012 and can be affected in 2025 by Alzheimer’s
Acetyl cholinesterase

Acetyl cholinesterase inhibitor or anti-cholinesterase is a chemical that prevents the breaking down of acetylcholine by the enzyme acetyl cholinesterase, which helps in the increment of level and action of the acetylcholine neurotransmitter. The main three acetyl cholinesterase that have been under studies and research are

Donepezil

Donepezil was accepted in 1996 for mild-moderate Alzheimer’s treatment based on a study carried out by Rogers et al., in which 468 patients were divided into a group of three. Within three and nine week’s improvement and significant effect were shown up but the patients who were given a high dose suffered from transient nausea, diarrhea, and insomnia. Donepezil are believed to have not only a neurotransmitter level action but also act at cellular and molecular level including AChE neuroprotective isofrom inducing, glutamate induced excitotoxic cascade blocking, oxidative stress mitigating and inflammatory cytokines expression reduction. Donepezil are said to have not only a strong signal transduction molecular detection of biomarkers helps for the nano diagnostic approach. In this approach, detection technique used includes micro Raman spectroscopy, Rayleigh Spectroscopy, and magnetic resonance imaging technique uses for the detection of Alzheimer’s disease happened. Centrally mediated cholinergic gastrointestinal events are the most unfavorable event of rivastigmine, can be minimized by intervals of slower dose-escalation and full meal administration. Rivastigmine is a highly potential and beneficial for the treatment hence have been widely accepted.

Galantamine

Galantamine is an effective and efficient symptomatic treatment for Alzheimer’s disease. It was approved in 2001 and used for gentle and reasonable treatment of the Alzheimer’s disease. Major improvements in cognition, behavioral symptoms and daily activities where shown by the patients who were treated with galantamine, compared with the placebo recipients which was achieved in spite of subscale apolipoprotein E ε4 allele count of the Alzheimer’s disease. Below table contain information about various acetylcholinesterases that are available presently in the market for the treatment purpose the Alzheimer’s disease including the above three.

Rivastigmine

Rivastigmine was approved in 2000 and had been used for the treatment of dementia caused by Parkinson’s and of Alzheimer’s type. The administration of this drug is done either orally or through transdermal patch. But in the form of capsule it exhibited side effect such as nausea, vomiting, anorexia, and diarrhea. In 1997 capsule and liquid form of this drug became available and in 2006 the global approval of first product for treatment of mild and moderate Alzheimer’s disease happened. Rivastigmine is an effective and efficient symptomatic treatment for Alzheimer’s disease. It was approved in 2001 and used for gentle and reasonable treatment of the Alzheimer’s disease. Major improvements in cognition, behavioral symptoms and daily activities where shown by the patients who were treated with galantamine, compared with the placebo recipients which was achieved in spite of subscale apolipoprotein E ε4 allele count of the Alzheimer’s disease. Below table contain information about various acetylcholinesterases that are available presently in the market for the treatment purpose the Alzheimer’s disease including the above three.

<table>
<thead>
<tr>
<th>Name of the compound</th>
<th>Trade name</th>
<th>Routes</th>
<th>Chemical name</th>
<th>Chemical formula</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physostigmine</td>
<td>Antilirum</td>
<td>Intravenous, Intramuscular, Ophthalnic</td>
<td>(3αR,8αS)-1,3α,8-Trimethyl-1H,2H,3H,4α,8αA-pyrrolo[2,3-b]indol-5-yl N-methylcarbamate</td>
<td>C_{9}H_{25}N_{3}O_{2}</td>
<td>Eseroline-major metabolite</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>Prostigmin</td>
<td>Oral, Intravenous</td>
<td>3-[(dimethylamino)carbonyl]oxo)-N,N,N-trimethylbenzenaminium</td>
<td>C_{9}H_{25}N_{3}O_{2}</td>
<td>Slow hydrolysis by acetylcholinesterase and plasma esterase</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Mestinon</td>
<td>Oral, Intravenous</td>
<td>3-[(dimethylcarbamoyl]oxo]-1-methylpyridinium</td>
<td>C_{9}H_{15}N_{3}O</td>
<td></td>
</tr>
<tr>
<td>Ambenonium Chloride</td>
<td>Mytelase</td>
<td>Oral</td>
<td>2,2’-[1,2-dioxoethane-1,2-dihydridinno]bis[N(2-chlorobenzyl)-N,N-diethylethanaminium]</td>
<td>C_{20}H_{20}Cl_{2}N_{5}O_{2}</td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Exelon</td>
<td>Oral, Transdermal</td>
<td>(S)-3-[(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate</td>
<td>C_{10}H_{19}N_{3}O</td>
<td>Hepatic, via pseudocholinesterase</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Razadyne/ Nivalin</td>
<td>Oral</td>
<td>(4αS,6R,8αS)- 5,6,9,10,11,12- hexahydro- 3-methoxy- 11-methyl- 4αH-[1]benzofuro[3a,3,2-eff] [2] benzaazepin- 6-ol</td>
<td>C_{13}H_{20}NO_{3}</td>
<td>Haptic partially CYP450: CYP2D6: 3A4 Substrate</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Aricept</td>
<td>Oral tablets</td>
<td>(4S)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-2,3- dihydroidenidone-1-one</td>
<td>C_{20}H_{30}NO_{3}</td>
<td>CYP 450 iso enzyme 2D6 and 3A4</td>
</tr>
</tbody>
</table>

Nano Technology in Alzheimer’s Disease

Nanotechnology is an emerging field in the detection, diagnosis and treatment of many diseases that have been a challenge to the human race ever, including cancer and neurodegenerative disorders. Their property to perform molecular detection of biomarkers helps for providing highly strong signal transduction and controllable production of the required devices of desired structure in nano scale (1-100nm). The diagnostic method followed in nanotechnology for Alzheimer’s disease include

Nanodiagnostics approach in vitro conditions

In this approach, method of detection includes conjugates of DNA-nano particle in which protein biomarkers can be detected at attomolar scale and the technique is called barcode assay. Biomarkers are identified by using DNA barcodes along with the amplification by polymerase chain reaction. System of scanning tunneling microscopy is another technique used in this approach in which a scanning tunneling microscopy is used for the molecular detection. Two-Photon-Rayleigh Spectroscopy technique uses Two-Photon-Rayleigh scattering signal for the detection of tau protein, a biomarker, at a concentration below 1pg /ml within 35 minutes for the nano diagnostic approach.

Nanodiagnostics approach in vivo conditions

In this approach, detection technique used includes micro magnetic resonance imaging. In the recent decades iron oxide nano particles has been researched widely as a contrast agent in the magnetic resonance imaging technique. This technique cannot be used for early detection of the disease because amyloid plaue formation occurs only at high stage of the disease. Thus this technique has limitation in the detection of the disease compared to the other technique established by the researchers using nanotechnology.
The treatment strategies in nano technology for Alzheimer’s disease include neuroprotective and neuroregenerative approaches\textsuperscript{21}. There are many nano carriers used in nanotechnology for the drug delivery applications. The major nano carriers presented are:

a) Cholinesterase inhibitors nanocarriers
b) Acetylcholine nanocarriers
c) Metal chelator nanocarriers
d) Gene nanocarriers
e) Curcuminoids nanocarriers

Early diagnosis of Alzheimer’s disease is a very valuable step to be taken to prevent the irretrievable and out of control effect of this neurodegenerative disease. Currently available approaches for the analysis and treatment methods for the prevention are not powerful enough to dodge the consequences of this disease. However nanotechnology has shown some strength to the researches, and created a belief on them to move on with their experiments.

**Alzheimer’s disease and Disease Modifying Drugs**

Disease modifying drugs are agents that are mainly used to create a hindrance to the progression of Alzheimer’s disease. The need for a biomarker is again, an unavoidable matter for the deciding the efficiency of disease modifying drugs. Reducing the production of Aβ-amyloid, preventing the aggregation of Aβ-amyloid, clearing the promotion of Aβ-amyloid and tau phosphorylation are main targets of disease modifying drugs so far\textsuperscript{24}. The splitting of Amyloid Precursor Protein (APP) by β-secretase 1 (Beta-site amyloid precursor protein cleaving enzyme 1 or BACE1) results in the concentration of C99 which is a soluble extracellular and is cell membrane bound fragment. Further splitting of C99 results in the generation of Aβ\textsuperscript{24}. But by cleaving APP initially prevents the production of Aβ\textsuperscript{23}. For suppressing the expression of β-secretase the thiazolidinediones-rosiglitazone and pioglitazone have been tested under randomized control trials\textsuperscript{25}. Rosiglitazone is an anti-diabetic drug PPARγ binding and following transcription of gene concerned in metabolic control. Different studies were conducted using rosiglitazone but none proved to an ultimate solution to the treatment purposes. All the studies lacked the presence of a perfect biomarker and a biological hypothesis. Developments of γ-secretase inhibitors are also going on. Semagacestat is the first γ-secretase to been clinically tested, showed Aβ concentration reduction in plasma and reduction in the production of Aβ in central nervous system\textsuperscript{27,28}. Non-steroidal anti-inflammatory drugs (NSAIDs) have also been introduced. Tarenflurbil was a failure due to its low effectiveness and poor brain incursion\textsuperscript{29}. Nilvadipine is on test under clinical conditions as a dependable treatment for Alzheimer’s. They are currently used for Antihypertensive, but helps in increasing Aβ clearance and inhibiting the properties of Aβ. They also help in restoring the blood flow in the regional cerebral part. PBT2 (8-hydroxy quinoline analog) and Scylo-inositol (stereo isomers of inositol) are the two orally administered disease modifying therapies to prevent Aβ aggregation. Some other small molecules, epigallocatechin-3-gallate and grape seed extract are also used to prevent Aβ aggregation\textsuperscript{30}. Passive immunotherapy was introduced as a treatment for Alzheimer’s disease but it possessed the side effect of causing extreme vasogenic oedema, alternative to this bapineuzumab and solanezumab, anti-Aβ monoclonal antibodies are studied on. Tau phosphorylation is the destabilization of neuronal micro tubular dynamics resulting in impairment of synaptic function, which is involved with the GSK3β enzyme. Lithium and valporate are presently used to prevent this but have proved to be less effective due to some side effects. There are a vast number of drugs that are used for the treatment purpose of other diseases, have found use in the treatment of Alzheimer’s disease. These drugs are commonly known as repurposed agents, studies have been proving that they are capable of showing a path to the future weapon for defending this neurodegenerative disease. Paclitaxel and Exenatide which are currently used for in the field of oncology and diabetes respectively, have been found to be neuroprotective and helps in reducing tau phosphorylation in relation to Alzheimer’s disease. While azithromycin and amphotericin B, currently used as antimicrobials are studied for alteration in Amyloid Precursor Protein processing and delays the formation of Aβ fibrils. Drugs that are used in field of antipsychotic such as Risperidone and Quetiapine are good neuro protective agent. Even insulin which is for diabetes treatment can facilitate the reduction of Aβ production and increase Aβ clearance.

**CONCLUSION**

The treatment strategies for Alzheimer’s disease that are currently available are never ending. Since the researches and studies are going on anxiously for finding an ultimate and permanent solution, which is still an unknown conclusion that can be put forward. Emerging field of nanotechnology has already joined the race as a final solution for Alzheimer’s disease treatment and is successfully maintaining the lead to win the race. β-Amyloid is a compound whose presence cannot be forgotten while considering the treatment strategies of Alzheimer’s disease, so as the studies and researches are still going on them. Numerous drugs have been proposed, in which some are still under screening and investigation. Various receptors (Nicotinic receptor and NMDA receptors) are also inevitable while considering the studies for the treatment of Alzheimer’s disease. Even though studies on this entire field are going on, the path to find final answers are long and puzzling.

**REFERENCES**

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