TREATMENTS FOR ALZHEIMER'S DISEASE: AN OVERVIEW

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ABSTRACT

Several diagnostic procedures have been carried out for implementing a successful treatment procedure for Alzheimer's disease. Most of the researches went in vain and many other scientists continued their researches for the same. Recent researches in Neurological areas have found an innovative diagnostic procedure for detecting the primary stages of Alzheimer's disease. As only symptomatic treatments are now available for Alzheimer's disease (AD), safe and effective mechanism-based therapies remain a great unmet need for patients with this neurodegenerative disease. Biochemical derivatives of complex molecules have been derived for the treatment of Alzheimer's disease in its primary stage. Thus we propose that targeting cholinesterase and Beta-secretase (BACE1) may be an effective and safe treatment strategy for AD. Nanotechnology and Disease modifying drugs has delivered significant developments in the early detection of Alzheimer's disease, has also been depicted here.

KEYWORDS: Alzheimer's, β -amyloid, Cholinesterase, Nanotechnology, BACE1

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 1906¹. 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 elder 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 neurofibrillary tangles formation, nicotinic acetylcholine receptors (nAChRs) expression reducing, cholinergic markers and certain risk factor genes and mutation presences². 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 where the AChE is primarily present. The two acetyl cholinesterase used for the improvement of the cholinergic neuro transmission and cognitive functions comprise donepezil and rivastigmine³. 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 patients⁴. 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 on⁵. 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 80years 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 insomnia⁶. Donepezil are believed to have not only a neurotransmitter level action but also act at cellular and molecular level including AChE neuroprotective isoform inducing, glutamate induced excitotoxic cascade blocking, oxidative stress mitigating and inflammatory cytokines expression reduction⁷. Donepezil are said to have a comparative oral bioavailability of 100% and in 3 to 4 hours it reaches its peak concentration of plasma. CYP 450 isoenzymes 2D6 and 3A4 metabolizes donepezil.

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^{8,9}. 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 happened⁹. Centrally mediated cholinergic gastrointestinal events are the most unfavorable event of rivastigmine, can be minimized by intervals of slower dose-escalation and full meal administration¹⁰. 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 disease¹¹. 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 were 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 1: Information on Various Acetyl cholinesterase Inhibitors

Name of the compound	Trade name	Routes	Chemical name	Chemical formula	Metabolism
Physostigmine	Antilirum	Intravenous, Intramuscular, Ophthalmic	(3aR, 8aS)-1,3a,8-Trimethyl-1H,2H,3H,3aH,8H,8aH-pyrrolo[2,3-b]indol-5-yl N-methylcarbamate	C ₁₅ H ₂₁ N ₃ O ₂	Eseroline-major metabolite
Neostigmine	Prostigmine		3-[[[(dimethylamino)carbonyl]oxy]-N,N,N-trimethylbenzenaminium	C ₁₂ H ₁₉ N ₂ O ₂	Slow hydrolysis by acetylcholinesterase and plasma esterase
Pyridostigmine	Mestinon	Oral, Intravenous	3-[[[(dimethylcarbamoyl)oxy]-1-methylpyridinium	C ₇ H ₁₃ N ₂ O ₂	
Ambenonium Chloride	Mytelase	Oral	2,2'-[[1,2-dioxoethane-1,2-diyl]diimino]bis[N-(2-chlorobenzyl)-N,N-diethylethanaminium]	C ₂₈ H ₄₂ Cl ₂ N ₄ O ₂ ¹²	
Rivastigmine	Exelon	Oral, Transdermal	(S)-3-[1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate	C ₁₄ H ₂₂ N ₂ O ₂	Hepatic, via pseudocholinesterase
Galantamine	Razadyne/ Nivalin	Oral	(4aS,6R,8aS)-5,6,9,10,11,12-hexahydro-3-methoxy-11-methyl-4aH-[1]benzofuro[3a,3,2-ef][2] benzazepin-6-ol	C ₁₇ H ₂₁ NO ₃	Hepatic partially CYP450: CYP2D6/3A4 Substrate
Donepezil	Aricept	Oral tablets	(RS)-2-[(1-benzyl-4-piperidyl)methyl]-dimethoxy-2,3-dihydroinden-1-one	C ₂₄ H ₂₉ NO ₃	CYP450 iso enzyme 2D6 and 3A4

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)^{12,13}. The diagnostic method followed in nanotechnology for Alzheimer's disease include

Nanodiagnostic approach in 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 bio-barcode assay. Biomarkers are identified by using DNA barcodes along with the amplification by polymerase chain reaction¹⁸. System of scanning tunneling microscopy is

another technique used in this approach in which a scanning tunneling microscopy is used for the molecular detection^{19,20}. 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 minutes²¹ for the nano diagnostic approach.^{14,15}

Nanodiagnostic approach in in-vivo conditions

In this approach, detection technique used includes micro magnetic resonance imaging²¹. In the recent decades iron oxide nano particles has been researched widely as a contrast agent in the magnetic resonance imaging technique^{22,23}. This technique cannot be used for early detection of the disease because amyloid plaque 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.^{16,17}

The treatment strategies in nano technology for Alzheimer's disease include neuroprotective and neuroregenerative approaches²¹. 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 A β -amyloid, preventing the aggregation of A β -amyloid, clearing the promotion of A β -amyloid and tau phosphorylation are main targets of disease modifying drugs so far²⁴. The splitting of Amyloid Precursor Protein (APP) by β -secretase 1 (Beta-site amyloid precursor protein cleaving enzyme 1 or BACE1) results in the production of C99 which is a soluble extracellular and is cell membrane bound fragment. Further splitting of C99 results in the generation of A β ²⁴. But by cleaving APP initially prevents the production of A β ²⁵. For suppressing the expression of β -secretase the thiazolidinediones-rosiglitazone and pioglitazone have been tested under randomized control trials²⁶. Rosiglitazone is an anti-diabetic drug PPAR γ 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 be clinically tested, showed A β concentration reduction in plasma and reduction in the production of A β in central nervous system^{27,28}. Non-steroidal anti-inflammatory drugs (NSAIDs) have also been introduced. Tarenflurbil was a failure due to its low effectiveness and poor brain incursion²⁹. Nilvadipine is on test under clinical conditions as a dependable treatment for Alzheimer's. They are currently used for Antihypertensive, but helps in increasing A β clearance and inhibiting the properties of A β . They also help in restoring the blood flow in the regional cerebral part. PBT2 (8-hydroxy quinoline analog) and Scyllo-inositol (stereo isomers of inositol) are the two orally administered disease modifying therapies to prevent A β aggregation. Some other small molecules, epigallocatechin-3-gallate and grape seed extract are also used to prevent A β aggregation³⁰. 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-A β 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 GSK3 β enzyme. Lithium and valproate 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 A β 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 A β production and increase A β 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

1. Erchtold NC, Cotman CW. Evolution in the Conceptualization of Dementia and Alzheimer's disease: Greco-Roman Period to the 1960s. *Neurobiology. Aging*, 1998; 19(3): 173–89. [http://dx.doi.org/10.1016/S0197-4580\(98\)00052-9](http://dx.doi.org/10.1016/S0197-4580(98)00052-9)
2. Alfred Maelicke, Marek Samochocki, Ruth Jostock, Andreas Fehrenbacher, Jürgen Ludwig, Edson X Albuquerque and Marion Zerlin. Allosteric Sensitization of Nicotinic Receptors by Galantamine, a New Treatment Strategy for Alzheimer's Disease -*Biol Psychiatry A*. 2001; 49: 279–288.
3. Valtteri Kaasinen Md, Kjell Nägren, Tarja Järvenpää, Anne Roivainen, Meixiang Yu, Vesa Oikonen, Timo Kurki And Juha O. Rinne. Regional Effects of Donepezil and Rivastigmine on Cortical Acetyl cholinesterase Activity in Alzheimer's Disease, Departments of Neurology and Radiology, University of Turku, and Turku PET Centre, Turku, Finland. *Journal of Clinical Psychopharmacology*. 2002; 22(6): 615–620. <http://dx.doi.org/10.1097/00004714-200212000-00012>
4. Martin Citron, Alzheimer's disease: strategies for disease modification. *Nature Reviews Drug Discovery*. 2010; 9: 387. <http://dx.doi.org/10.1038/nrd2896> PMID:20431570
5. Judith Neugroschl and Mary Sano. Current Treatment and Recent Clinical Research in Alzheimer's disease. *Mount Sinai Journal of Medicine*, 2010; 77(1): 3–16. <http://dx.doi.org/10.1002/msj.20165> PMID:20101716 PMCid:2922037
6. SL Rogers, RS Doody, RC Mohs and LT Friedhoff. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. *Archives of Internal Medicine*. 1998; 158 (9): 1021–1031. <http://dx.doi.org/10.1001/archinte.158.9.1021> PMID:9588436
7. SA Jacobson and MN Sabbagh. Donepezil: potential neuroprotective and disease modifying effects. *Expert Opinion on Drug Metabolism and*

- Toxicology, 2008; 4(10): 1363–1369. <http://dx.doi.org/10.1517/17425255.4.10.1363> PMID:18798705
8. Winblad B, Grossberg G, Frolich L, Farlow M, Zechner S, Nagel J, Lane R. Ideal: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. *Neurology* 2007; 69(4 Suppl. 1): 14–22. <http://dx.doi.org/10.1212/01.wnl.0000281847.17519.e0> PMID:17646619
9. Abdu Adem and Marwan Sabbagh .New Acetyl cholinesterase Inhibitors for Alzheimer's Disease Mona Mehta, , Hindawi Publishing Corporation International Journal of Alzheimer's Disease 2012;2012
10. Abhilash K Desai & George T. Grossberg. Rivastigmine for Alzheimer's disease. 2005; 5(5): 563-580.
11. Lesley J Scott, Karen L Goa. Galantamine 2000; 60(5): 1095-1122.
12. Mansoori GA. Principles of Nanotechnology: Molecular-Based Study of Condensed Matter in Small Systems. World Scientific Pub. Co; 2005.
13. Mansoori GA. Principles of Nanotechnology (Molecular-Based Study of Condensed Matter in Small Systems), World Sci Pub Co; 2005.
14. Mansoori GA, Mohazzabi P, McCormack P, Jabbari S. Nanotechnology in cancer prevention, detection and treatment: bright future lies ahead. *WRSTSD* 2007; 4(2/3): 226-57. <http://dx.doi.org/10.1504/WRSTSD.2007.013584>
15. Jain KK. The role of nanobiotechnology in drug discovery. *Drug Discovery Today*. 2005; 10(21): 1435-42. [http://dx.doi.org/10.1016/S1359-6446\(05\)03573-7](http://dx.doi.org/10.1016/S1359-6446(05)03573-7)
16. Modi G, Pillay V, Choonara YE. Advances in the treatment of neurodegenerative disorders employing nanotechnology. *Annals of the New York Academy of Sciences*. 2010; 1184: 154-72. <http://dx.doi.org/10.1111/j.1749-6632.2009.05108.x> PMID:20146696
17. Mansoori GA, Brandenburg K, Shakeri-Zadeh A. Cancerous Cells Targeting and Folate-A Comparative Study of Two Folate-Conjugated Gold Nanoparticles for Cancer Nanotechnology Applications. *Cancers*. 2010; 2(4): 1911-1928. <http://dx.doi.org/10.3390/cancers2041911>
18. Georganopoulou DG, Chang L, Nam JM, Thaxton CS, Mufson EJ, Klein WL, *et al.* Nanoparticle based detection in cerebral spinal fluid of a soluble pathogenic biomarker for Alzheimer's disease. *Proc Natl Acad Sci USA*. 2005; 102(7): 2273-2276. <http://dx.doi.org/10.1073/pnas.0409336102> PMID:15695586 PMID:548981
19. Kang DY, Lee JH, Oh BK, Choi JW. Ultra-sensitive immunosensor for - amyloid (1-42) using scanning tunneling microscopy-based electrical detection. *Biosensor Bioelectronics*. 2009; 24(5): 1431-6. <http://dx.doi.org/10.1016/j.bios.2008.08.018> PMID:18829296
20. Kang DY, Lee JH, Oh BK, Choi JW. Ultra-sensitive immunosensor for amyloid-beta (1-42) using scanning tunneling microscopy-based electrical detection. *Biosensors and Bioelectronics*. 2009; 24(5): 1431-6. <http://dx.doi.org/10.1016/j.bios.2008.08.018> PMID:18829296
21. Amir Nazem, G.Ali Mansoori. Nanotechnology for Alzheimer's disease detection and treatment. *Insciences J*. 2011; 1(4): 169-193. <http://dx.doi.org/10.5640/insc.0104169>
22. Skaat H, Margel S. Synthesis of fluorescent-maghemite nanoparticles as multimodal imaging agents for amyloid-beta fibrils detection and removal by a magnetic field. *Biochem. Biophys. Res. Commun*. 2009; 386(4):645-9. <http://dx.doi.org/10.1016/j.bbrc.2009.06.110> PMID:19559008
23. Hofmann-Amttenbrink M, Hofmann H, Montet X. Superparamagnetic nanoparticles - a tool for early diagnostics. *Swiss Med Wkly* 2010; 140(w13081). PMID:20853192
24. Salvatore Salamone, Filippo Caracai, Gian Marco Leggio, Julia Fedotova and Filippo Drago. New pharmacological strategies for treatment of Alzheimer's disease: focus on disease modifying drygs, - *BJCP*. 2012; 73(4): 504-517.
25. Lichtenthaler SF, Haass C, Steiner H. Regulated. Intra membrane proteolysis – lessons from amyloid precursor protein processing. *J Neurochem* 2011; 96: 117-779
26. Landreth G, Jiang Q, Mandrekar S, Heneka M. PPAR gamma agonists as therapeutics for the treatment of Alzheimer's disease. *Neurother*. 2008; 5: 481–9. <http://dx.doi.org/10.1016/j.nurt.2008.05.003> PMID:18625459 PMID:2593876
27. Henley DB, May PC, Dean RA, Siemers ER. Development of semagacesta (LY450139), a functional gamma-secretase inhibitor, for the treatment of Alzheimer's disease. *Expert Opin Pharmacother* 2009; 10:1657–64. <http://dx.doi.org/10.1517/14656560903044982> PMID:19527190
28. Bateman RJ, Siemers ER, Mawuenyega KG, Wen G, Browning KR, Sigurdson WC, Yarasheski KE, Friedrich SW, Demattos RB, May PC, Paul SM, Holtzman DM. A gamma-secretase inhibitor decreases amyloid-beta production in the central nervous system. *Ann Neurol*. 2009; 66: 48–54. <http://dx.doi.org/10.1002/ana.21623> PMID:19360898 PMID:2730994
29. Imbimbo BP, Giardina GA. Gamma-secretase inhibitors and modulators for the treatment of Alzheimer's disease: disappointments and hopes. *Curr Top Med Chem*. 2011; 11: 1555–70. <http://dx.doi.org/10.2174/156802611795860942>
30. Amijee H, Scopes DI. The quest for small molecules as amyloid inhibiting therapies for Alzheimer's disease. *J Alzheimers Dis*. 2009; 17: 33–47. PMID:19221409

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