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Current Advancements in the Treatment of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) has been the most prevalent form of dementia since its initial discovery in the 20th century. Despite the technological innovation and groundbreaking research that has been developed and completed, there hasn't been any reported fix that can cure its symptoms, presenting a need to find more effective therapeutic solutions. From targeting amyloid plaques to the tau regions of neurons in the brain, there have been several attractive targets that may hold the solution to curing AD. With many different experimental drugs and therapies being tested every day, the purpose of this literature review is to summarize what some of the various treatments entail with regards to the neurobiology behind Alzheimer's, how they affect those selected regions, as well as potential future therapeutic solutions for this disease.

Introduction

Alzheimer's disease is classified as a neurodegenerative disorder that was discovered in 1906 by the German psychiatrist Alois Alzheimer. Since its initial discovery, the number of cases globally of AD has skyrocketed, with an approximated range of 33 to 38.5 million people with dementia caused by AD in 2021 with nearly 10 million new cases every year as reported by the World Health Organization (WHO) (Dementia, n.d.), and approximately 6.5 million Americans age 65 and older living with AD in 2022. In addition to this, it has been reported that from 2000 to 2019, the number of deaths from Alzheimer's have more than doubled while the number of deaths from heart attack has decreased (Alzheimer's Association, n.d.), showing how even with the current technological innovations and equipment, scientists have been unable to discover an effective cure for AD.

In addition to the large number of cases of AD patients, due to the coronavirus disease 19 (COVID-19) caused by the severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV2) which emerged since November of 2019, it has been reported that there was a 17% increase in AD and dementia deaths (Alzheimer's Association, n.d.). Despite there being no cure for Alzheimer's disease, there are treatments available to improve patients' symptoms, and many advancements have been made towards finding the cure which can nullify the effects of Alzheimer's and subsequently dementia caused by AD as well. The development of various experimental drugs, physical therapies, and memory care therapies are all currently being researched on AD patients with varying parameters to determine their overall effectiveness and practicality as well.

Alzheimer's disease can be defined as a slowly progressive degeneration of the neurons in the brain beyond what might be expected from the usual consequences of biological aging, making it the most common cause of dementia (Breijyeh, 2020; Alzheimer's Association, n.d.). In the brain of a patient with Alzheimer's, the cerebral cortex and hippocampus regions are shrunk in comparison to those of a healthy brain, while the ventricles are enlarged. Amyloid plaques, composed of Amyloid-beta peptides (Aβ), accumulate in the medial temporal lobe and neocortical structures, which in turn result in the development of neuritic plaques and tau neurofibrillary tangles in neurons (Breijyeh, 2020). Under normal conditions, tau promotes stabilization of microtubules in neurons, but during AD, tau becomes hyperphosphorylated into tangles composed of paired helical filaments (Cummings, 2018), causing them to quickly deteriorate and die. The slow but progressive loss of these neurons due to Aβ results in memory loss and other

cognitive difficulties, such as learning, sensory processing, conscious thought, and reasoning (Alzheimer's Disease Fact Sheet, n.d.).

Considering how the number of AD cases is expected to exceed around 100 million cases by 2050 (Cummings, 2018), there has been a wealth of research conducted and reported with data to discuss the possibilities of viable and improved treatments for AD, which have the potential to serve as the cure as well. As such, the purpose of this review article is to highlight the key advancements in experimental drugs developed to target specific subsections of AD, the impacts it has on scientists' understanding of AD as a whole, and future therapies in the work which can potentially surface the fix required to effectively treat Alzheimer's disease.

Amyloid Beta (Aβ)

Amyloid beta (Aβ) is a protein that plays an essential role in neural growth and repair within the brain and other regions of the nervous system (PDB101: Molecule of the Month: Amyloid-beta Precursor Protein, n.d.), which exists in various conformational states, including soluble monomers and aggregates of increasing size (i.e. oligomers, protofibrils) as well as insoluble fibrils and plaque (Swanson, 2021). Aβ is a 42-amino acid peptide chain derived from the precursor protein amyloid beta precursor protein (APP), a 771 amino acid transmembrane glycoprotein that spans the membrane once, which is then cleaved by two enzymes known as the β-site APP-cleaving enzyme 1 (BACE1, β-secretase) and γ-secretase (Rukmangadachar, 2021; What are Amyloid Plaques? 2014; Portelius, 2014). While Aβ is absolutely crucial for the health of the brain, when aggregated, insoluble plaques form, which can destroy nerve cells, subsequently leading to the loss of memory and thought commonly seen in cases of AD (What are Amyloid Plaques? 2014). Scientists are experimenting to develop therapeutic solutions which can target both insoluble and soluble conformational states of Aβ.

Insoluble Conformational States of Aβ

In early onset AD, mutations occur either in the APP for Aβ, or in presenilin-1 (PS1) or presenilin-2 (PS2). Either PS1 or PS2 can be used as the catalytic subunit of γ-secretase, the final endoprotease in the pathway that generates the overall peptide. It is important to note that these Aβ consist of highly insoluble peptides, meaning that as the number of Aβ peptide chains increases, the proteins synthesize with each other which allows for the creation of amyloid fibrils, one of the key components of large, extracellular neuritic plaques in the brain parenchyma. These plaques are believed to cause severe damage to the brain in the form of synaptic dysfunction and degeneration, disrupting neural connectivity, leading to neuronal death in brain regions which disrupts neuronal homeostasis to a point where the damage is irreparable (Murphy, 2010; Saeed, 2015). This cessation of the brain's functions subsequently results in the symptoms of AD that have been observed as well.

There have been many experiments done towards preventing the growth of this Aβ plaque, with one notable advancement being the development of anti-Aβ drugs. One such example is the development and experimentation of the drug aducanumab, an amyloid plaque removing agent. Aducanumab is a human immunoglobulin G1 (IgG1) monoclonal anti-Aβ antibody that selectively targets aggregated forms of Aβ, including both soluble oligomers and insoluble fibrils. In clinical trials for aducanumab with AD patients, demonstrated concentration-dependent reductions in composite standard uptake value ratio (SUVR), which is a sensitive pharmacodynamic marker of brain Aβ removal. The experiment also utilized positron emission tomography (PET) scanning, a test which reveals the metabolic or biochemical function of tissues and organs, which yielded similar results when revealing the effects of aducanumab in Aβ plaque growth. In other words, the use of aducanumab in clinical trials showed a decline in Aβ removal (Muralidharan, 2021). As of June 2021, this drug has received FDA approval for mild Alzheimer's dementia (Dunn, 2021).

Soluble Conformational States of Aβ

While many researchers experiment on insoluble conformational states of Aβ, studies have shown that there are cases of AD where the Aβ is water-soluble. While there haven't been any largely effective therapies of disrupting the growth of the insoluble conformational states, much of the knowledge from those trials have carried over to experimentation on soluble conformational states, including the development of Aβ plaques, which has many structural commonalities with the soluble monomers and soluble aggregates.

It has been determined that soluble Aβ aggregates have been found to be more toxic than soluble monomers or insoluble fibrils, meaning the reduction of these soluble Aβ aggregates could prove to become an effective therapeutic solution during early stages of AD (Swanson, 2021). Similar to the makeup of aducanumab, lecanemab is a humanized IgG1 monoclonal anti-Aβ antibody that binds to soluble Aβ aggregates including oligomers and protofibrils, with high selectivity over soluble monomers and insoluble fibrils. In clinical trials using animal models, a murine version of lecanemab demonstrated a reduction of Aβ protofibrils and Aβ plaques as well as prevention of Aβ deposition before the plaques can even develop. As a follow up, when experimenting on human subjects with early AD to determine the difference in effectiveness of lecanemab versus a placebo, a larger proportion of human subjects with early stages of AD on lecanemab (10 mg/kg biweekly) converted to amyloid negative (81%) compared to the placebo (22%). This is consistent with PET SUVR results from other evaluated studies as well (Swanson, 2021), meaning very similar to how aducanumab can serve as a potential insoluble conformational state anti-Aβ antibody, lecanemab can serve as a potential soluble conformational state anti-Aβ antibody to similar capacities.

Tau

Tau is a 441 amino acid protein that helps stabilize the internal cytoskeleton of neurons in the brain along with other microtubule-associated proteins (MAP). It plays a role in the assembly of the various microtubules, axon development and navigation, as well as dendritic spine function (Avila, 2016), meaning tau protein is integral for the overall structure of the brain and its growth throughout an organism's lifespan. Tau's ability to bind microtubules is what proves to be both beneficial but at the same time consequential. The beneficial effect of tau is that it stabilizes microtubules, permitting neurites' extension and stabilization, while the negative effect is that tau may be competing with the motor protein kinesin for microtubule binding, leading to decreased axonal transport. In addition to this, tau is considered a phosphoprotein, and the phosphorylation of tau negatively regulates its activity in promoting microtubule activity.

Abnormally hyperphosphorylated tau leads to the creation of paired helical filaments (PHF), which are commonly seen in brains affected by AD. Even though the PHF-tau loses its ability to stimulate microtubules, studies have suggested that loss of normal function due to tau hyperphosphorylation isn't enough to cause neurodegeneration, rather it gained a toxic ability to inhibit normal tau protein and other MAPs, which causes microtubule disassembly. This toxic ability is a better explanation than the loss of normal activity as MAPs other than tau protein can compensate for the assembly (Gong, 2008). To inhibit this toxic activity released by hyperphosphorylated tau, many biochemical agents are being experimented on, with one notable drug being hydromethylthionine.

Methylthioninium (MT), a tau aggregation inhibitor, can exist in oxidized (MT^+) or reduced forms (LMT). Leuco-methylthioninium bis(hydromethansulphonate) (LMTM), also known as methylene blue, is a stabilized salt of LMT, which allows for better brain uptake than oxidized MT^+. In recent studies, LMT has been seen to be the active species involved in the inhibition of tau aggregation in vitro and that it acts more efficiently at a tau in comparison to MT^+ (Shiells, n.d.). LMTM was given as monotherapy or with an add-on to patients with AD, and the results collected showed that there was a significantly smaller decline in SUVR normalized with respect to the cerebellum with LMTM as monotherapy in comparison with add-on in the frontal and parietal cortices. Since LMTM is shown to have a smaller decline in SUVR, the inhibition of tau aggregation was more, meaning that there was less neurological damage in the subjects' brains. The overall results of the experiment suggested that the effects of LMTM on tau aggregation are

consistent. Further experimentation on LMTM can provide insight on its ability to safely be used in patients with AD (Wilcock, 2018).

Future Solutions

While scientists have made substantial advancements contributing to the current understanding of the mechanisms behind Alzheimer's disease, there are still many forms of treatment that are early in their research phase. The potential these treatments exhibit greatly outweigh the fact that they are still works in progress and require more time and funding for legitimate experimentation. Some experimental designs that have little to no data reported but have serious potential given the current resources and facilities include an approach from stem cell therapy and regenerative medicine, as well as electromagnetic treatment.

Stem Cell Therapy and Regenerative Medicine

Stem cells are a culmination of raw resources from the body, or cells from which all other cells with specialized functions are generated. These stem cells, under the right conditions, divide to form a new subgroup of cells called daughter cells. These daughter cells have multiple abilities: 1) become new stem cells and continue mitotic cell division, or 2) become a specialized cell with a more specific function (i.e. heart cell, brain cell). What makes these stem and daughter cells so unique is that no other cell in the entire body has this inherent ability to generate or regenerate new cell types ("Stem cells: What they are and what they do"—Mayo Clinic, n.d.). This vast variability serves as an opportunity for many scientists, as the natural regeneration of cells could provide for viable treatment for a massive plethora of medical conditions across all fields. In the case of AD, one study involved the intracerebroventricular injection of human umbilical cord blood mesenchymal stem cells in patients. The umbilical cord is also a unique part of the body because its fluid has a large concentration of stem cells, something crucial to an experiment designed to understand the effectiveness of regenerative medicine in cases of AD. The umbilical cord fluid was injected directly into the right lateral ventricle of the brains of the patients, and the intended result was to observe a decrease in the neurodegenerative damage seen in brains of AD patients. While there indeed was a noticeable decrease in SUVR amongst the patients, all of them developed a fever within 6 to 24 hours of mesenchymal stem cell injection. There is no concrete justification as to why this occurred, hence the reason that more time and resources need to be allocated in order to pursue such a new venue of treatment. Stem cell therapy proved to be effective against the effects of AD, but further replication and experimentation must be pursued in order to ensure guaranteed safety for the patients and proof of effectiveness as well (Kim, 2021).

Electromagnetic Treatment

The inability of drugs to slow down, reverse, or halt the cognitive impairment caused by AD has also prompted scientists to propose non-pharmaceutical alternatives. One group of such alternatives which is currently being experimented on are the neuromodulatory approaches. These approaches include transcranial magnetic stimulation (tMS), transcranial direct current stimulation, and deep brain stimulation. All of these approaches have the fundamental goal of inhibiting neuronal activity in the brain, which in the case of AD, would halt or slow down the damage from neurodegeneration. The newest neuromodulatory approach which has emerged is electromagnetic treatment, the use of electromagnetic radiation to treat a plethora of diseases. The Transcranial Electromagnetic Treatment (TEMT) is different from tMS because TEMT involves perpendicular magnetic and electric waves emitted by the source while tMS's magnetic waves oscillate between the target and the source. The electromagnetic waves released by TEMT can easily penetrate through the human cranium and underlying brain areas, making treatment that much more feasible. Administering TEMT into subjects ultimately appeared to be safe as shown by evidence of stable brain functionality

and provided cognitive enhancement while combatting the effects of AD, but similar to the situation of regenerative medicine, there aren't enough replicated trials that can show similar success over a larger sample of patients with AD who underwent electromagnetic treatment. However, this opens up yet another new venue for scientists to explore, as non-pharmaceutical interventions against Alzheimer's have now been seen to be possible, and additional experimentation can justify their validity and effectiveness (Arendash, 2019).

Conclusions

Overall, current studies reveal that Alzheimer's disease is an incredibly complex neurodegenerative illness that has become a significant threat to many people's livelihoods. While the two hallmarks of the disease, the amyloid-beta and tau regions, have had significant research invested into them, other potential venues of research have remained relatively unexplored, which is slowly prompting an increased number of scientists to pursue them. While many people have focused their research on pharmaceutical interventions, non-pharmaceutical interventions have recently gained a lot of popularity and are also being pursued with similar rigor. All in all, regardless of which area of Alzheimer's is being researched, the goal is to determine a safe and effective cure to clear all symptoms of Alzheimer's from patients, and with the surge of scientific innovation, it is within reach.

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References

[1] *Dementia*. (n.d.). Retrieved August 27, 2022, from https://www.who.int/news-room/fact-sheets/detail/dementia

[2] *Alzheimer's Facts and Figures Report | Alzheimer's Association*. (n.d.). Retrieved August 27, 2022, from https://www.alz.org/alzheimers-dementia/facts-figures

[3] Breijyeh, Z., & Karaman, R. (2020). Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules*, *25*(24), 5789. https://doi.org/10.3390/molecules25245789

[4] Cummings, J. L., Tong, G., & Ballard, C. (n.d.). Treatment Combinations for Alzheimer's Disease: Current and Future Pharmacotherapy Options. *Journal of Alzheimer's Disease*, *67*(3), 779–794. https://doi.org/10.3233/JAD-180766

[5] *Alzheimer's Disease Fact Sheet*. (n.d.). National Institute on Aging. Retrieved August 27, 2022, from https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet

[6] *PDB101: Molecule of the Month: Amyloid-beta Precursor Protein*. (n.d.). RCSB: PDB-101. Retrieved August 27, 2022, from http://pdb101.rcsb.org/motm/79

[7] Swanson, C. J., Zhang, Y., Dhadda, S., Wang, J., Kaplow, J., Lai, R. Y. K., Lannfelt, L., Bradley, H., Rabe, M., Koyama, A., Reyderman, L., Berry, D. A., Berry, S., Gordon, R., Kramer, L. D., & Cummings, J. L. (2021). A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. *Alzheimer's Research & Therapy*, *13*, 80. https://doi.org/10.1186/s13195-021-00813-8

[8] Rukmangadachar, L. A., & Bollu, P. C. (2021). Amyloid Beta Peptide. In *StatPearls [Internet]*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK459119/

[9] *What are Amyloid Plaques?* (2014, January 17). News-Medical.Net. https://www.news-medical.net/health/What-are-Amyloid-Plaques.aspx

[10] Portelius, E., Dean, R. A., Andreasson, U., Mattsson, N., Westerlund, A., Olsson, M., Demattos, R. B., Racke, M. M., Zetterberg, H., May, P. C., & Blennow, K. (2014). β-site amyloid precursor protein-cleaving enzyme 1(BACE1) inhibitor treatment induces Aβ5-X peptides through alternative amyloid precursor protein cleavage. *Alzheimer's Research & Therapy*, *6*(5), 75. https://doi.org/10.1186/s13195-014-0075-0

[11] Murphy, M. P., & LeVine, H. (2010). Alzheimer's Disease and the β-Amyloid Peptide. *Journal of Alzheimer's Disease : JAD*, *19*(1), 311. https://doi.org/10.3233/JAD-2010-1221

[12] Sadigh-Eteghad, S., Sabermarouf, B., Majdi, A., Talebi, M., Farhoudi, M., & Mahmoudi, J. (2015). Amyloid-Beta: A Crucial Factor in Alzheimer's Disease. *Medical Principles and Practice*, *24*(1), 1–10. https://doi.org/10.1159/000369101

[13] Kandadi Muralidharan, K., Tong, X., Kowalski, K. G., Rajagovindan, R., Lin, L., Budd Haberlain, S., & Nestorov, I. (2022). Population pharmacokinetics and standard uptake value ratio of aducanumab, an amyloid plaque–removing agent, in patients with Alzheimer's disease. *CPT: Pharmacometrics & Systems Pharmacology*, *11*(1), 7–19. https://doi.org/10.1002/psp4.12728

[14] Dunn, B., Stein, P., & Cavazzoni, P. (2021). Approval of Aducanumab for Alzheimer Disease—The FDA's Perspective. *JAMA Internal Medicine*, *181*(10), 1276–1278. https://doi.org/10.1001/jamainternmed.2021.4607

[15] Avila, J., Jiménez, J. S., Sayas, C. L., Bolós, M., Zabala, J. C., Rivas, G., & Hernández, F. (2016). Tau Structures. *Frontiers in Aging Neuroscience*, *8*, 262. https://doi.org/10.3389/fnagi.2016.00262

[16] Gong, C.-X., & Iqbal, K. (2008). Hyperphosphorylation of Microtubule-Associated Protein Tau: A Promising Therapeutic Target for Alzheimer Disease. *Current Medicinal Chemistry*, *15*(23), 2321–2328.

[17] Shiells, H., Schelter, B. O., Bentham, P., Baddeley, T. C., Rubino, C. M., Ganesan, H., Hammel, J., Vuksanovic, V., Staff, R. T., Murray, A. D., Bracoud, L., Wischik, D. J., Riedel, G., Gauthier, S., Jia, J., Moebius, H. J., Hardlund, J., Kipps, C. M., Kook, K., … Wischik, C. M. (n.d.). Concentration-Dependent Activity of Hydromethylthionine on Clinical Decline and Brain Atrophy in a Randomized Controlled Trial in Behavioral Variant Frontotemporal Dementia. *Journal of Alzheimer's Disease*, *75*(2), 501–519. https://doi.org/10.3233/JAD-191173

[18] Wilcock, G. K., Gauthier, S., Frisoni, G. B., Jia, J., Hardlund, J. H., Moebius, H. J., Bentham, P., Kook, K. A., Schelter, B. O., Wischik, D. J., Davis, C. S., Staff, R. T., Vuksanovic, V., Ahearn, T., Bracoud, L., Shamsi, K., Marek, K., Seibyl, J., Riedel, G., … Wischik, C. M. (2018). Potential of Low Dose Leuco-Methylthioninium Bis(Hydromethanesulphonate) (LMTM) Monotherapy for Treatment of Mild Alzheimer's Disease: Cohort Analysis as Modified Primary Outcome in a Phase III Clinical Trial. *Journal of Alzheimer's Disease: JAD*, *61*(1), 435–457. https://doi.org/10.3233/JAD-170560

[19] *Stem cells: What they are and what they do—Mayo Clinic*. (n.d.). Retrieved August 27, 2022, from https://www.mayoclinic.org/tests-procedures/bone-marrow-transplant/in-depth/stem-cells/art-20048117

[20] Wilcock, G. K., Gauthier, S., Frisoni, G. B., Jia, J., Hardlund, J. H., Moebius, H. J., Bentham, P., Kook, K. A., Schelter, B. O., Wischik, D. J., Davis, C. S., Staff, R. T., Vuksanovic, V., Ahearn, T., Bracoud, L., Shamsi, K., Marek, K., Seibyl, J., Riedel, G., … Wischik, C. M. (2018). Potential of Low Dose Leuco-Methylthioninium Bis(Hydromethanesulphonate) (LMTM) Monotherapy for Treatment of Mild Alzheimer's Disease: Cohort Analysis as Modified Primary Outcome in a Phase III Clinical Trial. *Journal of Alzheimer's Disease: JAD*, *61*(1), 435–457. https://doi.org/10.3233/JAD-170560

[21] Arendash, G., Cao, C., Abulaban, H., Baranowski, R., Wisniewski, G., Becerra, L., Andel, R., Lin, X., Zhang, X., Wittwer, D., Moulton, J., Arrington, J., & Smith, A. (2019). A Clinical Trial of Transcranial Electromagnetic Treatment in Alzheimer's Disease: Cognitive Enhancement and Associated Changes in Cerebrospinal Fluid, Blood, and Brain Imaging. *Journal of Alzheimer's Disease: JAD*, *71*(1), 57–82. https://doi.org/10.3233/JAD-190367