A Comparative Analysis on Alzheimer’s Medication

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ABSTRACT

Alzheimer’s disease (AD) is a neurodegenerative disorder in which brain cells, or neurons, slowly degenerate and die resulting in a gradual cognitive decline. AD does not have a known cure; this requires effective strategies to manage symptoms and slow its progression of this disease. This review paper delves into treatments, for Alzheimer’s disease (AD) such as cholinesterase inhibitors, NMDA antagonists and immunotherapies. The focus will be on exploring their effectiveness in early and mild to AD cases as well as examining any potential side effects. This paper highlights the importance of treatment plans that take into account the nature of AD and emphasizes the significance of addressing both the underlying pathology and symptoms. After conducting an analysis on clinical trials, the conclusion is that cholinesterase inhibitor therapy stands out as the approach, for managing mild to moderate AD based on comprehensive clinical trial results and a comparative analysis.

Introduction

Alzheimer’s disease (AD) is a neurodegenerative disorder in which brain cells, or neurons, slowly degenerate and die resulting in a gradual cognitive decline (Wang & Reddy, 2017). The impact of AD is significant, with more than 60 million individuals estimated to be currently living with some form of Alzheimer’s Disease (Wang & Reddy, 2017). Alzheimer’s disease places a load on patients and their loved ones who often encounter physical difficulties while providing care and support (Wang & Reddy, 2017). Moreover, as the disease progresses individuals frequently need long term interventions and care which puts pressure on healthcare resources and facilities (Wang & Reddy, 2017).

The progression of neurodegeneration in Alzheimer’s involves mechanisms that lead to the deterioration of structure and function. In AD neurodegeneration primarily affects brain regions associated with memory, cognition and behavior like the hippocampus and cerebral cortex due to the accumulation of abnormal protein aggregates such, as beta amyloid plaques and tau tangles (Wang & Reddy, 2017). Initially in AD pathogenesis, beta amyloid protein accumulates outside of neurons leading to plaque formation (Wang & Reddy, 2017). These plaques disrupt neuronal communication and contribute to their dysfunction (Wang & Reddy, 2017). As Alzheimer’s disease (AD) progresses, the affected areas of the brain start to shrink leading to a loss of nerve cells and their connections. This reduction, in brain size results in a decline in abilities, including memory loss, confusion, difficulties with language and problem-solving skills as well as changes in mood and behavior (Figure 1). In addition to AD conditions such as strokes, traumatic brain injuries or infections can also cause widespread brain shrinkage. It is widely believed that AD is influenced by a combination of factors, genetics and lifestyle choices. Researchers are actively studying aspects of neurodegeneration to identify targets for therapy and develop effective strategies, for managing Alzheimer’s disease and other neurodegenerative disorders. This review will provide an overview and critical analysis of the three most common treatments for AD, cholinesterase inhibitors, NMDA antagonists, and immunotherapy.
Cholinesterase Inhibitors

One group of drugs used to treat AD are cholinesterase inhibitors, which help manage cognitive symptoms such as memory loss, confusion, and difficulties with thinking and problem solving (Cholinesterase Inhibitors | British Columbia Medical Journal, n.d.). Examples of these cholinesterase inhibitors include galantamine, donepezil, and rivastigamine, which are all FDA approved for individuals with mild to moderate stages of Alzheimer’s. Cholinesterase inhibitors function by blocking the activity of the acetylcholinesterase enzyme (AChE) which breaks down acetylcholine (ACh), a neurotransmitter (Figure 2) (Cholinesterase Inhibitors | British Columbia Medical Journal, n.d.). Neurotransmitters are chemicals that facilitate communication through the transmission of signals and information through synapses or gaps between neurons (Cholinesterase Inhibitors | British Columbia Medical Journal, n.d.). Cholinesterase inhibitors therefore increase the levels of acetylcholine, which promotes communication between nerve cells and may alleviate symptoms associated with AD, thus restoring better activity flow within muscle tissue therefore slowing neurodegeneration (Figure 2) (Cholinesterase Inhibitors | British Columbia Medical Journal, n.d.). These medications prove beneficial during the early stages of Alzheimer's disease.

Prior to their FDA approval, various clinical trials were conducted to examine the efficacy of cholinesterase inhibitors in individuals with mild to moderate Alzheimer's disease. One such clinical trial explored
the efficacy of the cholinesterase inhibitor rivastigmine (Cummings & Winblad, 2007). This randomized double-blind trial was conducted in over 1,000 participants, with some patients receiving rivastigmine and others a placebo (Cummings & Winblad, 2007). The rivastigmine group demonstrated improved scoring compared to the placebo on (ADAS cog scale) which assess aspects of function such as memory, language orientation, reasoning and other cognitive abilities (Cummings & Winblad, 2007). The improved scoring suggests that rivastigmine may have helped slow down cognitive decline and potentially enhance memory, language skills, attention and orientation (Kueper et al., n.d.). Although the study did show that there were signs of nausea, diarrhea, dizziness, and headache (Kueper et al., n.d.).

**Figure 3. ADAS cog scale** *(Table 1. Items Assessed by the 11-Item ADAS-Cog a, Divided into The..., n.d.)*

The efficacy of another cholinesterase inhibitor, galantamine, was examined in over 1,200 patients in the GALINT 6 trial (Erkinjuntti et al., 2008). The GALINT 6 trial aimed to assess the effectiveness of the cholinesterase inhibitor galantamine in over 1,200 patients (Erkinjuntti et al., 2008). They found that galantamine treatment yielded noteworthy improvements, in ADAS cog/11 scores in the experimental galantamine treated group (galantamine group; 0.9 point; 95 increase) (Erkinjuntti et al., 2008). This trial concluded, there was an overall improvement in cognitive function, daily living activities, and overall clinical status with galantamine treatment when compared to a placebo Due to it meeting the endpoint goals on the ADAS cog scale (Erkinjuntti et al., 2008).

A third cholinesterase inhibitor, donepezil, has been investigated in a six-month placebo-controlled trial, followed by a 1-year study (Cacabelos, 2007). The trial found sustained cognitive improvement in the donepezil treated group (Cacabelos, 2007). The benefits of donepezil compared to a placebo were also seen in improved daily functioning as evaluated through the Mini Mental State Examination (MMSE) at weeks 24, 36, 52, and at the endpoint (p < 0.02) (Figure 5) (Cacabelos, 2007). The MMSE scale is a list of 11 questions asked by the doctor that assesses your orientation, attention, short term memory, visual and spatial abilities, and ability to follow directions (Australia, 2022). This study also showed that side-effects were seen in 6%–13% of the participants. These side effects were nausea, diarrhea, and etc. The data indicates that donepezil is a treatment option that's both well tolerated and effective for patients with AD in the term (Cacabelos, 2007).
These past clinical trials stated in the previous paragraphs indicate how cholinesterase inhibitors may lead to modest cognitive function improvements such as memory and attention spans. The ICTUS trial was a randomized double-blind clinical trial, conducted in 2013, that aimed to evaluate the efficacy and safety of rivastigmine in patients with mild to moderate Alzheimer’s disease (Hoedemaker et al., 2017). The participants were assigned to receive either rivastigmine or a placebo treatment. (Hoedemaker et al., 2017) The rivastigmine treated group showed significant improvements in cognitive function, as seen in memory, attention, language skills, and problem-solving abilities compared to the placebo group (Hoedemaker et al., 2017). The improved cognitive function indicated that rivastigmine was effective in mitigating the cognitive decline associated with both Alzheimer’s disease (Hoedemaker et al., 2017). In addition to cognitive improvements, patients treated with rivastigmine also experienced better functional outcomes with notable enhancement in their ability to perform everyday tasks and maintain their independence in daily living activities, such as mobility and medication management in addition to others (Hoedemaker et al., 2017).
Cholinesterase inhibitors like galantamine, donepezil, and rivastigamine are not a cure for AD or a way to stop its progression entirely, however, they offer benefits to patients with mild to moderate AD (Hoe-demaker et al., 2017). For example, they make an impact on managing symptoms and enhancing overall quality of life. The cognitive improvements they offer can assist individuals in preserving their abilities for a period potentially delaying the decline, in independence and enhancing day to day functioning. Cholinesterase inhibitors are primarily utilized for long term therapy, at present. They are not intended to address moderate to stages of Alzheimers disease.

**NMDA Antagonists**

Another group of drugs used to treat AD are NMDA (N-methyl-D-aspartate) antagonists, which slow down the decline in cognitive abilities, by enhancing performance in areas like attention, executive function, and daily activities for patients with AD (Wang & Reddy, 2017). NMDA antagonists function by regulating activity in the hippocampus and prefrontal cortex, which are regions associated with memory and cognition, by reducing excitation and preserving function (Wang & Reddy, 2017). More specifically, NMDA antagonists block the activation of NMDA receptors, which helps to maintain the balance between excitation and inhibition in the brain by preventing excitotoxicity (Figure 3) (Wang & Reddy, 2017). Excitotoxicity occurs when glutamate is released in excess, or when it is not efficiently cleared from the space between neurons, resulting in the overstimulation of the NMDA receptors (Wang & Reddy, 2017). This overstimulation results in an influx of calcium ions into neurons, which activates pathways that can disrupt normal cellular processes and activate factors that promote cell death (Wang & Reddy, 2017). NMDA antagonists help reduce the consequences associated with excessive stimulation, such as the triggering of a process called programmed cell death or apoptosis. These drugs are used mainly for treatment in moderate to severe stage AD.

![Figure 6. Mechanism of action of an NMDA antagonist](Figure 2, n.d.)

Memantine is an FDA-approved NMDA antagonist that has been tested in clinical trials in patients with moderate to severe Alzheimer’s disease. A 2003 randomized clinical trial had 252 participants, split into a memantine treated group and a placebo treated group (Reisberg et al., 2003). This study utilized the Clinicians Interview Based Impression of Change Plus Caregiver Input (CIBIC Plus) and the Alzheimer’s Disease Cooperative Study Activities of Daily Living Inventory adjusted for dementia (ADCS ADLsev) as its measures to determine effectiveness (Reisberg et al., 2003). The CIBIC assesses the clinical progress/perception of the patient’s condition including their cognitive abilities, behavior and everyday functioning, while the ADCS...
ADLsev evaluates an individual’s capabilities and daily activities specifically designed for those with dementia (Reisberg et al., 2003). Of the 252 patients, 181 individuals (72%) completed the study and underwent evaluation at week 28, while 71 patients discontinued treatment prematurely (42 from placebo group and 29 from memantine) (Reisberg et al., 2003). The results from the CIBIC Plus assessment showed that patients who received memantine had positive outcomes compared to those who received a placebo (P=0.03) (Reisberg et al., 2003). Similar findings were observed when evaluating the ADCS ADLsev scale (P=0.003) (Reisberg et al., 2003). Notably there was no increase in adverse events associated with memantine usage (Reisberg et al., 2003). This suggests that memantine improved overall cognitive abilities, behavior and everyday functioning from before taking the drug. Thus, memantine may play a crucial role in helping to reduce clinical deterioration associated with moderate to severe Alzheimer’s disease.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Description</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>ADCS-ADLsev</td>
<td>Assesses daily activities for patients with severe AD</td>
<td>Maximum score of 54, decrease in score shows deterioration</td>
</tr>
<tr>
<td>BGP_care-depency</td>
<td>Assesses cognition, function and behavioral disturbances using care-dependency scale</td>
<td>Maximum score of 46, higher scores mean worse function</td>
</tr>
<tr>
<td>CIBIC-plus, CGIC</td>
<td>Provides global rating of patient function (general, cognitive, behavioral and activities of daily living)</td>
<td>1=very much improved 4=no change 7=very much worse</td>
</tr>
<tr>
<td>SIB</td>
<td>Assesses cognition in advanced AD</td>
<td>Maximum score of 100, lower score shows greater impairment</td>
</tr>
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ADCS-ADLsev=AD Cooperative Study-Activities of Daily Living inventory modified for severe AD, BGP=Behavioural Rating Scale for Geriatric Patients, CGIC=Clinical Global Impression of Change, CIBIC-plus=Clinician’s Interview-Based Impression of Change Plus Caregiver Input, SIB= Severe Impairment Battery.

**Figure 7.** Description of ADCS-ADLsev scale and CIBIC-plus scale ([PDF] Memantine for Treatment of Moderate to Severe Alzheimer’s Disease, | Semantic Scholar, n.d.)

In addition to being investigated as a single agent, memantine has also been studied in combination with cholinesterase inhibitors as a treatment approach to further enhance outcomes in AD (Guo et al., 2020). This combination therapy of memantine and cholinesterase inhibitors aims to target multiple aspects of the neurodegenerative processes in Alzheimer’s disease (Guo et al., 2020). While memantine regulates signaling to prevent excitotoxicity, cholinesterase inhibitors enhance function and help improve cognitive performance, resulting in a synergistic approach to treating AD (Guo et al., 2020). For example, one clinical trial assessed the pairing of memantine with donepezil and the results demonstrated that this combination therapy brought benefits in terms of cognition, global assessment, daily activities, and neuropsychiatric symptoms compared to using donepezil alone (Guo et al., 2020). The combination therapy showed effectiveness, in enhancing abilities with a 0.86 on the Alzheimer’s Disease Assessment Scale Cognitive Subscale (Guo et al., 2020). This revealed that the combined therapy resulted in improvements in cognition and reduction in cognitive decline (Guo et al., 2020). These studies long with others, provides evidence supporting the use of combination therapy involving memantine and cholinesterase inhibitors for Alzheimer’s disease. The benefits seen by NMDA antagonists are
diverse encompassing mechanisms such as promoting flexibility, maintaining a balance of neurotransmitters, and diminishing neuroinflammation (Guo et al., 2020). The disadvantage with NMDA Antagonist is its generalized therapy, whereas immunotherapy is tailored towards targeting molecules that play a role in the disease. This provides an approach that's more personalized and focused. This targeted approach helps maximize the effectiveness of treatment.

**Immunotherapies**

Immunotherapies harness the power of our body’s immune system by boosting and guiding the body’s response in identifying and eradicating foreign cells or substances (Song et al., 2022). For example, monoclonal antibodies are man-made proteins that act like human antibodies in the immune system (Song et al., 2022). These antibodies have been used in the context of AD to combat beta amyloid, which is responsible for forming plaques in the brain (Song et al., 2022). The antibodies can act as guides and direct cells to locations where plaques accumulate, by binding to the beta amyloid protein clusters (Song et al., 2022). This activates microglia found in the brain and which act as the first line of defense responsible for monitoring, responding, and clearing away cellular debris, such as beta amyloid plaques found in Alzheimer’s disease (Figure 4) (Song et al., 2022). Microglial cells employ phagocytosis, a process whereby cells engulf and break down particles or cellular waste, as a mechanism for clearing cellular debris, including beta amyloid plaques (Song et al., 2022). In AD it is crucial to reduce the burden of pathological protein aggregates, like beta amyloid plaques (van Dyck et al., 2023). Researchers have been exploring strategies to boost the immune response and optimize phagocytosis in an attempt to reduce the burden of beta-amyloid plaques and potentially slow down Alzheimer’s progression by addressing its underlying pathology (van Dyck et al., 2023). The novel monoclonal antibodies Lecanemab and aducanumab have undergone clinical trials to evaluate their efficacy in treating AD (van Dyck et al., 2023).

Figure 8. Monoclonal antibodies such as Lecanemab and Aducanumab collect and relocate beta amyloid plaques for phagocytosis to treat AD (Zampar & Wirths, 2020)

Lecanemab, an FDA approved drug as of July 6, 2023, has been tested in Phase II and Phase III clinical trials to assess its safety and efficacy. In the phase II trial of 1,795 individuals, lecanemab treatment was shown to contribute to a substantial reduction in beta amyloid plaque accumulation compared to a placebo group (van Dyck et al., 2023). In another study involving 698 participants, it was observed that Lecanemab led to reductions
in brain amyloid burden compared to placebo (van Dyck et al., 2023). It should be noted that infusion related reactions were experienced by 4% of participants receiving Lecanemab while amyloid related imaging abnormalities, with edema or effusions were observed in (6%) (van Dyck et al., 2023). In the study it was found that Lecanemab showed a decrease, in amyloid markers in individuals with early stage Alzheimers disease (van Dyck et al., 2023). Amyloid markers are substances or indicators that doctors use in imaging and tests to identify the existence of amyloid protein clumps in the brain (Hampel et al., 2010). By detecting and tracking these amyloid clumps healthcare professionals can help diagnose and manage conditions effectively (Hampel et al., 2010). Additionally, compared to the placebo group, those taking Lecanemab experienced a slower decline in cognitive abilities and functional performance over an 18 month period (van Dyck et al., 2023).

Aducanumab has also undergone clinical trials to assess its effectiveness as an alternative treatment approach for Alzheimer’s (Budd Haeberlein et al., 2022). In EMERGE and ENGAGE phase III clinical trials, aducanumab was found to contribute to the reduction of Beta amyloid plaques, while also significantly slowing down cognitive decline compared to the placebo (Budd Haeberlein et al., 2022). The trial were conducted to assess the effectiveness of aducanumab a type of monoclonal antibody that targets beta amyloid plaques, in slowing down decline and disease progression, in individuals diagnosed with cognitive impairment caused by Alzheimers disease or mild Alzheimers dementia (Budd Haeberlein et al., 2022). The main objective was achieved in the EMERGE study which was a score of p=0.12. Data from EMERGE showed a change across all four secondary clinical measures (Budd Haeberlein et al., 2022). Secondary outcomes that assessed cognition, function, and behavior; and biomarker endpoints (Budd Haeberlein et al., 2022). However, ENGAGE did not meet its secondary goals. Both trials revealed a reduction in amyloid markers associated with Alzheimer's disease that was dependent on the dosage and duration of treatment (Budd Haeberlein et al., 2022). The U.S. Food and Drug Administration accelerated its approval in June 2021 based on the results of these trials.

Clinical tests conducted for lecanemab and aducanumab have had a specific focus on patients’ earlier onset stages of Alzheimer’s disease. Therapeutic intervention when beta amyloid plaques are more pronounced at this point potentially slows down disease progression rates (Budd Haeberlein et al., 2022). The initial phase results show promising outcomes for immunotherapies such as aducanumab regarding reducing beta amyloid plaques and even delaying cognitive decline rates.

**Comparative Analysis**

NMDA antagonists, cholinesterase, and immunotherapies are strategies being used in the field of Alzheimer’s disease. NMDA antagonists work by targeting the receptor system to regulate excessive excitatory signaling associated with neurodegeneration. Cholinesterase inhibitors enhance neurotransmission by preventing acetylcholine breakdown, providing relief from cognitive symptoms. Finally, immunotherapies involve using the system to target amyloid beta plaques, a characteristic feature of Alzheimer’s disease, using monoclonal antibodies like aducanumab. Each approach tackles various aspects of the disease. For example, NMDA antagonists and cholinesterase inhibitors address issues related to neurotransmission deficits, while immunotherapies focus on addressing amyloid pathology. This makes immunotherapies a more specific solution for patients with the disease since it targets only amyloid protein clusters. Another important thing to evaluate are the adverse effects that generally come with each drug. cholinesterase inhibitors and NMDA antagonists mainly cause headaches and dizziness but the same cannot be said about immunotherapies (Singh & Sadiq, 2023). In rare clinical trial cases there have been signs of microhemorrhages which result from ruptures of small blood vessels in the brain (Song et al., 2022). This is caused by the phagocytosis process. That being said, Cholinesterase inhibitors are considered the best therapy for Alzheimer's disease for several reasons. Of all the treatment types discussed, cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, have been extensively studied and have consistently demonstrated their superior efficacy, compared to the other drugs mentioned, in managing the cognitive symptoms of AD. Cholinesterase inhibitors are considered the standard of care for treating AD
and held a share of revenue of AD medication in 2022 accounting for over 51.24% (Alzheimer’s Therapeutics Market Size & Share Report, 2030, n.d.).

**Conclusion**

Currently there are 60 million individuals living with Alzheimer’s disease. According to projections this number is expected to rise to around 78 million by the year 2030, this could significantly escalate to a 139 million by 2050 (Dementia Cases Set to Triple by 2050, Still Largely Ignored, n.d.). Researchers are actively investigating new and current for Alzheimer’s disease, as we know due to the empirical data that cholinesterase inhibitors, NMDA antagonists, and immunotherapies are effective therapies for AD (Dementia Cases Set to Triple by 2050 but Still Largely Ignored, n.d.). Each of these 3 categories of medications targets different aspects of the pathology associated with AD. Cholinesterase inhibitors like galantamine, donepezil and rivastigmine function by augmenting acetylcholine levels in the brain, which enhances communication between neurons and helps alleviate symptoms (Hoedemaker et al., 2017). NMDA antagonists such as regulate activity to protect against excitotoxicity and neurodegeneration. It is important to recognize that these treatments have their limitations and cannot cure or prevent AD entirely. This underscores the need for research and exploration, into therapies related to Alzheimer’s disease.

**Future Directions**

Moving forward it is important to prioritize Alzheimer’s research by focusing on treatment strategies that address various aspects of the disease. These include the buildup of protein clumps and excitotoxicity, in the brain. One approach to this type of therapy involves using combination treatments that simultaneously target beta amyloid plaques and tau protein tangles both, which are considered as markers of AD (Zampar & Wirths, 2020). Currently researchers are examining the advantages of drugs that can reduce amyloid accumulation and prevent protein aggregation Zampar & Wirths, 2020). This combined approach has shown effects, in slowing down disease progression. On one hand disease modifying therapies aim to slow down the advancement of the disease itself but on the other hand symptom relieving treatments aim to alleviate symptoms experienced by patients (Zampar & Wirths, 2020). By combining these approaches, it may be possible to manage Alzheimer’s by addressing its underlying pathology well as its immediate symptoms (Zampar & Wirths, 2020). For instance, a combination therapy involving a drug targeting beta amyloid and cholinesterase inhibitors could potentially enhance function while also targeting disease progression (Zampar & Wirths, 2020).

Moreover, the future of Alzheimer’s research is focused on investigating customized or individualized combination therapies that are specifically designed for each person based on their makeup. This precision medicine uses the analysis of biomarkers (Mantzavinos & Alexiou, 2017). Biomarkers serve as indicators or substances that help evaluate processes, disease conditions, or responses, to treatments (Mantzavinos & Alexiou, 2017). They offer insights into determining the suitable combination of treatments for every patient (Mantzavinos & Alexiou, 2017). This personalized approach entails tailoring therapy according to factors such, as genetics, biomarker profiles, cognitive abilities and other unique characteristics in order to achieve effectiveness (Mantzavinos & Alexiou, 2017).

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References


Figure 2: Depicting the mechanism operative for an NMDA antagonist. The... (n.d.). ResearchGate. Retrieved August 18, 2023, from https://www.researchgate.net/figure/Depicting-the-mechanism-operative-for-an-NMDA-antagonist-The-NMDA-receptor-can-be_fig2_273287556


