Title
Alzheimer’s Disease and Its Treatment Options

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Alzheimer's Disease and Its Treatment Options

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Abstract

The goal of this literature review is to analyze various treatment options for Alzheimer's Disease, a neurodegenerative disorder that affects many Americans. Four drugs being studied in the paper include Donepezil, Memantine, Lecanemab, and Rivastigmine. Donepezil is an acetylcholinesterase inhibitor that is used for patients with mild or moderate AD. Memantine is used to block the overflow of glutamate through NMDA receptors and to treat patients with moderate to severe AD. It can be used in combination therapy with Donepezil and Galantamine. Lecanemab is used to target amyloid-beta plaques and to reduce aggregates. Rivastigmine is a carbamate cholinesterase inhibitor that can be used to inhibit both acetylcholinesterase and butyrylcholinesterase for mild to moderate cases of AD. All four drugs have been shown to slow down the progression of AD by increasing cognitive performance and to improve the quality of life for patients and their caregivers.

Introduction to Alzheimer's Disease

Alzheimer's Disease (AD) is a neurodegenerative disorder that leads to impaired cognitive and motor functions in patients. AD is most prevalent in patients who are 65 or older, accounting for 50 to 75% of dementia cases; it is estimated that more than 6 millions of Americans have AD.[1]

The exact causes of AD are not known yet, but a few potential mechanisms are proposed. One of the theories is the accumulation of beta-amyloid plaques and/or the tau neurofibrillary tangles. Those disruptions in protein structure can impact the normal function of neurons in the brain, leading to larger scale atrophies in specific areas for memory or other cognitive functions.[1] Some of those changes are caused by genetic mutations. However, the progression of AD doesn't necessarily correlate to the level of protein accumulation in the brain.

One factor that is associated with AD progression is synaptic loss. The loss of cholinergic neurons and a lower level of the neurotransmitter acetylcholine are linked to attention and memory problems. The enzyme acetylcholinesterase hydrolyzes acetylcholine, leading to its reuptake by the presynaptic neuron.[2] Scientists speculate that inhibiting acetylcholinesterase can slow down the reuptake of acetylcholine and increase the time acetylcholine stays at the synapse.[3]

In this paper, we are going to explore various drugs that target different pathological and symptomatic features of AD. Our hope is to pave the way for future drug development and treatment combinations that would yield better results.

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[1] Lane CA, Hardy J, Schott JM. Alzheimer's disease. *European Journal of Neurology*. 2017;25(1):59-70. doi:10.1111/ene.13439
[2] Ferreira-Vieira TH, Guimaraes IM, Silva FR, Ribeiro FM. Alzheimer's disease: Targeting the Cholinergic System. *Curr Neuropharmacol*. 2016;14(1):101-115. doi:10.2174/1570159x13666150716165726
[3] Mehta M, Adem A, Sabbagh M. New acetylcholinesterase inhibitors for Alzheimer's disease. *Int J Alzheimers Dis*. 2012;2012:728983. doi:10.1155/2012/728983

Donepezil

Introduction

Donepezil, which is sold under the brand names Aricept and Aricept Evess, is an FDA-approved medication used to treat dementia in individuals with mild, moderate, and severe Alzheimer's disease (AD). Although it does not cure the condition, it can significantly slow down its symptoms. The medication functions as an acetylcholinesterase inhibitor; it binds to the enzyme cholinesterase and prevents it from breaking down the neurotransmitter acetylcholine. Therefore, it increases the amount of acetylcholine at the synapses, promoting cholinergic transmission. The United States approved donepezil for marketing in 1996, and it was closely followed by Canada and the European Union in 1997. Today, it is supported in over 90 countries worldwide. While it was rejected by the United States and Europe in 2006 for the treatment of vascular dementia, it has since been approved for Lewy body dementia. In the following sections, we will compile findings from a meta-analysis and a study on the effectiveness of donepezil for patients with mild to moderate AD, as well as its safety concerns.

Analysis

In a 2004 meta-analysis titled, "Donepezil for the symptomatic treatment of patients with mild to moderate Alzheimer's disease: a meta-analysis of individual patient data from randomized controlled trials" by Whitehead et al., the researchers examine the efficacy and tolerability of 5 and 10 mg/day of donepezil compared to a placebo for patients with mild to moderate AD.[4] As a result, this review looks at patient data from Phase II and III double-blind,

[4] Whitehead A, Perdomo C, Pratt RD, Birks J, Wilcock GK, Evans JG. Donepezil for the symptomatic treatment of patients with mild to moderate Alzheimer's disease: a meta-analysis of individual patient data from randomised controlled trials. *Int J Geriatr Psychiatry*. 2004;19(7):624-633. doi:10.1002/gps.1133

randomized, placebo-controlled studies of up to 24 weeks that were done by 1999. The dependent variables in this review are the ADAS-cog, the CIBIC-plus, and the reports of adverse effects. Within the review, 2376 patients from 10 trials were randomized to either 5 mg/day of donepezil (n=821), 10 mg/day (n=662), or a placebo (n=893). After 12 weeks, the cognitive performance for those taking both 5 mg/day and 10 mg/day of donepezil was higher than those taking the placebo: the differences in ADAS-cog scores were −2.1 [95% confidence interval (CI), −2.6 to −1.6; $p < 0.001$] for the 5 mg/day compared to the placebo and −2.5 (−3.1 to −2.0; $p < 0.001$) for the 10 mg/day compared to the placebo. At 24 weeks, these differences were −2.0 (−2.7 to −1.3; $p < 0.001$) and −3.1 (−3.9 to −2.4; $p < 0.001$) respectively. For the CIBIC-plus, the odds ratios (OR) of improvement at 12 weeks were 1.8 (1.5 to 2.1; $p < 0.001$) for the 5 mg/day compared to the placebo and 1.9 (1.5 to 2.4; $p < 0.001$) for the 10 mg/day compared to the placebo. After 24 weeks, these results were 1.9 (1.5 to 2.4; $p = 0.001$) and 2.1 (1.6 to 2.8; $p < 0.001$) respectively. Furthermore, there were few reports of side effects; the only adverse effects were cholinergic in nature and generally mild and quick. Therefore, donepezil increases cognitive performance compared to a placebo and produces few side effects.

Another study titled, "A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Donepezil in Patients with Alzheimer's Disease in the Nursing Home Setting" by Tariot et al. published in 2005 focuses on the efficacy and safety of donepezil, this time in a nursing home setting.[5] The study includes 27 nursing homes around the United States and 208 nursing home residents with mild to moderate AD. The primary efficacy outcome measure was the Neuropsychiatric Inventory—Nursing Home Version (NPI-NH). The secondary efficacy measures were the Clinical Dementia Rating (Nursing Home Version)—Sum of the

[5] Tariot PN, Cummings JL, Katz IR, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc. 2001;49(12):1590-1599.

Boxes (CDR-SB), MMSE, and the Physical Self-Maintenance Scale (PSMS). The researchers studied safety by taking physical examinations, vital signs, clinical laboratory tests, electrocardiograms (ECGs), and recording treatment-emergent adverse events (AEs). During the experiment, 82% of donepezil patients completed the trial while 74% of placebo-control patients completed the trial. 11% of donepezil patients and 18% of placebo-control patients dropped out of the trial because of AEs. The mean NPI-NH 12-item scores increased for both groups. However, the mean change from the baseline CDR-SB total score dramatically improved for patients with donepezil compared with placebo at Week 24 ($p < .05$). Furthermore, the differences in the mean change from baseline on the MMSE also favored donepezil over placebo at Weeks 8, 16, and 20 ($p < .05$). There were no significant differences observed between the groups on the PSMS. Gastrointestinal AEs occurred for both donepezil and placebo-control patients but they were more common for those taking donepezil. The AEs were similar for both older and younger patients although weight loss seemed to occur more for older patients. Finally, there were no significant differences between groups in vital sign changes, bradycardia, or rates of clinically significant laboratory or ECG abnormalities.

Conclusion

In conclusion, in spite of its potential AEs, donepezil provides a significant reduction in symptoms associated with AD compared to those taking a placebo. Donepezil is a valuable drug because of its ability to improve mental functioning. However, it doesn't cure the root cause of AD and can potentially have AEs such as weight loss and gastrointestinal complications. Nevertheless, donepezil should stay on the market because it is generally well-tolerated in the long term for those with AD while improving their quality of life, making it a significant drug for

the treatment of AD. In the future, those who manufacture donepezil should try to reduce the frequency of side effects that the drug causes in order to make it even more tolerable.

Memantine

Introduction

Memantine is a drug to treat moderate to severe Alzheimer's Disease, FDA-approved in 2003. It blocks the overflow of glutamate through N-methyl-Dasparate (NMDA) receptors which is common in AD patients. Since glutamate is an excitatory neurotransmitter, a high concentration can cause brain damage and cell death, which memantine actively tries to prevent. This drug will stick to the glutamate receptors, which decreases the excess calcium from moving into the brain cells. Compared to other drugs that block NMDA receptors, such as ketamine, memantine has limited side effects.[6] Since NMDA receptor activity is necessary for normal neuronal function, it is vital that memantine only inhibits excess flow without disruption of normal flow. Memantine is able to achieve this as an open-channel blocker, entering the receptor channels only when it is excessively open and its fast off-rate to ensure it doesn't prevent necessary transmission of glutamine and calcium.[7] Other NMDA-blocker drugs, such as ketamine, can cause memory deficits and other damaging symptoms which have been avoided in memantine.[6] Memantine is also one of the only drugs that treat specifically for moderate to severe cases of AD, as the other drugs mentioned previously in this paper are best suited for mild cases. However, there has been research into the combination therapy of memantine and other

[6] Johnson JW, Kotermanski SE. Mechanism of action of memantine. Curr Opin Pharmacol. 2006 Feb;6(1):61-7. doi: 10.1016/j.coph.2005.09.007. Epub 2005 Dec 20. PMID: 16368266.

[7] Lipton, S. A. (2004). Failures and Successes of NMDA Receptor Antagonists: Molecular Basis for the Use of Open-Channel Blockers like Memantine in the Treatment of Acute and Chronic Neurologic Insults. NeuroRX, 1(1), 101-110. https://doi.org/10.1602/neurorx.1.1.101

acetylcholinesterase inhibitors, such as galantamine and donepezil. Memantine is not a cure for Alzheimer's. Instead, it can only slow down the progression of symptoms of the late stages of AD, maintaining higher levels of autonomy and cognition for a greater amount of time than without the drug.

Methods - Memantine alone

Benoît Rive conducted a study in 2004 where each subject was derived from a randomized double-blind clinical trial, studying the efficacy and long-term tolerability of a memantine daily dose vs placebo for 28 weeks.[8] The effects of memantine were tracked through their Activities of Daily Living (ADL) capabilities measured by the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) modified for more severe dementia (ADCS-ADLsev). The scores on the ADCS-ADLsev scale were standardized (mean = 0, SD = 1) allowing the patients' basic (eating, walking, bathing, etc.) and instrumental capability scores to have equal weightage. This scale compares the patient's evolution to ultimately determine the autonomy of the patient after treatment.

Serge Gauthier conducted a study from pooled data from six 24/28-week studies—three in patients with mild to moderate AD and three in patients with moderate to severe AD—to further investigate how memantine affects behavioral symptoms of AD.[9] All six of the studies were multicentre, randomized, placebo-controlled, parallel-group, double-blind studies of memantine 20 mg/day with out-patients who were aged 50 years at baseline. The behavioral outcomes were measured with The Neuropsychiatric Inventory (NPI)—12 item scale that

[8] Rive, B., Vercelletto, M., Delamarre Damier, F., Cochran, J. and François, C. (2004), Memantine enhances autonomy in moderate to severe Alzheimer's disease. Int. J. Geriat. Psychiatry, 19: 458-464. https://doi.org/10.1002/gps.1112

[9] Gauthier, S., Loft, H. and Cummings, J. (2008), Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. Int. J. Geriat. Psychiatry, 23: 537-545. https://doi.org/10.1002/gps.1949

assesses a range of different behavioral symptoms—based on caregiver interviews, where decreasing total score indicates an improvement in psychopathology.

Patrizia Mecocci conducted a study with data pooled from six randomized, double-blind, placebo-controlled, 6-month clinical trials on the efficacy and safety of memantine to determine the effect of memantine on single cognitive items in patients with moderate to severe AD.[10] This study calculated the changes from baseline in cognitive function at weeks 4, 12, and 24/28 through the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) for mild to moderate AD or the Severe Impairment Battery (SIB) assessment scale for moderate to severe AD.

Analysis - Memantine alone

Through these case studies, it is clear that memantine has significant benefits to patients with moderate to severe AD by increasing their autonomy without being dependent on their caregivers,[11] reducing and preventing behavioral symptoms indicating disease progression (ex. aggression, delusions, etc.[12]), and enhance overall cognitive abilities.

Memantine Combination Therapy

Galantamine and donepezil are both acetylcholinesterase inhibitors that treat mild to moderate AD that have been suggested to be combined with memantine treatment. In fact, Namzaric, a combination of donepezil and memantine, was FDA approved in 2014 as a

[10] Mecocci, P., Bladström, A. and Stender, K. (2009), Effects of memantine on cognition in patients with moderate to severe Alzheimer's disease: post-hoc analyses of ADAS-cog and SIB total and single-item scores from six randomized, double-blind, placebo-controlled studies. Int. J. Geriat. Psychiatry, 24: 532-538. https://doi.org/10.1002/gps.2226

[11] Rive, B., Vercelletto, M., Delamarre Damier, F., Cochran, J. and François, C. (2004), Memantine enhances autonomy in moderate to severe Alzheimer's disease. Int. J. Geriat. Psychiatry, 19: 458-464. https://doi.org/10.1002/gps.1112

[12] Gauthier, S., Loft, H. and Cummings, J. (2008), Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. Int. J. Geriat. Psychiatry, 23: 537-545. https://doi.org/10.1002/gps.1949

fixed-dose, once-a-day oral capsule.[13] Through meta-analyses conducted by Jiaxun Guo[14] and Ruey Chen,[15] having a combination of both donepezil and memantine lead to increased cognitive function, if only minimal. Galantamine and memantine have not been approved by the FDA to be administered, but the rationale behind the combination is very similar to donepezil and memantine.[16]

Discussion

Memantine is one of the only drugs that has consistently been beneficial to patients with moderate to severe AD with minimal drawbacks. Although it does not have drastic impacts on the patient's battle with AD nor does it cure the disease, the lifestyle advantages granted through this drug such as cognitive awareness and basic autonomy are vital to a patient's life. Since memantine is able to increase patient autonomy along with other bodily functions, the cost-effectiveness of the drug increases as the patient will not have to rely on a full-time caregiver as if they were not taking the drug.[17] Furthermore, since this drug is an uncompetitive NMDA receptor antagonist and not an acetylcholinesterase inhibitor, it is able to combine with other drugs in combination therapy to better aid patients more long term. As we move forward, having combinations of memantine and other acetylcholinesterase inhibitor drugs that could give more comprehensive treatment for AD patients.

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[13] https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206439lbl.pdf

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Lecanemab

Introduction

Lecanemab, also known as Leqembi, is a humanized IgG1 monoclonal antibody that targets and binds to soluble amyloid-beta (Aβ) plaques and aggregates (protofibril) with high selectivity.[18] Amyloid-beta (Aβ) are proteins that form abnormal clumps called plaques, which play an essential role in damaging brain cells, disrupting neurochemical communication, and the development of Alzheimer's Disease (AD). The Lecanemab drug is an artificially produced antibody that targets Aβ proteins to help reduce aggregate Aβ plaques, decreases soluble Aβ, and reduces the production of Aβ prone species.[18] This decline and removal of Aβ protein in the brain suggests a slowed down progression of AD. This drug is used to treat individuals with early stages of Alzheimer's Disease, specifically people with mild cognitive impairment or mild dementia due to AD.[19] Clinical trials have shown promising results in the reduction of amyloid beta levels that work to moderately slow down cognitive and function decline for those with early stage AD.[20] Ultimately, the goal of this treatment is to improve cognitive function and slow down the progression of Alzheimer's Disease.

Methods and Results

Starting its research in Switzerland, Biogen research facility has been working with Eisai pharmaceutical company for the development of Lecanemab. After conducting trials on animal

[18] McDade E, Cummings JL, Dhadda S, et al. Lecanemab in patients with early alzheimer's disease: Detailed results on biomarker, cognitive, and clinical effects from the randomized and open-label extension of the phase 2 proof-of-concept study. Alzheimer's research & therapy. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9768996/. Published December 21, 2022. Accessed March 19, 2023.
[19] Dyck CHvan. Lecanemab in early alzheimer's disease | nejm. https://www.nejm.org/doi/10.1056/NEJMoa2212948. Published January 5, 2023. Accessed March 19, 2023.
[20] MacMillan C. Lecanemab, the new alzheimer's treatment: 3 things to know. Yale Medicine. https://www.yalemedicine.org/news/lecanemab-leqembi-new-alzheimers-drug#:~:text=The%20Food%20and%20Drug%20Administration,stage%20cases%20of%20the%20disease. Published January 19, 2023. Accessed March 19, 2023.

models and human clinical trials, the Food and Drug Administration (FDA) approved Lecanemab in January 2023 as an Accelerated Approval Pathway for treating Alzheimer's Disease.[21] Several trials have been conducted to assess the safety and effectiveness of Lecanemab. In 2022, a Phase 3, multicentered, double-blind, randomized trial was conducted on 1795 adults who were 50 - 90 years of age, had early AD, and confirmed to have amyloids in the brain. Half the subjects received Intravenous Infusion of Lecanemab of 10 mg/kg every two weeks while the other half received placebo. The primary efficacy endpoint was determined from the change from baseline in the score on the Clinical Dementia Rating (CDR) - Sum of Boxes (CDR-SB). The CDR validates cognitive function of Alzheimer's Disease by assessing Memory, Orientation, Judgement & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care. After 18 months, the mean change of CDR-SB was smaller in the Lecanemab Group than the placebo, indicating a smaller cognitive and functional decline. The secondary clinical end point was the amyloid burden change shown in PET, which had the same results as the primary end points. The cerebrospinal fluid substudy that assessed the biomarkers of amyloid, tau, neuroinflammation, and neurodegeneration were reduced greatly for those who had Lecanemab than with placebo.[19] Lecanemab demonstrated to have the largest effect among tested doses such as a faster decline in amyloid PET SUVr, increase in plasma Aβ42/40 ratio (a very sensitive biomarker among amyloid cascade), and decrease in plasma p-tau181.[18] Finally, Lecanemab CL showed a decline in increasing albumin levels. As neonatal Fc receptors (FcRn) facilitate albumin homeostasis, higher concentrations of albumin may be an indicator of increased RcRn and a decrease in Lecanemab removal.[22]

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[21] Commissioner Of the. FDA grants accelerated approval for alzheimer's disease treatment. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment. Published January 6, 2023. Accessed March 19, 2023.

[22] Hayato S. Population pharmacokinetic‐pharmacodynamic analyses of amyloid positron ... https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/psp4.12862. Published September 27, 2022. Accessed March 19, 2023.

Analysis

Lecanemab has shown in clinical trials to significantly reduce beta-amyloid protein levels in the brain, which is a hallmark of Alzheimer's disease. This could potentially slow down or halt the progression of the disease. Clinical trials have also shown that Lecanemab is associated with a dose-dependent improvement in cognitive function in patients with Alzheimer's disease. Lecanemab has been shown to be well-tolerated and safe for the treatment of Alzheimer's disease, with a low incidence of adverse events. However, most of Phase 3 trials were conducted during the COVID-19 pandemic, so there were challenges of missed dose, intercurrent illnesses, and delayed assessment.[19] Furthermore, more testing must be conducted as there is limited data.[23] Clinical studies have only been tested on early stage AD patients, but the effects of Lecanemab on patients with later stages is not known. Finally, Eisai reported the cost of Lecanemab as $26,000 per year, which is unaffordable for many people.[20]

Discussion

Lecanemab reduces brain amyloid levels and has less cognitive functional decline in people who have early Alzheimer's Disease. However, continued Lecanemab treatment is needed to achieve continuous therapeutic benefit. This will improve multiple biomarkers that are used to track the AD processes. Continuous dosage till normalization of plasma Aβ42/40 and p-tau181 levels will prevent the gradual reaccumulation of amyloid plaque levels and pathological biomarkers.[18] The next steps for Lecanemab will be to further its research and development for various stages of AD, long-term safety and efficacy, and evaluation of synergy therapies with other drugs to treat advanced Alzheimer's Disease. Challenges of affordability and accessibility

[23] Swanson CJ, Zhang Y, Dhadda S, et al. 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. BioMed Central. https://alzres.biomedcentral.com/articles/10.1186/s13195-021-00813-8. Published May 21, 2022. Accessed March 19, 2023.

of this treatment for patients, especially in low-middle income countries, must be tackled. All in all, Lecanemab has proven to be the first treatment to show an "equivocal slowing of decline in Alzheimer's Disease.[20]"

Rivastigmine

Introduction

Rivastigmine (Brand name: Exelon) is a powerful slow-reversible, noncompetitive carbamate cholinesterase inhibitor that is approved for the treatment of mild-to-moderate Alzheimer's disease. Rivastigmine is most commonly used to treat dementia in Alzheimer's and is mostly used for older populations. It has two routes of administration, one through oral which consists of a capsule or liquid solution, and the other through a transdermal patch.[24] Rivastigmine is currently the only cholinesterase inhibitor (ChEIs) drug inhibiting acetylcholinesterase and butyrylcholinesterase enzymes in the brain.[24] Alzheimer's Disease results from the breakdown of acetylcholine and the purpose of cholinesterase inhibitors are to prevent the breakdown of acetylcholine. Since rivastigmine binds to and inhibits acetylcholinesterase and butyrylcholinesterase, it helps slow the progression of Alzheimer's disease because acetylcholinesterase and butyrylcholinesterase both work similarly to break down acetylcholine within the brain leading to the development of Alzheimer's disease.[25] Rivastigmine was developed by Marta Weinstock-Rosin in the department of pharmacology at Hebrew University; it was later introduced in 1985 and eventually approved by the FDA in 1997 as a medication to slow down the progression of Alzheimer's disease.[25] In the next section, we will discuss the case

[24] Nguyen K, Hoffman H, Chakkam;parambil B, Grossberg GT. Evaluation of rivastigmine in Alzheimer's disease. Future Medicine.
[25] Patel PH, Gupta V. Rivastigmine. National Library of Medicine.

studies of the effectiveness of rivastigmine in slowing down the progression of mild to moderate AD and any safety concerns.

Methodology Meta-Analysis

For this section, we examined the research article called *Rivastigmine for Alzheimer's Disease*, which examines the efficacy and safety of rivastigmine for patients with Alzheimer's Disease. The research is looking at the effectiveness and safety of an oral form of rivastigmine compared to a transdermal form of rivastigmine. There are 13 different trials, each trial having a different number of weeks in which the patients were tested with the medication ranging from 13 weeks to 52 weeks.[26] The amount of medication being administered to the patient varied in oral form from 6 mg to 12 mg daily while with the transdermal form, it remained constant at 9.5 mg per day with a placebo. In this experiment, the Alzheimer's Disease Assessment Scale-Cognitive (ADS-Cog), the ADS-Cog has been considered the gold standard for determining the efficiency of antidementia treatments since its development in the 1980s.[27] The ADS-Cog often consists of tasks such as word recall, naming objects and fingers, commands, etc.[27] These different tasks are used to test the cognitive abilities of Alzheimer's patients, with the score of each task ranging from 0-10 with 0 being the best score for each different task. The range for ADS-Cog ranges from 0-70 with a score of greater or equal to 18 indicating greater cognitive impairment.[28] After 26 weeks, the ADS-Cog score (mean difference (MD) -1.79; 95% confidence interval (CI) -2.21 to -1.37, n = 3232, 6 studies).[26] This result is important because it indicates that the typical ADS-Cog score of each patient is 1.37 to 2.21 similar to each other, meaning that they are often

[26] Birks JS, Evans JG. Rivastigmine for Alzheimer's disease. The Cochrane database of systematic reviews
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[28] Rockwood K, Fay S, Gorman M, Carver D, Graham JE. The clinical meaningfulness of Adas-cog changes in Alzheimer's disease patients treated with Donepezil in an open-label trial. BMC neurology.

in the same score range with a 95% confidence interval.[26] This might suggest that rivastigmine can be effective as a lot of patients who after taking rivastigmine scored in the same range meaning that the drug is effective but we do not know how effective it is because we don't get to see the before and after results. Along with assessing the ADS-Cog, this research also examines the results of the Mini-Mental State Examination (MMSE) score. The MMSE is similar to ADS-Cog as it examines the cognitive function of older adults through different tasks like orientation, registration, attention, recall, etc.[29] However, one difference is that in MMSE the higher the score the higher the chance that the patient does not have cognitive impairment.[29] After 26 weeks of administering rivastigmine to patients, the researchers claimed the MMSE score (MD 0.74; 95% CI 0.52 to 0.97, n = 3205, 6 studies). This suggests that rivastigmine can be beneficial as a lot of patients within this test group receive a similar score and the difference in the score is usually from 0.52 to 0.97. Similarly, we do not know the exact effectiveness of this drug because the research did not mention the score in both ADS-Cog and MMSE before and after the treatment. However, we can claim that rivastigmine can be beneficial to AD patients as they all scored mainly in the same range after receiving the treatment.

Discussion

Even though rivastigmine is a widely used anti-AD medication it still has some drawbacks along with its own strengths. One of the major strengths of rivastigmine is that it is the only ChEIs that inhibits both acetylcholinesterase and butyrylcholinesterase,[25] this is a major strength of rivastigmine because it can suggests that rivastigmine can be really effective in reducing the progression of AD as it targets two of the main enzymes that break down acetylcholine. However, one of the drawbacks of rivastigmine is that the transdermal patch is

[29] Wallace M. The Mini Mental State Examination (MMSE). Try this: Best Practices in Nursing Care to Older Adults.

often very expensive compared to the oral route and this is important because the transdermal patch has been proven to have a lower development of adverse effects compared to the capsule.[30] Another major strength of rivastigmine is that it has two routes of administration which allow a larger target population as patients who cannot take rivastigmine orally can have the option of using a transdermal patch. This is an important reason for keeping rivastigmine in the drug market because it has proven to be effective in slowing down the progression of rivastigmine while it provides more ways of administration as well.

Conclusion

Through the analysis of five different drugs that target various potential mechanisms of Alzheimer's Disease, it is shown these drugs slow down the progression of AD with the aim to best improve the quality of life for patients and their caregivers. More drugs and combination therapies are still being developed, and our hope is that having a greater understanding of different treatment options can provide all of us with a better insight into AD and its future research directions.

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