Gaps in Literature for Treatments in Alzheimer's

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Lean On Us Foundation

LOU Research Initiative

Summer 2024

Abstract

Alzheimer's Disease (AD) is a common disease which affects cognitive functions, usually found in the elderly population (National Institute of Health, 2021). There are various treatment methods to manage symptoms of this disorder such as cognitive rehabilitation therapy, different types of medications, and lifestyle changes (Mayo Clinic, 2023). The main purpose of these treatments is to keep Alzheimer's stable and under control as well as supporting patients (Mayo Clinic, 2023). Most studies done took anywhere from three months to year on a certain patient population to gather results (Efficacy of Cognitive Rehabilitation in Alzheimer Disease: A 1-Year Follow-Up Study. *Journal of Geriatric Psychiatry and Neurology*, by Germain, S). The conclusion of most studies showcased the many benefits and aids these treatments had on the patients (Memantine Treatment in Patients with Moderate to Severe Alzheimer Disease Already Receiving Donepezil, by Tariot, P.N. and Effects of intensive lifestyle changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: a randomized, controlled clinical trial, by Ornish, D.).

Cognitive Rehabilitation Therapy

Alzheimer's Disease (AD) is a common cognitive disorder that affects brain functions, such as memory loss, cerebral thinking, character changes, confusion, and more (National Institute of Health, 2021). Risk factors for AD are brain changes such as Amyloid plaques, genetics, cognitive impairment, previous head injuries or trauma, and age as Alzheimer's typically affects the elderly population (Mayo Clinic, 2023). One standard treatment method for Alzheimer's is cognitive rehabilitation therapy (CRT) which is useful in relieving and supporting patients with cognitive disorders (Mayo Clinic, 2023). CRT is a group of various therapies that healthcare professionals implement into standard procedure to assist those with AD. Some techniques used in CRT include memory exercises, problem solving games, memory aids and more (Mayo Clinic, 2023). Rehabilitation therapy is great for strengthening cognitive function, reducing symptoms of other mental illnesses such as anxiety and depression, and from neurofeedback it can show delays in the cognitive decline of the patient (Mayo Clinic,2023).

In the article released by Medical New Today titled, "What to know about cognitive rehabilitation therapy", the two most commonly practiced approaches to CRT include restorative CRT and compensatory CRT. Restorative CRT approach is used to improve cognitive abilities of a patient struggling with AD (Vilines, 2021). Due to repeated use in activities such as attention span exercises and memory games neural connections were strengthened. Compensatory CRT is another approach to rehabilitation which is mainly used to help a patient with daily tasks. Compensatory CRT can be both a short-term solution when helping a person use assistive devices, but also a long-term treatment when the patient has trouble regaining cognitive skills. Experts use CRT to make an individualized treatment plan for the patient to regain as much cognitive function as possible (Villines, 2021). CRT can also provide coping tools to patients to

aid them in their daily lives if regaining function is not possible (Villines, 2021). This typically involved the introduction of assistive devices, memory tools, calendars, and alarms into patient's routines (Villines, 2021).

A study published in Sage Journals, *Efficacy of cognitive rehabilitation in Alzheimer Disease: A 1-year follow up study,* was conducted to examine the effects of CRT on patients with AD. A sample size of 52 patients had a customized CRT plan for weekly sessions over a course of three months and monthly contact for nine months. The results showed a decrease of global cognition over one year (Germain,2018). The study showed how CR clinical treatments can highly benefit patients with mild stages of AD (Germain,2018). This study illustrates the many benefits of using CR as a treatment source for patients struggling such as the regain in cognitive function through the therapy (Germain,2018).

Lifestyle Changes

Lifestyle changes can also be extremely beneficial in reversing and decelerating the progress of Alzheimer's. Patients' lifestyle may be a contributing factor to why they have developed AD (Bradely, 2022). Having interventions and support groups can help make the day to day life of patients much more conducive to progress in motor and medical functions, (Bradely, 2022). Support groups are also a way for patients to encourage each other and get any assistance they may need (Bradely, 2022).

An article published by BMC, *Effects of Intensive Lifestyle Changes on the Progression of Mild Cognitive Impairment or Early Dementia due to Alzheimer's Disease: a Randomized, Controlled Clinical Trial,* supervised the lifestyle of 51 patients with Alzheimer's or Dementia and Mild Cognitive Impairment (MCI) using an intervention (Ornish,2024). The objective of the study was to see how different lifestyle changes such as diet, exercise, stress management, and

group support affect patients (Ornish,2024). The patients were offered an intervention with individual nutritional plans, personalized exercise prescriptions, and support groups. The results of this study showed that after 20 weeks there was significant improvement in cognition and function after comprehensive lifestyle changes (Ornish,2024). This study displays how important a patient's lifestyle can be relative to health and how interventions and support groups can be serviceable to those with AD (Ornish, 2024).

Diet and exercise are known to help for many various matters throughout life. Aerobic exercise boosts dopamine, and can help maintain cholesterol levels. And diet can control growth, cognition, pigment of the skin and more. However, recent studies have been looking at the correlation of diet at Alzhiemers. The *Mediterranean Diet and Risk for Alzheimer's Disease* explored the rate of patients with AD and a Mediterranean Diet. 2,258 people in the same community were evaluated in New York City (Scarmeas et al., 2006). Evaluations were conducted every 1.5 years with age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, smoking, medical comorbidity index, and body mass index being considered. A Mediterranean diet did indeed lower the risk of AD (Scarmeas et al., 2006). The percentage is not definite, but there is a correlation between lower risk of AD and a Mediterranean diet (Scarmeas et al., 2006). The study itself did not specify that the key components of a Mediterranean diet are mostly plant based foods with healthy fats, mainly olive oil (Scarmeas et al., 2006).

In the *Physical Activity and Alzheimer Disease Course,* researchers explored how physical activity may lower the mortality risk among Alzheimer's Disease patients (Scarmeas et al., 2011). There were 57 participants—people over 65 in New York City. They were followed up with neurologic and neuropsychological tests every 1.5 years. Age, gender, ethnicity, education,

and comorbidities were considered. 54% of the participants died through the study because of natural causes (Scarmeas et al., 2011). Physically active people were at lower risk of mortality. Exercise did not affect the actual symptoms of AD (Scarmeas et al., 2011). This study opens the door for future research and the effects of physical activity on the brain (Scarmeas et al., 2011). Due to the lower mortality risk, links between plaques and physical exercise could be made (Scarmeas et al., 2011).

Medical Treatment of Alzheimer's

Alzheimer's Disorder, commonly known as AD, has many effects, including but not limited to memory loss, cerebral thinking, character changes, and confusion (National Institute of Health, 2021). The effectiveness of memantine, a medication that targets the protein that causes Alzheimers, in conjunction with donepezil, another Alzheimer's treatment, for moderate to severe Alzheimer's, is explored in *Memantine Treatment in Patients With Moderate to Severe Alzheimer Disease Already Receiving Donepezil* (Tariot et al., 2004). This research is conducted through a double-masked study involving 403 people, of whom 322 completed it. Patients who were already on a steady unidentified dose of donepezil started with five mg/d of memantine and increased to a 20 mg/d dose. This combined treatment of donepezil and memantine was well tolerated with patients as there were no adverse effects (Tariot et al., 2004). The treatment effectiveness was measured based on cognition, activities of daily living, global outcome, and behavior (Tariot et al., 2004). The study proves that memantine with donepezil is more effective than just getting doses of memantine or a placebo, as shown through a series of data graphs (Tariot et al., 2004). Compared to the placebo, there was 10% effectiveness of patients remaining the same or getting better, keeping in mind that patients are already being dosed with donepezil (Tariot et al., 2004).

The effectiveness of aducanumab against the AD is being researched in the journal article, *The Antibody Aducanumab Reduces Aβ Plaques in Alzheimer's Disease* (Sevigny et al., 2016). Aducanumab is an Alzhiemer's drug that targets the (Aβ) plaques, which are accredited for causing Alzhiemers in the brain. The study originally involved mice brains with AD, but it was eventually cleared for a human trial (Sevigny et al., 2016). 65 people with moderate AD were given monthly infusions of either a placebo or the aducanumab in increments. The tests focused on baseline characteristics, which mainly includes cognitive ability (Sevigny et al., 2016). The treatment in higher dosages heavily reduced plaques, as shown in brain scans, proving effective. (Sevigny et al., 2016). This reduction of plaques means that there is a prolonged life due to the fact that the actual protein that causes Alzhiemers is shrinking in the brain (Sevigny et al., 2016). This also means that the patient has a greater quality of life due to the fact they can do more tasks as the plaques aren't harming the brain as severely anymore (Sevigny et al., 2016).

Safety, Tolerability, and Pharmacokinetics of Crenezumab in Patients with Mild-to-Moderate Alzheimer's Disease Treated with Escalating Doses for up to 133 Weeks, explored the effectiveness of Crenezumab doses against Alzhiemers (Guthrie et al., 2020). Crenezumab is an antibody against the (Aβ) plaques which cause Alzheimer's (Guthrie et al., 2020). The treatment was doses of a maximum of 120 mg/kg that could be administered every 4 weeks for up to 133 weeks (Guthrie et al., 2020). It was a double-blind study, which means that the patients and researcher are oblivious to what treatment the patient is getting until after the trial is over (Guthrie et al., 2020). Participants were ages 50-90 years old. 71 participants with mild to moderate AD participated in the study. 94% experienced at least one adverse event (fatigue, headache, dizziness, and cerebral micro hemorrhage). The treatment was well tolerated

with no adverse reactions (Guthrie et al., 2020). However, this treatment did not decrease the number of plaques; instead, it kept them stable at higher dosages (Guthrie et al., 2020) This means that no matter how long a patient is under treatment, they do not seem to actually get better. Though this would prolong life, it will not help the quality of a patient's life (Guthrie et al., 2020). However, this can benefit the earlier stages of Alzhiemer's disease as it keeps the number of plaques at a minimum, which in turn means the Alzhiemer's does not get worse (Guthrie et al., 2020).

In *Donanemab in Early Alzheimer's Disease,* the objective was to determine the effectiveness of donanemab in fighting the first stages of the amyloid plaque protein, which rapidly grows and is a cause of AD (Mintun et al., 2021). Donanemab is an antibody which targets a modified version of the Alzhimer causing (Aβ) plaques (Mintun et al., 2021). Two trials with 56 sites across the USA involved 257 people who fit the criteria. 131 were assigned donanemab, and 126 received a placebo (Mintun et al., 2021) Patients were between 60 and 85 and had early signs of Alzheimer's Disease. Those who received the treatment had a lower rate of cognitive decline (Mintun et al., 2021). There were no adverse side effects, and the treatment successfully reduced plaques (Mintun et al., 2021). Adverse reactions included fatigue, headache, dizziness, depression, anxiety, etc (Mintun et al., 2021). Donanemab may increase the patient's life because of how it slows down Alzhiemers, however, it does not stop nor reverse the effects.

Gaps in Literature:

These articles showcase the variety of benefits of treatments such as cognitive rehabilitation therapy as well as lifestyle changes and interventions (Mediterranean diet and risk for Alzheimer's disease. *Annals of Neurology,* by Scarmeas, N. and Effects of intensive lifestyle

changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: a randomized, controlled clinical trial. *Alzheimer's Research & Therapy*, by Ornish, D.). A common theme is that most of these treatments are highly effective for patients with early or mild stages of Alzheimer's or Dementia (Efficacy of Cognitive Rehabilitation in Alzheimer Disease: A 1-Year Follow-Up Study. *Journal of Geriatric Psychiatry and Neurology*, by Germain, S.). This is a great place for growth in the treatments by doing studies on how these methods would affect patients who are further in cognitive decline. This can show what benefits therapy, lifestyle changes, and medications can give patients in late stages of AD or Dementia as well as showing where the treatments lack in supporting the patient. Doing a variety of studies with patients in different stages can help us understand the potential and limits of these treatments as well as how beneficial they are to the patients.

Studies using patient populations from different age ranges would be helpful in understanding how patients in different stages of AD will respond to the different types of treatments. Although treatments are custom to the individual, it would be beneficial to better understand the needs of patients at different stages of disease progression Based on the response of the patients, the results can show what can be done differently or how treatments can be catered for those suffering in the later stages. This can not only help the innovation and diversity of the treatments but can also provide a deeper understanding of the disorder and what really differs from the beginning to later stages of AD.

Throughout the studies conducted, a common finding is the need for consistency with the treatments. For instance when patients are given lifestyle interventions they must stick with it for a long period of time to see results. This can also be seen with cognitive rehabilitation therapy as these sessions span over the course of months or years to support patients until they

no longer need assistance. These treatments are based on stability and persistence so the patients can receive the maximum benefit out of these methods.

In most studies, most CRT treatments span 3 months to 1 year. Since consistency is highly important for these patients, it would be beneficial to investigate how the patients are doing after the treatment stops to see if the results of the patients are still there or if there is a decline in the patients growth. The same research should be done with lifestyle interventions to see if patients gain the ability to still practice a lifestyle which can support them, after the interventions are over. It may be possible for patients to fall back into their old lifestyles or the conditions they were in before CRT treatments which can lead to patients having to go through these processes again.

[Race in Treatment]

These articles show many different ways to help prevent and treat AD, yet the majority don't involve race and demography. Certain races and demographics are proven to be more susceptible and more diagnosed with AD than others (AAIC | July 16-20, 2023 | Alzheimer's Association (n.d.)). This alone can prove that someone would need more consistent or rigorous treatment because of a particular gene that was passed down, and in most studies, race has remained anonymous.

[Quality of Trials]

It is difficult to measure consistency/efficiency in research studies. Many research groups are trapped in urban areas (NYC) and having a more diverse population can provide a more honest and truthful response rate. Many medical treatments also do not follow through after the plaques are gone. It is important to research cognitive ability after plaques have been removed

because of the possibility of brain matter either staying stagnant or growing while the AD protein is being fought with medication.

References

AAIC | July 16-20, 2023 | Alzheimer's Association. (n.d.). AAIC. https://aaic.alz.org

Alzheimer's and dementia. (n.d.). National Institute on Aging. https://www.nia.nih.gov/health/alzheimers-and-dementia

health condition. *Systematic Reviews*, *11*(1). https://doi.org/10.1186/s13643-022-02067-3

Germain, S., Wojtasik, V., Lekeu, F., Quittre, A., Olivier, C., Godichard, V., & Salmon, E. (2018). Efficacy of Cognitive Rehabilitation in Alzheimer Disease: A 1-Year Follow-Up Study. *Journal of Geriatric Psychiatry and Neurology*, *32*(1), 16–23. https://doi.org/10.1177/0891988718813724

Guthrie, H., Honig, L. S., Lin, H., Sink, K. M., Blondeau, K., Quartino, A., Dolton, M., Carrasco-Triguero, M., Lian, Q., Bittner, T., Clayton, D., Smith, J., & Ostrowitzki, S. (2020). Safety, Tolerability, and Pharmacokinetics of Crenezumab in Patients with Mild-to-Moderate Alzheimer's Disease Treated with Escalating Doses for up to 133 Weeks. *Journal of Alzheimer's Disease: JAD*, *76*(3), 967–979. https://doi.org/10.3233/JAD-200134

Mayo Clinic Staff. (2023, August 30). Alzheimer's disease - symptoms and causes. Mayo Clinic; Mayo Foundation for Medical Education and Research

(MFMER)https://www.mayoclinic.org/diseases-conditions/alzheimer's-disease/symptoms-causes/syc-20350447

Mintun, M. A., Lo, A. C., Duggan Evans, C., Wessels, A. M., Ardayfio, P. A., Andersen, S. W., Shcherbinin, S., Sparks, J., Sims, J. R., Brys, M., Apostolova, L. G., Salloway, S. P., & Skovronsky, D. M. (2021). Donanemab in Early Alzheimer's Disease. *New England Journal of Medicine*, *384*(18). https://doi.org/10.1056/nejmoa2100708

National Institute on Aging. (2021, December 16). *Data shows racial disparities in Alzheimer's disease diagnosis between Black and white research study participants*. National Institute on Aging. https://www.nia.nih.gov/news/data-shows-racial-disparities-alzheimers-disease-diagnosis-between-black-and-white-research

Ornish, D., Madison, C., Kivipelto, M., Kemp, C., McCulloch, C. E., Galasko, D., Artz, J., Rentz, D., Lin, J., Norman, K., Ornish, A., Tranter, S., DeLamarter, N., Wingers, N., Richling, C., Kaddurah-Daouk, R., Knight, R., McDonald, D., Patel, L., & Verdin, E. (2024). Effects of intensive lifestyle changes on the progression of mild cognitive impairment or early dementia due to Alzheimer's disease: a randomized, controlled clinical trial. *Alzheimer's Research & Therapy*, *16*(1), 122. https://doi.org/10.1186/s13195-024-01482-z

Salloway, S., Farlow, M., McDade, E., Clifford, D. B., Wang, G., Llibre-Guerra, J. J., Hitchcock, J. M., Mills, S. L., Santacruz, A. M., Aschenbrenner, A. J., Hassenstab, J., Benzinger, T. L. S., Gordon, B. A., Fagan, A. M., Coalier, K. A., Cruchaga, C., Goate, A. A., Perrin, R. J., Xiong, C., & Li, Y. (2021). A trial of gantenerumab or solanezumab in dominantly

inherited Alzheimer's disease. *Nature Medicine*, *27*(7), 1187–1196. https://doi.org/10.1038/s41591-021-01369-8

Scarmeas, N., Luchsinger, J. A., Brickman, A. M., Cosentino, S., Schupf, N., Xin-Tang, M., Gu, Y., & Stern, Y. (2011). Physical Activity and Alzheimer Disease Course. *The American Journal of Geriatric Psychiatry*, *19*(5), 471–481. https://doi.org/10.1097/jgp.0b013e3181eb00a9

Scarmeas, N., Stern, Y., Tang, M.-X., Mayeux, R., & Luchsinger, J. A. (2006). Mediterranean diet and risk for Alzheimer's disease. *Annals of Neurology*, *59*(6), 912–921. https://doi.org/10.1002/ana.20854

Sevigny, J., Chiao, P., Bussière, T., Weinreb, P. H., Williams, L., Maier, M., Dunstan, R., Salloway, S., Chen, T., Ling, Y., O'Gorman, J., Qian, F., Arastu, M., Li, M., Chollate, S., Brennan, M. S., Quintero-Monzon, O., Scannevin, R. H., Arnold, H. M., & Engber, T. (2016). The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature*, *537*(7618), 50–56. https://doi.org/10.1038/nature19323

Tariot, P. N., Farlow, M. R., Grossberg, G. T., Graham, S. M., McDonald, S., & Gergel, I. (2004). Memantine Treatment in Patients with Moderate to Severe Alzheimer Disease Already Receiving Donepezil. *JAMA*, *291*(3), 317. https://doi.org/10.1001/jama.291.3.317

Villines Z. What to know about cognitive rehabilitation therapy. Medical News Today. 2021.https://www.medicalnewstoday.com/articles/cognitive-rehabilitation-therapy