



A review of different non-pharmacological treatment options for Alzheimer's Disease

Janeisha Nayak, Caitlin Durkee

Abstract:

Alzheimer's disease is a neuro-degenerative disease that affects a plethora of people. It is estimated that around 44 million people around the world are living with Alzheimer's disease. In the U.S., about 6.5 million people of any demographic have Alzheimer's (Naqvi). The most common pharmacological treatment for Alzheimer's is donepezil, however there are many factors that prevent people from going with the pharmacological options. Methods such as acupuncture therapy, repetitive transcranial magnetic stimulation(rTMS), music therapy, and exercise therapy are all viable options for such non-pharmacological interventions and all appeal to a variety of different people. Many factors must be considered when deciding on an intervention such as the cost, side-effects, effectiveness, time constraints, and patient's physical capabilities. This review provides a comparison of various methods of non-pharmacological and pharmacological treatments in accessibility and efficaciousness. Efficacy will be measured and compared using various grading systems such as the Mini Mental State Exam(MMSE) and the Alzheimer's Disease Assessment Scale-cognitive(ADAS-Cog). Accessibility will be compared based on the monetary cost and the physical requirements of the patients to participate.

Introduction:

Alzheimer's disease

Alzheimer's disease is the most prevalent cause of dementia, as it accounts for 60-80% of dementia cases ("What"). It is a genetically transferred disease with an autosomal dominant pattern, which means one only copy of the mutated gene in each cell is enough to cause the disease. The pathophysiology of Alzheimer's isn't fully understood, but in brief, brain proteins fail to function normally, which disrupts the neurons and triggers toxic events. Neurons will get damaged, lose connections to each other, and at some point die. Alzheimer's disease can cause increased memory loss and confusion, inability to learn new things, shortened attention span, problems coping with new situations, and other various symptoms that can hinder one's way of life. Alzheimer's disease's main demographic is the elderly and is considered early-onset before the age of 65. Half of adults aged 85 and over have Alzheimer's and more than half of the 6.5 million Americans with the disease may not know they have it. Alzheimer's is a disease that worsens with time but has no cure, making it the 6th leading cause of death in the U.S. and totalling \$277 billion in long-term care services ("Top", "Alzheimer's"). With people who are diagnosed with Alzheimer's, on average, living 4 to 8 years after diagnosis, it inevitably becomes troubling considering there is no defined cure. Because of this, people will try various methods of pharmacological and non-pharmacological treatment to improve symptoms and quality of life.

Pharmacological Methods

The most common treatments for Alzheimer's disease are acetylcholinesterase inhibitors. In post-mortem brains of those with AD, it is found that the level of the transmitter acetylcholine

(ACh) is lower compared to those without AD. ACh serves many functions in both the central and peripheral nervous systems, and thus its loss leads to many of the cognitive and behavioral symptoms of AD. Acetylcholinesterase inhibitors are used in AD because they block the function of acetylcholinesterase, preventing it from breaking down ACh. If these enzymes are prevented from breaking down ACh, it will increase the duration of the neurotransmitter action, which is suspected to help with Alzheimer's. However, on the flip side, if ACh is not broken down at all and begins to build up, it can lead to over-stimulation and restricted neurotransmission, making it critical to find the correct dose. Donepezil is one of these acetylcholinesterase inhibitors, and it is the most frequently used intervention for mild to moderate Alzheimer's cases. However, pharmacological interventions come with an extensive side effect profile, leading to poor medication compliance with patients. Even more, Donepezil treatment is expensive and studies show that it only has a moderate benefit in cognition, behavior, and activities in severe and moderate AD. Additionally, it may take weeks or even months before any noticeable improvements in cognitive function appear. For donepezil, the amount of money saved by not being in full-time care does not offset the price of donepezil enough to bring the cost-effectiveness to a level acceptable by NHS policy (Loveman, Cacabelos, Seltzer).

Non-pharmacological Methods

Interventions such as acupuncture therapy, repetitive transcranial magnetic stimulation (rTMS), music therapy, and exercise therapy all fall under the category of non-pharmacological treatments. Acupuncture is a form of alternative medicine where thin needles are inserted into the body in specific locations to stimulate the body's various systems to improve the overall wellness of the patient. Despite the benefits of acupuncture therapy, the downsides are that it is an invasive procedure, it's quite expensive, and patients have to commute to receive treatment. rTMS is a form of non-invasive brain stimulation in which magnetic fields are changed, creating electric currents at specific locations in the brain. However, similar to acupuncture, it is expensive and patients must commute to a professional to receive the treatment. Music therapy is an evidence-based appliance of music interventions to accomplish a goal, in this case treat Alzheimer's disease. Music therapy is far more affordable because someone can simply just look up a video on the internet or search for a tutorial and follow the steps for music therapy. Alternatively, the patient can pay for a music therapy session with a professional and other patients. However, music therapy sometimes entails dancing or clapping to the music which may not be possible for some patients. Exercise therapy is an intervention that uses routine exercise as an alternate intervention. Like music therapy, you can choose whether you want to take part in the intervention at home for free, or pay to see a professional. However, exercise therapy requires a level of motility allowing the patient to go through with various things like running/jogging which may not be an option for a variety of patients. Unfortunately, despite the strong potential for these non-pharmacological treatment options, there hasn't been extensive research into the efficacy of these interventions. Following is a review comparing the effectiveness and accessibility of Donepezil with non-pharmacological treatment options, because as stated by Frontiers in Aging Neuroscience, "Non-pharmacological therapy shows promise for the treatment of AD, but there is still a lack of high-quality evidence. In the future, the quality of the original research needs to be improved, and strictly designed meta-analysis should be carried out following methodological requirements" (YW).

Evidence:

Donepezil

Donepezil, being one of the most prescribed medications for mild to moderate Alzheimer's, is one of the first options patients go to when looking for a treatment. However, this medication comes with many pros and cons. For example, donepezil has a very extensive side effect profile, including bloody vomit, vomit that looks like coffee grounds, difficulty urinating or pain when urinating, lower back pain, fever, seizures, discoloration or bruising of the skin, and many other serious side effects that turn people away from obtaining benefits from the drug. Another factor that must be considered is how long the patient is prescribed Donepezil. This will help the patient consider how often they must drive to pick up the medication and how many prescriptions they must pay for. Donepezil (5 and 10 mg) is taken on a simple once-daily dosage schedule. The price range can be a problem for people with a limited budget, since 5 mg of donepezil can range from \$13.99 – \$58.59 for 30 tablets, which can stack up very quickly for those who take the drug daily for an extended amount of time. Despite the costs, this treatment has been shown to improve cognition and function in the short term of around 24 weeks and in the long term of about 1 year in patients with mild to moderate Alzheimer's disease (HM). For example, a meta-analysis of Donepezil versus placebo studies found that cognition as measured using the ADAS-Cog and MMSE showed Donepezil improvement over placebo (Table 1).

Acupuncture

Acupuncture is an intervention hailing from China in which needles are inserted into the body to glean various positive results. Acupuncture points are believed to stimulate the central nervous system. This, in turn, releases chemicals into the muscles, spinal cord, and brain. These biochemical changes may stimulate the body's natural healing abilities and promote physical and emotional well-being ("Acupuncture."). Acupuncture, however, has various limiting factors such as cost and accessibility of acupuncture facilities. Initial consultations can cost \$100 - \$300 and subsequent sessions can cost \$50 - \$90 per session, with around six sessions being the norm. Along with the steep prices, accessibility might be an issue since locations providing acupuncture therapy are much less common in general, especially in more remote areas, and the total number of licensed acupuncturists in the US is much lower than the number of physicians. . Another problem that may decrease overall patient compliance is that participants may have an aversion to needles. Also, although quite rarely, some people experience mild, short-term side effects such as pain, bleeding, or bruising where the needles puncture the skin ("Healthcare").

rTMS

rTMS is an external device that delivers repetitive pulsed magnetic fields at various magnitudes to cause neural action in the prefrontal cortex. rTMS is used for improving cognition, memory, and language of AD patients, especially in the milder stages. rTMS is not an invasive treatment and a patient would not have to worry about needles or consuming medication. The side effects of rTMS, such as headaches, scalp discomfort, or brief lightheadedness, are all mild or moderate in severity. Therefore, the side effects of rTMS are fairly limited in intensity and patient dropouts for this reason are far less than the previously mentioned treatments. However, similar to acupuncture, the cost of treatment is quite high at \$200-300 per session. Clinical trials

have found that maximal therapeutic effects of rTMS treatment occur by 26–28 sessions of stimulation, totalling \$5,200-8,400 for a full course of the treatment (Modirrousta). Similar to acupuncture, you will have to commute to receive treatment and not all clinics may be equipped for rTMS, so the costs may not be worth the payoff.

Music Therapy

Music therapy is the employment of music to focus on the physical, cognitive, and social needs of a group or individual. It uses a plethora of activities, such as listening to melodies, playing an instrument, drumming, writing songs, and guided imagery. Research has found that listening to or singing songs can provide emotional and behavioral benefits for people with Alzheimer's disease (H). Music therapy can be done at home or with a professional depending on what the patient finds most applicable to their situation. However, if music therapy is done at home, the patient must have access to a music player. To partake in music therapy it is also necessary to have a certain level of motility to be able to take part in clapping and dancing to the music without being a danger to yourself. Music therapy is fairly safe in general and has no side effects. However, very loud music or particular types of music might irritate some people or make them feel uncomfortable. For music therapy with a professional, average hourly rates for individual music therapy sessions are between \$50-90, and average hourly rates for group music therapy sessions are between \$60-90 (“Alzheimer’s”, “American”, MT-BC).

Exercise Therapy

Exercise therapy is an intervention that uses exercise to help maintain, promote, or restore one’s health. Exercise therapy is another treatment, like music therapy, that can be done at home or with a professional if the patient so desires. However, for exercise therapy, the bar for patient motility is much higher than music therapy where patients may even need to lightly jog or jump. This can be a problem for many Alzheimer's patients as the main demographic for this disease is fairly old. Exercise therapy is generally very safe as well; some minor side effects are pain, fatigue, and muscle soreness. Injuries in exercise therapy typically stem from mistakes on the patient’s or professional’s side rather than because of the intervention itself. The national average per session cost of physical therapy can range from \$30 - \$400, but again this therapy can just as easily be done by one self with the internet.

Table 1: The Cost, Efficacy, Physical Constraints, and Side- Effects of Various Pharmacological and Non-pharmacological Interventions.

	Cost	Efficacy	Physical	Side-Effects
--	-------------	-----------------	-----------------	---------------------



			Constraints	
Donepezil	The average cost for 30 Tablet(s), 10mg each of the generic (donepezil hcl) is \$64.91	ADAS-Cog: [MD: -2.67, p < 0.0001; Improvement over placebo] (Birks, Harvey 2018) MMSE: [MD: 1.05, p < 0.0001; Improvement over placebo] (Birks, Harvey 2018)	No constraints	<ul style="list-style-type: none"> - bloody vomit - vomit that looks like coffee grounds - difficulty urinating or pain when urinating - lower back pain - fever - seizures - discoloration or bruising of the skin - etc...
rTMS	The treatment itself costs about \$200-300 per daily session.	ADAS-Cog: [MD: -3.65, p=0.001; Improvement over placebo] (Dong et al 2018) MMSE: [MD: 0.49, p-value p>0.05; Improvement over placebo] (Dong et al 2018)	No constraints	<ul style="list-style-type: none"> - headaches - scalp discomfort - brief lightheadedness
Acupuncture	an acupuncture session costs between \$70 - \$150	ADAS-Cog [MD: -5.14, p<0.01; Improvement over drugs] (Wang et al review - Zhou et al 2015) MMSE: [MD: 1.05, p<0.05; Improvement over drugs] (Wang et al review - Zhou et al 2015) MMSE: [MD: 3.74, p <0.01 ; Improvement over no treatment] (Wang et al review - Zhou et al 2015)	Adversity to needles	<ul style="list-style-type: none"> - pain where the needles puncture the skin - bleeding or bruising where the needles puncture the skin

Music Therapy	Average hourly rates for individual music therapy sessions were between \$50-90, however if done by yourself using the internet it can be free.	ADAS-Cog: [MD:] MMSE [MD: -1.71, p= ; No improvement over placebo] (Lai et al 2020)	Clapping and dancing	<ul style="list-style-type: none"> - very loud music or particular types of music might irritate some people or make them feel uncomfortable
Exercise Therapy	The national average per session cost of physical therapy can range from \$30 - \$400, but again this therapy can just as easily be done by oneself if applicable.	ADAS-Cog: [MD: 0.61, p= ; Improvement over placebo] (Lai et al 2020) MMSE: [MD: -0.50, p= ; No improvement over placebo] (Lai et al 2020)	Various physical activities (stretching , jogging, etc...)	<ul style="list-style-type: none"> - pain - fatigue - muscle soreness.

Conclusion:

When it comes to cost, music and exercise therapy are the most accessible. They can be done at home if the patient so desires, unlike acupuncture and rTMS which have steep prices that are outside of many people’s price ranges. Donepezil has fairly moderate prices depending on if you have insurance or not, but the payments stack up with each purchase if you intend to take this medicine continuously. On the other hand, the cheaper options have various physical constraints that may not be possible to a significant portion of the main Alzheimer’s patient demographic. As 75% of Alzheimer’s patients are 75 years of age or older, activities such as dancing or jogging, which are integral aspects of music and exercise therapy, may not be a possibility for them. Most of the interventions, aside from acupuncture and Donepezil, have a fairly limited side-effect profile. Donepezil comes with the standard, expansive side effect profile usually associated with taking drugs. And acupuncture, although not having many side effects, involves an invasive method of treatment utilizing many needles. This may be a problem with patient compliance/participation as it involves multiple nicks in the skin which would barr patients with hemophilia, turn away those with a phobia of needles, and introduces the possibility of infection for those who are immunocompromised. Nonetheless, an extremely important factor when choosing a treatment would be efficacy. In this regard, all the interventions, other than music therapy, showed improvement over the placebo/drugs with regards to the ADAS-Cog. With regard to the MMSE, however, music therapy and exercise therapy failed to improve over the placebo/drug. Thus, the most economically accessible



interventions turned out to be the least effective ones, and the more effective cheaper intervention(exercise therapy) has a high barrier of entry in terms of physical requirements. Additionally, if the patient wishes to opt for donepezil and acupuncture (the cheapest options on the more efficacious but expensive side of the spectrum) they must tackle a widespread side effect profile or an invasive treatment with needles, both entailing continuous costs on the patient's part. And finally, rTMS, which has good efficacy and limited side effects, has extremely steep prices that not many people could afford to sustain. Considering the many costs and benefits to each treatment, the decision ultimately falls upon the patient and their families to weigh these factors when deciding on a treatment that's right for them.



Bibliography

1. "Acupuncture." JHM, 13 Mar. 2023, www.hopkinsmedicine.org/health/wellness-and-prevention/acupuncture#:~:text=Acupuncture%20points%20are%20believed%20to,physical%20and%20emotional%20well-being.
2. "Alzheimer's Disease." *Mayo Clinic*, 2 Feb. 2023, www.mayoclinic.org/diseases-conditions/alzheimers-disease/symptoms-causes/syc-20350447.
3. "American Music Therapy Association." *What Is Music Therapy? | What Is Music Therapy? | American Music Therapy Association (AMTA)*, www.musictherapy.org/about/musictherapy/. Accessed 21 June 2023.
4. "Aricept Prices, Coupons & Savings Tips - Webmdrx." *Aricept Prices, Coupons & Savings Tips - WebMDRx*, tinyurl.com/4d96zymn. Accessed 21 June 2023.
5. Cacabelos, Ramón. "Donepezil in Alzheimer's Disease: From Conventional Trials to Pharmacogenetics." *Neuropsychiatric Disease and Treatment*, June 2007, www.ncbi.nlm.nih.gov/pmc/articles/PMC2654795/.
6. Chu CS;Li CT;Brunoni AR;Yang FC;Tseng PT;Tu YK;Stubbs B;Carvalho AF;Thompson T;Rajji TK;Yeh TC;Tsai CK;Chen TY;Li DJ;Hsu CW;Wu YC;Yu CL;Liang CS; "Cognitive Effects and Acceptability of Non-Invasive Brain Stimulation on Alzheimer's Disease and Mild Cognitive Impairment: A Component Network Meta-Analysis." *Journal of Neurology, Neurosurgery, and Psychiatry*, pubmed.ncbi.nlm.nih.gov/33115936/. Accessed 21 June 2023.
7. Dong X;Yan L;Huang L;Guan X;Dong C;Tao H;Wang T;Qin X;Wan Q; "Repetitive Transcranial Magnetic Stimulation for the Treatment of Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials." *PloS One*, pubmed.ncbi.nlm.nih.gov/30312319/. Accessed 21 June 2023.
8. H, Leslie. "Music & Memories; the Power of Music on the Brain." *Dementia Training for NH Home Care & Hospice*, 16 Nov. 2020, nhdementiatraining.org/2020/11/16/music-memories-the-power-of-music-on-the-brain/.
9. "Healthcare Statistics for 2021: Policy Advice." *Healthcare Statistics for 2021 | Policy Advice | Policy Advice*, policyadvice.net/insurance/insights/healthcare-statistics/. Accessed 21 June 2023.
10. HM;, Dooley M;Lamb. "Donepezil: A Review of Its Use in Alzheimer's Disease." *Drugs & Aging*, pubmed.ncbi.nlm.nih.gov/10803860/. Accessed 21 June 2023.



11. Jia J;Wei C;Chen W;Jia L;Zhou A;Wang F;Tang Y;Xu L; “Safety and Efficacy of Donepezil 10 Mg/Day in Patients with Mild to Moderate Alzheimer’s Disease.” *Journal of Alzheimer’s Disease : JAD*, pubmed.ncbi.nlm.nih.gov/31985467/. Accessed 21 June 2023.
12. Jia Y;Zhang X;Yu J;Han J;Yu T;Shi J;Zhao L;Nie K; “Acupuncture for Patients with Mild to Moderate Alzheimer’s Disease: A Randomized Controlled Trial.” *BMC Complementary and Alternative Medicine*, pubmed.ncbi.nlm.nih.gov/29284465/. Accessed 21 June 2023.
13. Lai X;Wen H;Li Y;Lu L;Tang C; “The Comparative Efficacy of Multiple Interventions for Mild Cognitive Impairment in Alzheimer’s Disease: A Bayesian Network Meta-Analysis.” *Frontiers in Aging Neuroscience*, pubmed.ncbi.nlm.nih.gov/32581760/. Accessed 21 June 2023.
14. Loveman E;Green C;Kirby J;Takeda A;Picot J;Payne E;Clegg A; “The Clinical and Cost-Effectiveness of Donepezil, Rivastigmine, Galantamine and Memantine for Alzheimer’s Disease.” *Health Technology Assessment (Winchester, England)*, pubmed.ncbi.nlm.nih.gov/16409879/. Accessed 21 June 2023.
15. Lyu J;Zhang J;Mu H;Li W;Champ M;Xiong Q;Gao T;Xie L;Jin W;Yang W;Cui M;Gao M;Li M; “The Effects of Music Therapy on Cognition, Psychiatric Symptoms, and Activities of Daily Living in Patients with Alzheimer’s Disease.” *Journal of Alzheimer’s Disease : JAD*, pubmed.ncbi.nlm.nih.gov/29991131/. Accessed 21 June 2023.
16. Modirrousta, Mandana, et al. “Efficacy of Twice-Daily vs Once-Daily Sessions of Repetitive Transcranial Magnetic Stimulation in the Treatment of Major Depressive Disorder: A Retrospective Study.” *Neuropsychiatric Disease and Treatment*, 17 Jan. 2018, www.ncbi.nlm.nih.gov/pmc/articles/PMC5775741/.
17. Morris JK;Vidoni ED;Johnson DK;Van Sciver A;Mahnken JD;Honea RA;Wilkins HM;Brooks WM;Billinger SA;Swerdlow RH;Burns JM; “Aerobic Exercise for Alzheimer’s Disease: A Randomized Controlled Pilot Trial.” *PloS One*, pubmed.ncbi.nlm.nih.gov/28187125/. Accessed 21 June 2023.
18. MT-BC, Written by: Abby Klemm, and Reviewed by: Kristen Fuller MD. “Music Therapy: How It Works, Cost, & What to Expect.” *Choosing Therapy*, tinyurl.com/26zwtu9c. Accessed 21 June 2023.
19. “Music Therapy and Cancer.” *Music Therapy | Complementary and Alternative Therapy | Cancer Research UK*, 21 Nov. 2022, tinyurl.com/2vd3ptec.
20. Naqvi, Erum. “Alzheimer’s Disease Statistics.” *Alzheimer’s News Today*, 30 June 2017, alzheimersnewstoday.com/alzheimers-disease-statistics/.
21. Pisani S;Mueller C;Huntley J;Aarsland D;Kempton MJ; “A Meta-Analysis of Randomised Controlled Trials of Physical Activity in People with Alzheimer’s Disease and Mild Cognitive Impairment with a Comparison to Donepezil.” *International Journal of Geriatric Psychiatry*, pubmed.ncbi.nlm.nih.gov/34490652/. Accessed 21 June 2023.



22. PR;, Weiler M;Stieger KC;Long JM;Rapp. "Transcranial Magnetic Stimulation in Alzheimer's Disease: Are We Ready?" *eNeuro*, pubmed.ncbi.nlm.nih.gov/31848209/. Accessed 21 June 2023.
23. RJ;, Birks JS;Harvey. "Donepezil for Dementia Due to Alzheimer's Disease." *The Cochrane Database of Systematic Reviews*, pubmed.ncbi.nlm.nih.gov/29923184/. Accessed 21 June 2023.
24. Seltzer, Ben. "Efficacy of Donepezil in Early-Stage Alzheimer Disease." *Archives of Neurology*, 1 Dec. 2004, jamanetwork.com/journals/jamaneurology/fullarticle/787258.
25. Shao S;Tang Y;Guo Y;Tian Z;Xiang D;Wu J; "Effects of Acupuncture on Patients with Alzheimer's Disease: Protocol for a Systematic Review and Meta-Analysis." *Medicine*, pubmed.ncbi.nlm.nih.gov/30681612/. Accessed 21 June 2023.
26. "TMS (Transcranial Magnetic Stimulation): What It Is." *Cleveland Clinic*, my.clevelandclinic.org/health/treatments/17827-transcranial-magnetic-stimulation-tms#:~:text=Side%20effects%20of%20rTMS%2C%20such,procedure%20could%20cause%20a%20seizure. Accessed 21 June 2023.
27. "Top 10 Facts about Alzheimer's Disease." *A Place For Mom*, www.aplaceformom.com/caregiver-resources/articles/scary-facts-about-alzheimers-disease. Accessed 21 June 2023.
28. "What Is Alzheimer's?" *Alzheimer's Disease and Dementia*, www.alz.org/alzheimers-dementia/what-is-alzheimers. Accessed 21 June 2023.
29. Yu F;Vock DM;Zhang L;Salisbury D;Nelson NW;Chow LS;Smith G;Barclay TR;Dysken M;Wyman JF; "Cognitive Effects of Aerobic Exercise in Alzheimer's Disease: A Pilot Randomized Controlled Trial." *Journal of Alzheimer's Disease : JAD*, pubmed.ncbi.nlm.nih.gov/33523004/. Accessed 21 June 2023.
30. YW;, Wang LY;Pei J;Zhan YJ;Cai. "Overview of Meta-Analyses of Five Non-Pharmacological Interventions for Alzheimer's Disease." *Frontiers in Aging Neuroscience*, pubmed.ncbi.nlm.nih.gov/33324194/. Accessed 21 June 2023.