HIGH SCHOOL EDITION
Journal of Student Research
Volume 11 Issue 3 (2022)

Alzheimer's Disease and the Aging Brain: A Review of Current Etiology and Treatments

Alexandra Hulbert[1], Julia Bazinet[1], and Justine McClellan[#]

[1] Bronxville High School, Bronxville, NY, USA
[#]Advisor

ABSTRACT

Alzheimer's disease (AD) is currently one of the leading causes of death in the United States, and it continues to kill more patients every year. Although it is believed to have many different contributing causes, one of the main hypotheses is that unhealthy build-up of proteins in the brain blocks signaling and degrades neurons. Unfortunately, no current treatment is capable of preventing this build-up or reversing its effects. However, four treatment options exist to combat a different contributor to the disease's onset: acetylcholine inhibition. Cholinesterase inhibitors work by preventing the enzyme, cholinesterase, from breaking down acetylcholine, a chemical messenger with an important role in memory and learning that is more scarce in patients with Alzheimer's. Memantine is used alongside cholinesterase inhibitors, and it prevents the N-Methyl-D-aspartate receptor from over activating and causing neuron death. Though cholinesterase inhibitors and memantine are helpful medications for those suffering from AD, they do not stop progression of the disease or reverse the damage. This article will review the current research on AD and what it reveals about known causes and treatments.

Introduction

Alzheimer's disease (AD) is the most common form of dementia that currently affects over 6 million Americans. It is one of many age-related diseases, particularly impacting individuals over the age of 65 due to the degrading efficacy of systems in the brain. AD tends to be challenging to diagnose as its symptoms typically mimic those of various other diseases, like Parkinson's or Huntington's. When AD is in its early stages of development, mild symptoms occur: memory loss, poor judgment, lost or misplaced items, mood changes, anxiety, and aggression. However, as AD progresses, the symptoms will worsen; one with mild AD will face confusion, difficulty learning new things, difficulty with organization, a short attention span, hallucinogens, and paranoia. Patients that present with a severe case of Alzheimer's will experience intensified symptoms. Symptoms that likely exist in patients with severe cases of AD include unexplained weight loss, seizures, trouble with communicating, elongated sleeping periods, and possible loss of bladder control. Again, the symptoms existing in a patient suffering from AD really depends on the stage the disease is at.

Etiology

Risk Factors

The direct inheritance of Alzheimer's is rare; in fact, less than 1% of AD cases were caused by a specific, or deterministic, gene. Thus, the risk of developing AD simply due to a family history of the disease is relatively low. However, one can inherit "risk genes" that can increase their chances of developing AD. Indeed, the

APOE-e4 gene was found in over 50% of all AD patients. APOE-e4 is a variant of apolipoprotein, which normally functions in the movement of lipids and their transformation into lipoproteins. Inheriting one or more copies of the mutated APOE gene is correlated with the development of late-onset AD (Wolfe et al., 2019). Despite the apparent genetic risks involved in the development of Alzheimer's, an individual is much more likely to become susceptible to AD through sporadic, non-genetic variables. Age is one such variable; most AD patients are over the age of 65, and after reaching this age, the risk of developing this disease doubles every five years (Kumar et al., 2022). Additionally, non-genetic factors can cause a decrease in neuron activity in the brain and raise an individual's risk of developing AD. Low educational level and hearing impairment are linked to lower neurological activity in the brain and, thus, higher susceptibility to developing AD.

Tau and Amyloid-Beta

Tau and amyloid-beta (Aβ) build-up are essential components in the progression of Alzheimer's disease. While the accumulation of amyloid-beta typically occurs in the earliest stages of AD progression (prior to confirmed diagnosis), tau accumulation is constantly happening in the course of the disease. Tau begins to accumulate in the hippocampus and the entorhinal cortex and continues to build up as AD develops. And the total amount of tau present in the brain can directly be linked to the disease's stage and severity, making it a helpful asset during diagnosis.

In a healthy brain, tau proteins are involved in forming a structure known as a microtubule, which helps maintain the cell's structure, among other essential functions. Tau proteins in the brain of a person suffering from AD are misfolded and abnormally shaped. This variation in tau destabilizes the microtubule and results in the structure's malfunction. Without the guiding structure of the microtubule, tau proteins cluster to form neurofibrillary tangles, which are also highly associated with the onset of AD. Neurofibrillary tangles can block synaptic communication between neurons, eventually leading to the deterioration of the brain seen in later stages of Alzheimer's.

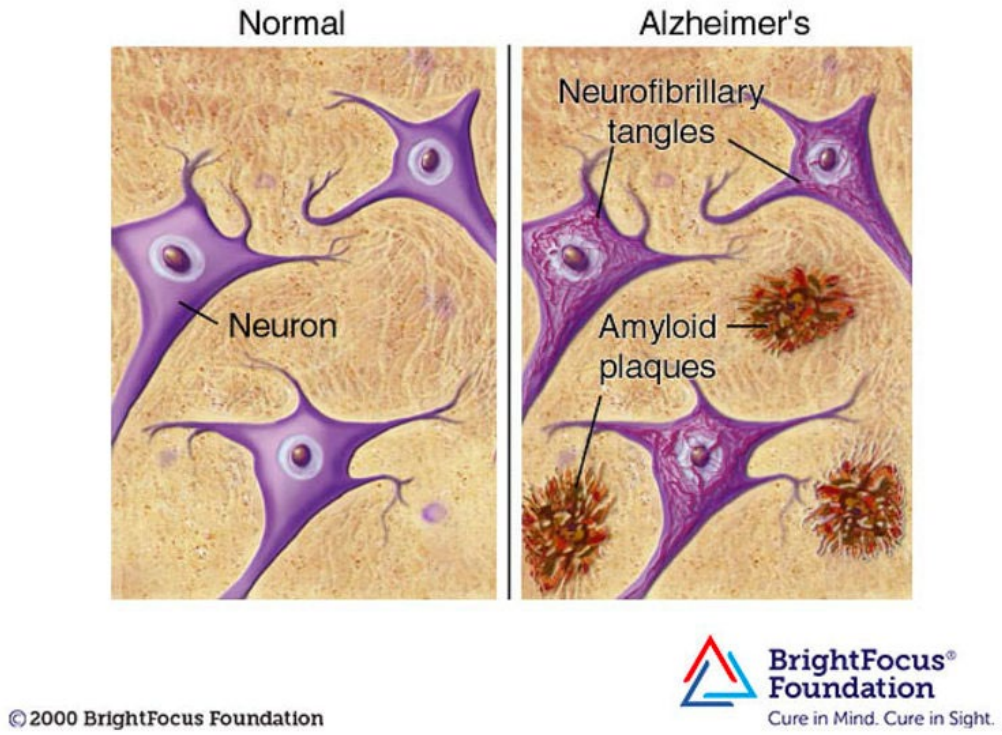

Figure 1. comparison of normal brain to AD brain with neurofibrillary tangles and amyloid plaques.

Another factor that blocks healthy neuron signaling is amyloid-beta plaques, produced by cleaved amyloid precursor proteins (APP). In a healthy brain, Aβ is broken down and dissipated immediately. However, a mutation in APP commonly seen in Alzheimer's patients causes an increase in cleaving and a build-up of Aβ. Because Aβ molecules are sticky, they cluster together and form plaques in the brain. These plaques can damage neurons and interfere with their ability to send signals. Combined with the neurofibrillary tangles, it is clear how synaptic signals in the brain can be blocked in by AD.

Microglia and TREM2

Microglia are a type of myeloid cell, or innate immune cell, that play a dichotomous role in AD. Early on, they have the ability to clear amyloid-beta plaques in the brain. However, as AD progresses, the microglia's plaque-clearing abilities are inhibited. Also, most AD risk genes are highly expressed in microglia (more so than other brain cells).

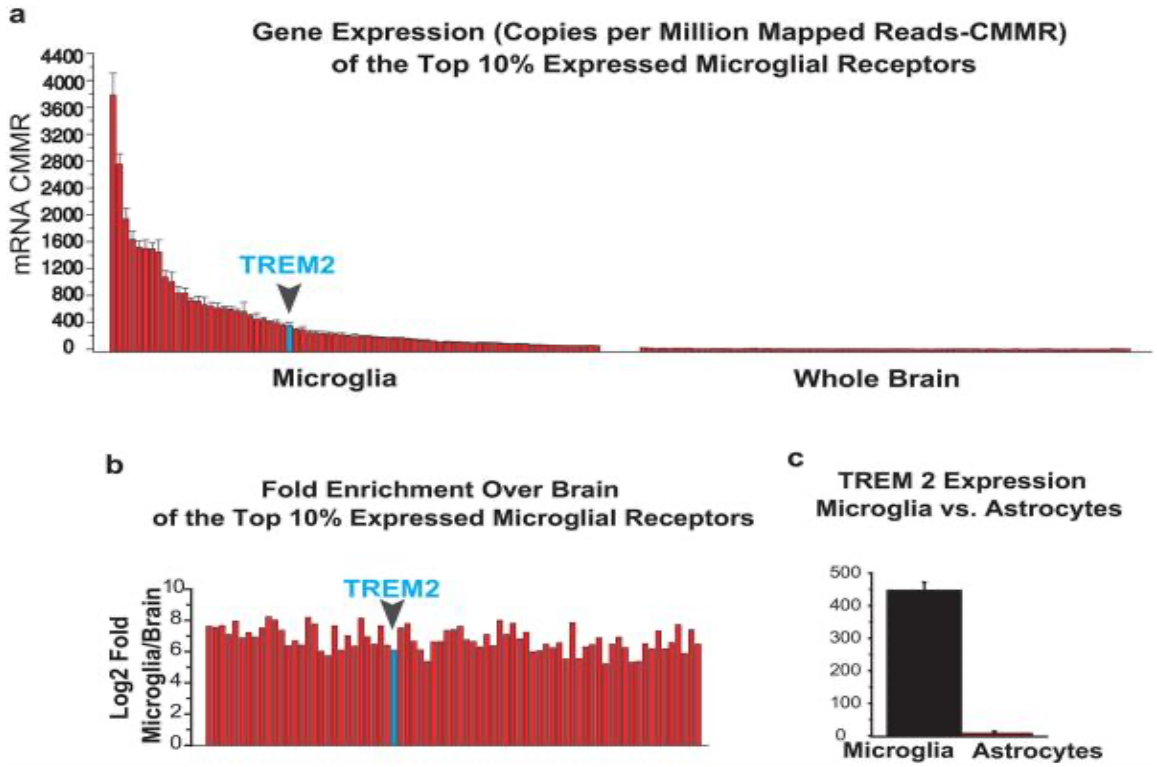

Figure 2. Expression of TREM2 in microglia cells. TREM2 is highly (a) expressed and (b) enriched on microglia compared to the brain as a whole and (c) compared to astrocytes.

Triggering receptor expressed on myeloid cells 2 (TREM2) is one of the highest expressed receptors on microglial cells, and its activation helps promote normal functioning of microglia. It is linked to the immune system and is typically activated for phagocytosis and secretion of inflammatory cytokines. When a TREM2 receptor is activated, parts of it can detach into the cerebrospinal fluid. Because an increase in TREM2 activity is caused by an increase in microglial activity, testing the cerebrospinal fluid is a good indicator of how active a body's microglia are. This could also aid in AD detection as mutations in TREM2 are associated with onset of AD. TREM2 levels can rise up to 21 years before AD onset, and it plays an important role in microglial function. Its variants can alter microglial activity and inhibit plague-clearing abilities. One example is TREM2-R47H (arginine to histidine at position 47), which is associated with unhealthy levels of tau proteins and inhibited ligand binding that increase AD risk by 400% (Wolfe et al., 2018).

Inflammation

The complement system is an integral part of the immune system – it clears damaged cells from an organism by heightening the abilities of antibodies and phagocytic cells. In addition, phagocytic microglia cells have been named as key contributors in neurogenesis (Rodríguez et al., 2021). In AD, these responses can be extremely helpful in clearing harmful build-up in the brain and repairing neural damage. Another key function of the complement system is its inflammatory responses; however, too much inflammation is damaging to the brain. Increased activity in the complement system can degrade neural tissue and block neural communication, giving inflammation an important role in AD pathology and progression.

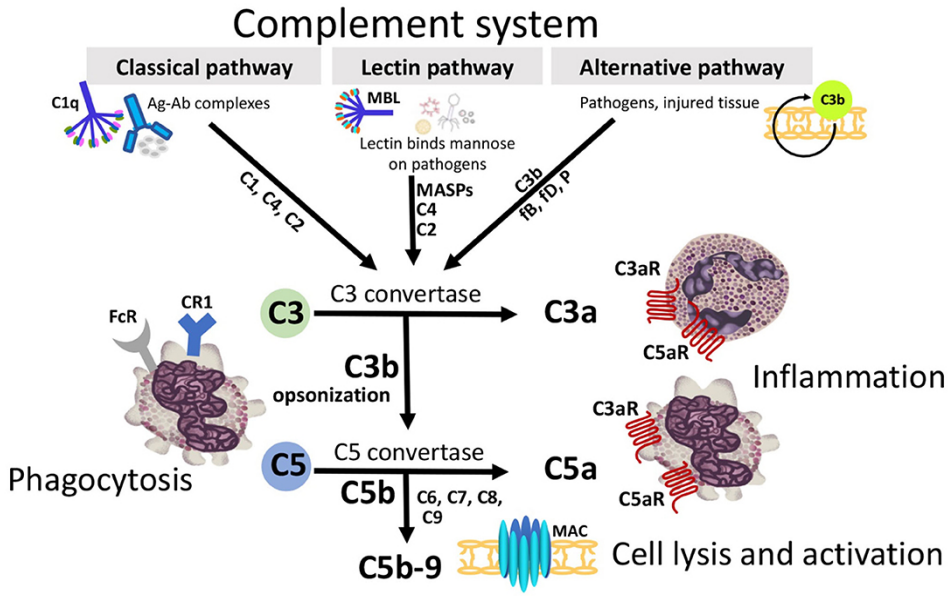

Figure 3. The different pathways of the complement system involved in immune responses.

Inflammatory responses in the body can contribute to AD for a number of reasons. They stimulate production of neurotoxins that damage or kill neurons, and they increase Aβ levels in the brain by upregulating Aβ-generating enzymes (Hickman et al., 2013). It is therefore plausible to assume that controlling neuroinflammation would be a cogent method of delaying AD progression.

Diet and Immune Responses

Factors such as the nutrients you intake through your food can influence inflammatory responses in the body and control the pathogenesis of AD. Consuming higher amounts of saturated fats can promote inflammation in the brain, which can contribute to the onset of dementia, whereas unsaturated fats have anti-inflammatory abilities (McGrattan et al., 2019).

The Mediterranean diet has delayed cardiovascular disease, and it has potential benefits for cognitive performance in long term usage as well. In one study, people who adhered strongly to the Mediterranean diet – primarily consisting of fruits, vegetables, fish, and wholegrain – had much healthier brain cognition and more reliable memory (Marseglia et al. 2018). Maintaining a healthy gut microbiome is also important when considering risk factors of AD. Research in this area is not extensive. However, studies have discovered correlation between diet and healthy gut microbiota. For example, the Mediterranean diet was found to increase the amount of helpful, anti-inflammatory bacteria in the gut (Garcia-Mantrana et al., 2018). The ability to control our gut microbiome can be critical in reducing risk of AD.

In addition, advanced glycation end products (AGEs), such as red meat and certain dairy products, have the potential to modify cell surface receptors and induce oxidative stress and inflammation (Breijyeh et al., 2020). These bodily reactions can cause degradation in cognitive abilities and heightened risk of AD. The receptor for AGEs, which can be found on microglia, causes neuroinflammation and neurodegeneration through amplifying pro-inflammatory signals. So, lower intake of AGEs can prevent neurodegeneration and potentially delay the onset of AD.

Melatonin and Circadian Rhythms

Melatonin is another factor that is highly correlated with AD. It is secreted from the Pineal Gland and regulates circadian rhythms (sleep-wake cycles). As a person ages, their levels of melatonin gradually decrease. In serious cases, this can cause severe sleep loss and an increased build-up of amyloid-beta and tau in the brain. A study published in the *Proceedings of the National Academy of Sciences* found that amyloid-beta levels increase by 5% after a sleepless night (NIH, 2018). In addition, melatonin is integral to preventing AD; it slows down neurodegeneration, and it inhibits amyloid-beta formation via antibiotic and anti-amyloid properties. Although there is strong evidence of a correlation between melatonin and AD, it is not yet known what causes the connection. It is unclear whether lack of sleep leads to AD, lack of sleep aggravates symptoms of AD, or AD leads to a lack of sleep. Or perhaps all are true. Further research is needed to solidify the connection between sleep and Alzheimer's to advance our understanding of the disease.

Current Treatments

Cholinesterase Inhibitors

In individuals with Alzheimer's, the chemical messenger acetylcholine (ACh) becomes more scarce. Acetylcholine is important for alertness, memory, and other brain functions. So, its scarcity causes certain nerve cells to be less active and decreases the frequency of brain signals. Inhibitors have been synthesized to prevent the enzyme, cholinesterase (ChE), from breaking down ACh, making the chemical messenger much more abundant in the brain. Three drugs that inhibit ChE are available to delay the deterioration of the brain: donepezil, rivastigmine, and galantamine. In some cases, these drugs improve memory; however, they do not have the ability to prevent AD development or repair damaged neurons (Singh et al., 2022).

Donepezil was first approved to treat AD in 1996. Along with inhibiting ChE, donepezil also inhibits glutamate-induced excitotoxicity and reduces inflammatory cytokine activity (Sharma, 2019). However, this drug comes with a myriad of side-effects, including insomnia, low blood pressure, and muscle weakness.

In 2000, a new drug was approved to treat mild to moderate AD: rivastigmine. Its methods are not entirely known, but evidence suggests that it increases cholinergic activity through targeting both AChE and BChE: a function that donepezil and galantamine lack. As with donepezil, the side-effects of rivastigmine can be serious: weight loss, vomiting, and in cases of overdose, irregular breathing and heartbeats (Patel et al., 2022).

Before approval to treat AD, Galantine had been used for decades to treat various neurological deficits and diseases. It was shown to bind to cholinergic receptors and inhibit ChE activity. In 2001, after the effects of cholinesterase inhibitors on AD became evident, galatine was put on the market as treatment for Alzheimer's. Unlike its forerunners, the side-effects of galantine tended to be more severe, such as convulsions, confusion, and muscle weakness (Kalola et al., 2022).

Memantine

The N-Methyl-D-aspartate receptor (NMDAR) antagonist, memantine, is currently used for treatment of AD alongside cholinesterase inhibitors. NMDAR plays an important role in memory, but its overactivation has correlations with neuronal cell death. Memantine's low affinity allows it to only block NMDA temporarily and avoid the negative impact on memory seen in long term blockage. Additionally, memantine has a positive effect regarding the amyloid cascade; it increases BDNF levels, synapses, improves cognition, decreases neuroinflammation, BACE-1 blockade, and NMDA receptor inhibition (Folch et al., 2018).

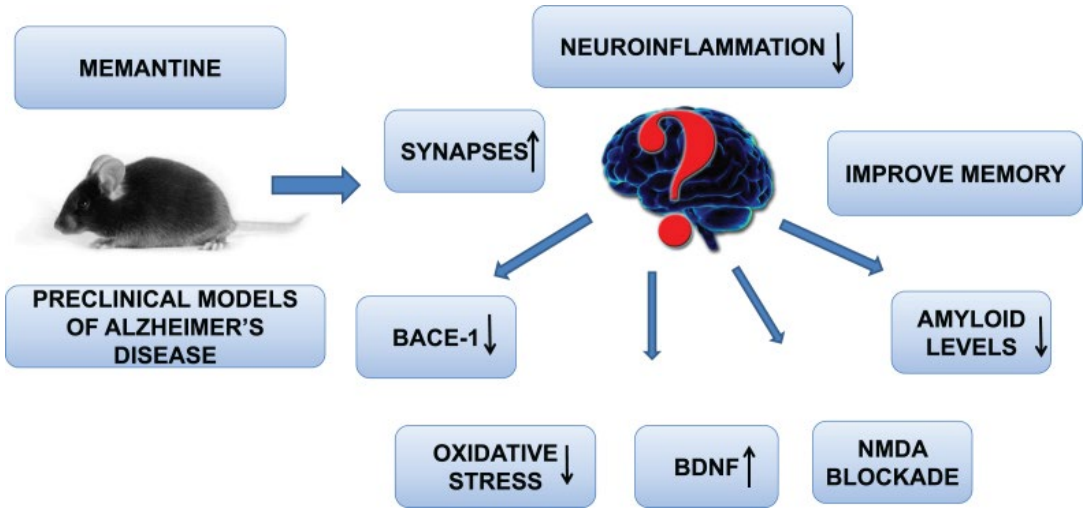

Figure 4. The effects of memantine on the amyloid cascade.

Novel Treatments

Light Therapy (Photo-biomodulation)

In the past, photo-biomodulation has given positive results in treating and preventing various diseases. In aging brains, it can improve cognitive function and serve as an anti-inflammatory agent (Cardoso et al., 2021).

Recent discoveries have proved light therapy to be a promising treatment option for Alzheimer's patients. Gamma oscillations are impaired in individuals with AD, and light therapy has been found to increase gamma oscillations in mouse brains and help restore certain cognitive brain functions. When 5XFAD mice (mice that express variants of the human APP and PSEN1 transgenes) are treated with 40 Hz light stimulation, microglial cell body diameter increased by 135.3%-138.7% and the length of phagocytosis reduced by 54.0%-38.5%. As a result, microglia activity was promoted, causing the overall reduction of Aβ abundance in the brain Light therapy was also performed on other animals with similar biological attributes. They were treated with 100 minutes of 40 Hz visual flicker each day for a week, and the results showed similar microglial responses to those seen in 5XFAD mice and an average reduction in visual cortex plaque levels by around 42% (Cho et al., 2018). This form of therapy has yet to be tested on humans, but the promising results from animal testing demonstrate its potential to restore brain function to deeply progressed Alzheimer's patients.

Aducanumab

Through clinical trials, Aducanumab has been proven to treat mild cognitive impairment or mild dementia associated with AD. The FDA approved Aducanumab in 2021 because the drug showed a significant decrease in the amount of Aβ plaques. However, for the drug to have continued approval for use and full approval, there will need to be further research done to verify its clinical benefits. Because Aβ plaques are located past the blood-brain barrier, Aducanumab has to cross the blood-brain barrier and begin selectively targeting and binding aggregated soluble oligomers and insoluble fibrils conformations of Aβ plaques in the brain. (Padda et al., 2022). Further, it was proven through biochemical and structural engineering that the drug binds to a linear epitope formed by Aβ amino acids. Aducanumab's biology shows great potential to be used in patients with AD, but it is not currently at a stage to be used for treatment.

Gilga-Med

TNF-α inhibitors have shown potential to delay, or even treat, AD, but none had been found to cross the blood-brain barrier (Chang et al., 2017). Recently, however, a new biomedical company has made advancements in this area. Gilga-Med is a company that is changing that game on how to treat age-related diseases. Their research team has discovered over 50 novel compounds that have been shown to delay proteotoxicity in C. elegans. This company's compounds are the first to cross the blood-brain barrier, and they reduce molecules that promote inflammation such as microglial IL-6 and TNF-α (Gilga-Med, 2022).

GM-310 is one auspicious molecule discovered by the team. It is a small molecule compound that penetrates the blood-brain barrier and inhibits neuroinflammation in animal models of AD. It was also found to be highly concentrated in the brain after oral delivery, which is a crucial aspect of drugs looking to treat AD.

The Impact of COVID-19

Since 2020 and the start of the COVID-19 spread in the U.S., there has been a 17% increase in dementia deaths (Lamont et al,. 2021). The cause of this increase is uncertain, but it is possible that it is due to the lack of socialization many faced during quarantine, particularly with at-risk seniors. Socialization stimulates more parts of the brain and deters the formation of dementia, so a lack of socialization can be detrimental to individuals over 65. This hypothesis could possibly explain the correlation between hearing loss and higher dementia rates – less socialization occurs among those who are hard of hearing, increasing the risk of developing dementia. For these reasons, socialization is vital to the health of people over the age of 65, especially those in quarantine.

Conclusion

In this review, we discussed the etiology of Alzheimer's disease, as well as research for current and future treatments. Our knowledge of AD is constantly evolving and leading us closer to discovering ways to treat or prevent the disease. But with its rates rising by the year, finding ways to prevent or reverse the damage of AD is becoming increasingly important. Research at companies like Gilga-Med is essential for us to move forward and make age-related diseases less of a risk to people across the globe.

Acknowledgments

I would like to thank my advisor for the valuable insight provided to me on this topic.

References

American Academy of Neurology. (2007, October 2). Low Education Level Linked To Alzheimer's, Study Shows. ScienceDaily. www.sciencedaily.com/releases/2007/10/071001172855.htm

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

Cardoso, F. dos S., Gonzalez-Lima, F., & Silva, S. G. da. (2021, July 26). Photobiomodulation

for the aging brain. Ageing Research Reviews. Retrieved from https://www.sciencedirect.com/science/article/pii/S1568163721001628

De la Rosa, A., Olaso-Gonzalez, G., Arc-Chagnaud, C., Millan, F., Salvador-Pascual, A., García-Lucerga, C., Blasco-Lafarga, C., Garcia-Dominguez, E., Carretero, A., Correas, A. G., Viña, J., & Gomez-Cabrera, M. C. (2020). Physical exercise in the prevention and treatment of Alzheimer's disease. Journal of sport and health science, 9(5), 394–404. https://doi.org/10.1016/j.jshs.2020.01.004

Folch, J., Busquets, O., Ettcheto, M., Sánchez-López, E., Castro-Torres, R. D., Verdaguer, E., Garcia, M. L., Olloquequi, J., Casadesús, G., Beas-Zarate, C., Pelegri, C., Vilaplana, J., Auladell, C., & Camins, A. (2018). Memantine for the Treatment of Dementia: A Review on its Current and Future Applications. Journal of Alzheimer's disease : JAD, 62(3), 1223–1240. https://doi.org/10.3233/JAD-170672

Garcia-Mantrana, I., Selma-Royo, M., Alcantara, C., & Collado, M. C. (2018). Shifts on Gut Microbiota Associated to Mediterranean Diet Adherence and Specific Dietary Intakes on General Adult Population. Frontiers in microbiology, 9, 890. https://doi.org/10.3389/fmicb.2018.00890

Gilga-Med Inc. Gilga-Med Research and Discovery. (2022). Retrieved from https://www.gilga-med.com/

Gwang Moo Cho, MS, Seo-Yeon Lee, PhD, Jung Hwa Park, MS, Min Jae Kim, MS, Kyoung-Jun Park, PhD, Byung Tae Choi, PhD, Yong-Il Shin, MD, PhD, Nam Gyun Kim, PhD, Hwa Kyoung Shin, PhD, Photobiomodulation Using a Low-Level Light-Emitting Diode Improves Cognitive Dysfunction in the 5XFAD Mouse Model of Alzheimer's Disease, The Journals of Gerontology: Series A, Volume 75, Issue 4, April 2020, Pages 631–639, https://doi.org/10.1093/gerona/gly240

Hickman, S. E., & El Khoury, J. (2014). TREM2 and the neuroimmunology of Alzheimer's disease. Biochemical pharmacology, 88(4), 495–498. https://doi.org/10.1016/j.bcp.2013.11.021

Hickman, S. E., Kingery, N. D., Ohsumi, T. K., Borowsky, M. L., Wang, L. C., Means, T. K., & El Khoury, J. (2013). The microglial sensome revealed by direct RNA sequencing. Nature neuroscience, 16(12), 1896–1905. https://doi.org/10.1038/nn.3554

Iaccarino, H. F., Singer, A. C., Martorell, A. J., Rudenko, A., Gao, F., Gillingham, T. Z., Mathys, H., Seo, J., Kritskiy, O., Abdurrob, F., Adaikkan, C., Canter, R. G., Rueda, R., Brown, E. N., Boyden, E. S., & Tsai, L. H. (2016). Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature, 540(7632), 230–235. https://doi.org/10.1038/nature20587

James, E. M. (n.d.). Tau protein and alzheimer's disease: What's the connection? Tau Protein and Alzheimer's Disease: What's the Connection? | BrightFocus Foundation. https://www.brightfocus.org/alzheimers/article/tau-protein-and-alzheimers-disease-whats-connection

Kalola UK, Nguyen H. Galantamine. [Updated 2022 Jun 26]. In: StatPearls [Internet]. Treasure

Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK574546/

Kumar A, Sidhu J, Goyal A, et al. Alzheimer Disease. [Updated 2022 Jun 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499922/

Lamont, H., Dey, J., & Oliveira, I. (2021, April 7). The impact of covid-19 on Medicare beneficiaries with dementia issue brief. Retrieved from https://aspe.hhs.gov/reports/impact-covid-19-medicare-beneficiaries-dementia-issue-brief

Marseglia, A., Xu, W., Fratiglioni, L., Fabbri, C., Berendsen, A., Bialecka-Debek, A., Jennings, A., Gillings, R., Meunier, N., Caumon, E., Fairweather-Tait, S., Pietruszka, B., De Groot, L., Santoro, A., & Franceschi, C. (2018). Effect of the NU-AGE Diet on Cognitive Functioning in Older Adults: A Randomized Controlled Trial. Frontiers in physiology, 9, 349. https://doi.org/10.3389/fphys.2018.00349

McGrattan, A. M., McGuinness, B., McKinley, M. C., Kee, F., Passmore, P., Woodside, J. V., & McEvoy, C. T. (2019). Diet and Inflammation in Cognitive Ageing and Alzheimer's Disease. Current nutrition reports, 8(2), 53–65. https://doi.org/10.1007/s13668-019-0271-4

Naseri, N. N., Wang, H., Guo, J., Sharma, M., & Luo, W. (2019). The complexity of tau in Alzheimer's disease. Neuroscience letters, 705, 183–194. https://doi.org/10.1016/j.neulet.2019.04.022

Padda IS, Parmar M. Aducanumab. [Updated 2022 Jul 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK573062/

Patel PH, Gupta V. Rivastigmine. [Updated 2022 Jul 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557438/?report=classic

Pérez-Rodríguez, D. R., Blanco-Luquin, I., & Mendioroz, M. (2021). The Participation of Microglia in Neurogenesis: A Review. Brain sciences, 11(5), 658. https://doi.org/10.3390/brainsci11050658

Rice, D. P., Fillit, H. M., Max, W., Knopman, D. S., Lloyd, J. R., & Duttagupta, S. (2001). Prevalence, costs, and treatment of Alzheimer's disease and related dementia: a managed care perspective. The American journal of managed care, 7(8), 809–818.

Silva, M., Loures, C., Alves, L., de Souza, L. C., Borges, K., & Carvalho, M. (2019). Alzheimer's disease: risk factors and potentially protective measures. Journal of biomedical science, 26(1), 33. https://doi.org/10.1186/s12929-019-0524-y

Singh R, Sadiq NM. Cholinesterase Inhibitors. [Updated 2022 Jul 18]. In: StatPearls [Internet].

Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544336/

Spangenberg, E. E., & Green, K. N. (2017). Inflammation in Alzheimer's disease: Lessons learned from microglia-depletion models. Brain, behavior, and immunity, 61, 1–11. https://doi.org/10.1016/j.bbi.2016.07.003

Sterling, J. (2022, June 1). Comorbidities impact biomarker levels to hinder alzheimer's blood test development. GEN. Retrieved from https://www.genengnews.com/topics/translational-medicine/comorbidities-impact-biomarker-levels-to-hinder-alzheimers-blood-test-development/?MailingID=%DEPLOYMENTID%25&utm_medium=newsletter&utm_source=GEN%2BDaily%2BNews%2BHighlights&utm_content=01&utm_campaign=GEN%2BDaily%2BNews%2BHighlights_20220531&oly_enc_id=6899D3347067I6A

Tampellini, D. (1AD, January 1). Synaptic activity and alzheimer's disease: A critical update. Frontiers. https://www.frontiersin.org/articles/10.3389/fnins.2015.00423/full

Tian, T., Qin, X., Wang, Y., Shi, Y., & Yang, X. (2021). 40Hz Light Flicker Promotes Learning and Memory via Long Term Depression in Wild-Type Mice. Journal of Alzheimer's disease : JAD, 84(3), 983–993. https://doi.org/10.3233/JAD-215212

U.S. Department of Health and Human Services. (2018, May 1). Sleep deprivation increases alzheimer's protein. National Institutes of Health. Retrieved from https://www.nih.gov/news-events/nih-research-matters/sleep-deprivation-increases-alzheimers-protein

U.S. Department of Health and Human Services. What are the signs of alzheimer's disease? National Institute on Aging. Retrieved from https://www.nia.nih.gov/health/what-are-signs-alzheimers-disease

Wolfe, C. M., Fitz, N. F., Nam, K. N., Lefterov, I., & Koldamova, R. (2018). The Role of APOE and TREM2 in Alzheimer's Disease-Current Understanding and Perspectives. International journal of molecular sciences, 20(1), 81. https://doi.org/10.3390/ijms20010081