Effects of Alzheimer's on America's Aging Population and a Comparison of Available Treatments

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Research Methods

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Alzheimer's disease is a neurodegenerative disorder defined by Amyloid-beta (Aβ) protein plaques and tau tangles in the brain, followed by a slow degeneration of brain tissue and deteriorating cognitive functions (*National Institute on Aging (NIA), n.d., a)*. Scientists are currently predicting a rapid increase in patients suffering from Alzheimer's disease in the next few decades (*Alzheimer's Association (A.A.), 2021, Jul 7*). Back in 2018, it was estimated that nearly 6 million Americans alone suffered from Alzheimer's disease, but scientists are expecting that the number will rise to 15 million in a few decades (*Winerman, 2018, May*). According to the *A.A. (n.d., a)*, the average age for diagnosis of Alzheimer's disease is 65, and the risk of diagnosis will double every 5 years. Currently, 16% of the American population is 65 and over according to a census in 2020 (*Administration for Community Living (ACL), 2021, May*), and 11.3% of Americans over the age of 65 have been diagnosed with Alzheimer's disease (*Texas Department of State Health Services, 2021, April 13*). The *ACL (2021, May)* is also predicting the percentage of Americans over the age of 65 to rise to 21.6% by 2040. Of those with Alzheimer's disease, 70% choose to live at home (*John Hopkins Medicine, n.d.*).

Moreover, the *A.A. (n.d., b)* reported that of the 83% of unpaid caregivers (including family and friends), almost half provide for patients with Alzheimer's and other dementias. Furthermore, the *Family Caregiver Alliance (n.d.)* announced that in a survey of its members on how many hours they work, more than half reported working 40+ hours a week. Alzheimer's patients in particular cannot be left alone for long, as they require constant supervision after the moderate stage (*Herrmann, 2018, Feb 1*). In addition, 49.6% of all current recorded cases of Alzheimer's in America are at the moderate to severe stages (*NIA, n.d., b*). This coupled with the statistic from *Senior Living (2021, May 27*) that caregivers can cost about $188 a day on average can be burdensome on families of the patient. Alzheimer's is also incurable and fatal

(*NIA, n.d., a*), both through killing the patient itself and through weakening their immune system for other diseases like Pneumonia to take root (*Brenner, et al, 1994*). Before death, patients and caregivers have to suffer through many symptoms that progressively get worse such as; cognitive impairment, confusion, mood swings, and wandering (*Alzheimer's Foundation of America, n.d.; NIA, n.d., a*). Caregivers also experience effects from caring for Alzheimer patients, namely depression (*Levine, 2003*). In a study from 2003 with 5000 participants, more than one-third of the caregivers exhibited high levels of depression, and the exhaustive care of the caregivers and difficulties with the healthcare system may have been to blame (*Levine, 2003*). Because there is no cure, many caregivers can only provide treatment to slow the progression and reduce the symptoms of the disease (*National Health Service, 2021, Jul 5*).

In spite of that, there are a variety of treatments available to Alzheimer's patients ranging from drug to behavioral and cognitive therapy (*American Psychological Association (APA), 2012, Jun 20*). There are currently seven drugs approved by the U.S. Federal Drug Administration (FDA) for Alzheimer's on the market; Aducanumab [Aduhelm], 3 cholinesterase inhibitors (Donepezil [Aricept] Galantamine [Razadyne], and Rivastigmine [Exelon]), Memantine [Namenda], Memantine + Donepezil [Namzaric], and Suvorexant [Belsomra] *(Mayo Clinic, 2019; A.A., n.d., c)*. All of these medications, while somewhat effective, have side effects and will not cure Alzheimer's (*Mayo Clinic, 2019)*. Aducanumab treats Alzheimer's by removing the Aβ in the body, which according to the *A.A. (n.d., c)*, is a well-known sign of Alzheimer's progression among doctors. The cholinesterase inhibitors increase the amount of acetylcholine in your brain, which is an essential neurotransmitter to the brain's activities (*Mayo Clinic, 2019)*. Cholinesterase does not cure Alzheimer's however and has side effects like nausea, vomiting, and diarrhea. Namenda and Namzaric are like the cholinesterase inhibitors,

but they treat moderate to severe dementia while the cholinesterase inhibitors treat mild to moderate *(A.A., n.d., c)*. In addition, they come with a plethora of harmful side effects like headaches, constipation, confusion, and dizziness for both, and vomiting, and a loss of appetite for Namzaric specifically. Belsomra is used to help non-cognitive symptoms like behavioral and psychological ones such as mood swings and insomnia, however, it does not prevent or slow the progression of Alzheimer's. Belsomra also has side effects like the others, such as heightened depression and suicidal thinking *(A.A., n.d., c)*. Research on these drugs shows that symptoms can be moderately slowed down or even improved. However, they only provide moderate relief for memory and behavioral symptoms and do little to nothing for late-stage patients other than slowing it down and providing mild relief *(Alzheimer's Society, 2021)*. This has led scientists to search for other kinds of treatments, which led to the creation of secondary prevention strategies, meant to slow or possibly prevent Alzheimer's.

There have been numerous secondary prevention strategies that appear promising as treatments for Alzheimer's Patients *(APA, 2012)*. One, from the Mayo Clinic, includes physical and cognitive exercises, strategies for counteracting memory loss, lessons on physical and mental wellness, and support groups. This showed an improvement in the long-term stability of patients and their capacity to function in daily life *(APA, 2012)*. The APA puts an importance on physical and cognitive exercise, saying that the exercise improves the mental state of the patient and helps long term. Other sources say this too, particularly about physical exercise *(Winerman, 2005; APA, 2019)*. According to *Winerman (2005)*, the stress exercise puts on your brain helps protect it against the future biomarkers of Alzheimer's like Aβ plaques. This stress acts as a weak poison, slowly building up the brain's tolerance to stress. Obesity and diabetes have also been found to have a strong connection to hurrying the progression of Alzheimer's *(APA, 2011)*.

Because of this, much of the non-chemical treatments in Alzheimer's involve memory tasks and physical exercise. While these physiotherapy treatments do work, as do the chemical treatments, they're still not a cure, and researchers are still searching for one. The most recent kind of treatment to be released is another chemical treatment, Aducanumab, which targets the Aβ in the brain. A new drug for Alzheimer's has not been released since 2003, so Aducanumab finally being released in June of 2021 (*FDA, 2021*) is exciting news. While it does have its side effects and is still very new, it is the most advanced treatment yet *(FDA, 2021)*. One that does not just treat the symptoms, but, according to the U.S. *Federal Drug Administration (2021)*, treats the disease as a whole and intends to reverse its effects on the brain. While Aducanumab is not perfect, continuing down this path seems promising for future Alzheimer's treatments.

To put it another way, Aducanumab is unalike other drug treatments for Alzheimer's because it treats the theorized cause of Alzheimer's disease, Aβ plaques, not just the symptoms (*FDA, 2021*). The approximate cause of Alzheimer's Disease, along with many other neurodegenerative diseases, however, is not known. Even so, the Aβ peptide misfolding and creating Aβ protein particles is believed to be the "hallmark" of Alzheimer's Disease by many according to *Uhlmann, et al (2020)*. Aβ plaques in the brain are believed to be a late-stage consequence of the Aβ protein particles and are also thought to cause the degeneration of the brain tissue, causing cognitive decline. Discovering these Aβ plaques before the disease progresses too far has proven to be difficult among the scientific community, and many have been trying to find ways to discern Aβ progression in the brain at early stages. *Uhlmann, et al* understood this, elaborating on the difficulties of seeing the early stages of Alzheimer's Disease progression in the brain. They briefly mention two ways of measuring Aβ proteins in the body before Aβ plaques (a sign of the later stage progression) show; Cerebral Aβ deposition through

Positron Emission Tomography (PET) scans and a spinal tap to measure Aβ in the cerebrospinal fluid. To *Uhlmann, et al (2020)*, this definitively shows that Alzheimer's Disease begins decades before the more commonly known signs begin to appear. *Uhlmann, et al* hope to discover a way to prevent the accumulation of Aβ plaques altogether. This is a rather difficult task though, as according to *Uhlmann, et al*, Aβ PET scans and cerebrospinal fluid Aβ only show positive when the Aβ degeneration has already started. So instead, they took a different approach by targeting Aβ "seeds". These seeds are, according to *Uhlmann, et al (2020)*, the earliest form of Aβ plaques, and therefore the perfect target. These seeds can be marked by antibodies, allowing a much earlier detection and destruction of Aβ proteins/plaques in the brain, similar to how a vaccine works. When different antibodies were tested on the mice, only aducanumab showed a decrease in the Aβ proteins, with one protein showing a 50% decrease.

To test these results, *Uhlmann, et al* injected mice with the Aβ proteins and had two groups, one as the control group, and the other as the Aducanumab group. The results were the same, with the Aducanumab group showing more than an 80% reduction in brain degeneration when compared to the control group. In pre-amyloid stages, only Aducanumab was effective at decreasing the Aβ seeds. This surprised *Uhlmann, et al* (2020) though, as another treatment, β1 antibodies, was found to block Aβ seeds in late-stage Alzheimer's brains. This suggests that Aβ seed's makeup differs between stages, allowing it to go undetected by Aducanumab and β1 in some stages. The only concern of note that *Uhlmann, et al* mentioned about Aducanumab was that it did not reduce Cerebral amyloid angiopathy(CAA) in the mice. Nevertheless, the progression of Alzheimer's Disease is heavily slowed in the mice treated with Aducanumab. From this, *Uhlmann, et al (2020)* believes it may be possible to prevent, or at least postpone the onset of Alzheimer's Disease, not just slow its progression like other available treatments.

This belief proves true in an experiment done by *Sevigny, et al (2016)*. According to *Sevigny, et al*, there is strong scientific evidence that targeting Aβ seeds could potentially benefit individuals afflicted with Alzheimer's Disease. Scientists believed that human memory B-cells (cells that are a part of the human immune system) could be the answer to targeting Aβ proteins in the body. This eventually led to the creation of a human monoclonal antibody that targets Aβ plaques and seeds *(Sevigny, et al, 2016)*.

This human monoclonal antibody, or aducanumab, and its effectiveness in removing Aβ plaques in patients with mild levels of Alzheimer's Disease was tested by *Sevigny, et al*. The treatment showed a positive result, with aducanumab decreasing the Aβ plaques in the brain, which was measured before and during the study with PET scans. They used a PET standard uptake value ratio to show the progression of Aβ plaques in the brain, with a baseline given in the charts shown in the article. The baseline was 1.44 at the start of the study. When treatment was finished, there was a significant decrease in the baseline for those receiving aducanumab. Those in the 10 mg kg^{-1} dosage group had a dramatic decline, from 1.44 to 1.16, close to the quantitative cut-point for positive or negative Aβ PET scans, 1.10. *Sevigny, et al (2016)* believe this shows a dose-dependent reaction to aducanumab for regression of Aβ plaques within the brain, with the greatest correlation coming from the participants receiving higher doses. A slowing of the disease progression was also observed in the Mini-Mental State Examination, showing best in the participant groups receiving the 3 and 10mg kg^{-1} doses.

However, there were adverse effects in the participant groups receiving aducanumab, specifically amyloid-related imaging abnormalities, along with headaches, and urinary and respiratory infection. Despite this, *Sevigny, et al (2016)* believe it is important to continue to research the beneficial effects of aducanumab on patients with Alzheimer's disease due to its

incredible ability to decrease Aβ plaques in the brain so quickly. From this, *Sevigny, et al* concluded that reducing the Aβ in the brain could provide a possible medical solution for Alzheimer's patients in the future. If further researched, aducanumab could show regression in the disease. However, *Sevigny, et al (2016)* cautions readers that this study is relatively short, only lasting a little more than a year, and further research is required to better interpret the results. They believe larger studies should be done (some of which are already in place) to better confirm the effects of aducanumab shown in this study, and effects that may not be known yet *(Sevigny, et al, 2016)*.

In short, Alzheimer's disease is a neurodegenerative disorder that affects a considerable amount of Americans, both those with and without the disease. Even with the numerous treatments, both chemical and physical, being available to most Americans, it remains incurable. But a promising new treatment, Aducanumab, which directly targets the anticipated cause of Alzheimer's, is now on the market. Though there have been multiple short-term studies on Aducanumab, few long-term studies, a necessity for long-term treatments, exist.

While we do not know whether Aducanumab will become a short-term or long-term treatment yet, it is necessary to study both to find the positives and negatives of using it as either-or. Physiotherapy also works, though maybe not as well as Aducanumab currently, but there could be a future in physiotherapy treatments. Maybe pairing low doses of Aducanumab with current physiotherapy treatments on moderate to severe stage Alzheimer patients could show improvement. A baseline should be taken beforehand, then measured once a year for 5-10 years while the patient goes through a combination of Aducanumab and physiotherapy. Recording their Aβ PET scans or simply doing a cognitive performance test every year to see how the combination affects Aβ plaques would help us to see the brain's progress. There are

high expectations for Alzheimer's treatments in the coming years, and there may be a good chance those expectations will be met.

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