An Analysis of Atypical Alzheimer's Disease Treatment Methods Using Virtue Ethics

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction

Imagine your parent or grandparent gradually started losing their memory and ability to perform everyday tasks. Your helplessness would be palpable, as you'd be forced to watch them lose their sense of self and identity. Alzheimer's disease (AD) is a devastating neurological disorder that does just that. According to the National Institute on Aging (NIA), AD is currently the 7th leading cause of death in the United States (*Alzheimer's Disease Fact Sheet*, 2023). As we age, our risk for developing Alzheimer's rises exponentially. The incidence rate for AD is 14 times higher for people older than 85 than for those aged 65-69 (Hebert et al., 1995, p. 1356). The lifespan of humans has been increasing over the last century. In just America, life expectancy increased from 69.9 years to 78.9 years from 1959 to 2016 (Woolf & Schoomaker, 2019, p. 4). Coupled together, these facts paint a troubling picture regarding the prevalence of AD in our senior citizens. AD is also a bit of a black box- its exact cause is currently unknown, but age, genetics and lifestyle are known to play a role in its development (Breijyeh & Karaman, 2020, p. 6). Symptoms vary with level of disease progression, but they may include difficulty eating, extreme memory loss, and difficulty speaking, among others (Joe & Ringman, 2019, p. 1).

Currently, a cure for AD does not exist. According to the NIA, there are only 7-10 drugs approved by the Food and Drug Administration (FDA) to treat AD, and the efficacy of some of these drugs drops with disease progression (*How Is Alzheimer's Disease Treated?*, 2023). Some non-pharmacological treatments (NPTs) for AD include exercise, cognitive rehabilitation, and psychological therapy (Zucchella et al., 2018, pp. 2-3). My technical project is focused on using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to create temporary holes in the blood-brain barrier (BBB) to allow drugs to enter brain tissue and treat diseases. To be effective, the DREADDs must genetically modify brain endothelial cells. Endothelial cells line the blood vessels of the BBB and control what substances can enter the bloodstream. Currently, DREADDs are only used in an academic context to study patterns of neuronal firing (Roth, 2016, p. 683).

With the standard course of treatment for AD (heavy emphasis on existing pharmaceutical treatment with NPTs as a supporting treatment), Mayo Clinic reports that the current prognosis for a patient diagnosed with AD is 3 to 11 years (*Alzheimer's Stages*, 2023). By not addressing alternate AD treatment methods, this prognosis stagnates. As a result, millions of families and AD patients continue to suffer the repercussions of this devastating disease.

The ethical considerations of treating AD with both NPT and the treatment proposed in my technical project have not been fully researched and weighed out. Understanding the ethics of both treatment options could provide both patients and loved ones with valuable information that might influence their ultimate choice of treatment. NPT is generally viewed as an acceptable, if accompanying, treatment for AD. However, the amount of benefit provided by this therapy is not clearly established by research (Wang et al., 2020, p. 9). As such, it is important to weigh out the benefits and drawbacks of this therapeutic approach. The treatment proposed in my capstone team's technical project utilizes genetic modification, which, although not germline editing, still gives many people pause.

In this paper, I analyze the ethical considerations of NPT and my capstone project for AD treatment. These ethical considerations will be examined through the framework of virtue ethics. I argue that analyzing these ethical considerations through virtue ethics provides a comprehensive and context-inclusive framework for AD patients and families to decide on an optimal treatment route.

Background

The most well-developed non-pharmaceutical treatment (NPT) in Alzheimer's disease (AD) symptom management is cognitive stimulation therapy (CST). The purpose of CST is to activate and engage multiple cognitive functions (attention, memory, etc.) (Zucchella et al., 2018, p. 4). A study published in the *Expert Review of Neurotherapeutics* found that participant-rated quality of life (QoL) improved for AD patients who underwent CST when compared to the control group (Spector et al., 2008, p. 756). Another cognitive-based approach is called reality orientation training. This form of training involves repeatedly presenting basic information to a patient (time, location, etc.) with the goal of improving a person's understanding of their environment (Chiu et al., 2018, p. 21).

Exercise has also been found to not only minimize risk of developing AD, but also potentially help rescue some level of cognitive function lost because of AD. A study found that irisin, a hormone released during exercise, regulates the cognitive benefits conferred by exercise (Islam et al., 2021, p. 1058). Another study conducted looked at the combined effects of physical and cognitive training on patients with mild cognitive decline (a familiar precursor to AD) and found that compared to the experimental group, patients who did not undergo the training regimen for 7 months experienced a significant decline in cognitive status (Maffei et al., 2017, pp. 6-9).

Improvements in QoL would lead to an improvement in another important consideration, caregiver burden. Caregivers are often family members, and research has shown that around one-third of this population struggles to balance their health with that of the patient, even skipping their own medical appointments to care for the patient (*The Hidden Reasons Why Alzheimer's Caregivers Are So Stressed*, 2018). A systematic review and meta-analysis found that for patients with dementia, 3 different NPTs led to a reduction in caregiver burden (Sun et al., 2022, p. 6).

While studies have shown benefits of NPT, there is not enough high-quality research (peer reviewed, backed by other studies) to definitively state that NPTs effectively help AD patients in not only improving QoL but also mood and independence (Wang et al., 2020, p. 9). For example, one potentially detrimental side effect of reality orientation training is a drop in self-esteem accompanied by frustration at not being able to complete a basic task repeatedly (Zanetti et al., 1995, p. 136).

A technical benefit conferred by NPTs is the cost compared to standard treatments. A study looking at four different NPTs for dementia found that patients saved between $2,800-13,000, reduced nursing home admissions and improved QoL (as compared to pharmaceutical treatments) (Jutkowitz et al., 2023, pp. 6-7). As almost three-quarters of dementia cases are caused by AD, it stands to reason that the treatments utilized in the study would be similarly effective for AD patients (Briggs et al., 2016, p. 247).

I will now explore the same considerations (QoL, caregiver burden, and cost) in the context of DREADDs. The blood-brain barrier (BBB) is a complex network of blood vessels that surrounds and protects the brain from foreign pathogens. While it serves its purpose well, it also limits the entrance of many therapeutics to the brain. To bypass this, my capstone group hopes to utilize DREADDs to create temporary pores in the BBB to allow drugs to enter brain tissue.

If this therapeutic platform were to succeed, it would increase the likelihood for preexisting drugs (that are not currently able to bypass the BBB) to be reconsidered as treatment for not just AD, but a variety of neurological disorders, a process known as drug repurposing. Drug repurposing takes an average of 3-12 years and typically costs up to $300 million, while developing a drug from scratch takes 10-15 years and can cost up to $2.5 billion (Parisi et al., 2020, p. 1043).

There are currently no similar therapeutic platforms to the one suggested in this paper, so it is not possible to examine ramifications of the therapy in a manner similar to NPTs. However, other therapies based on genetic modifications exist. As an aside, there are distinctions between different forms of genetic engineering/modification, but this paper exclusively refers to genetic modifications made to deoxyribonucleic acid (DNA) in a laboratory setting (*Genetic Engineering*, 2024).

An example of such a therapy is adoptive T cell therapy (most used in blood cancer treatment). A proven side effect of this therapy is an overactive immune response, which can segue into a potentially fatal inflammatory immune response (Imbach et al., 2018). Another hurdle to overcome with this therapy is the prohibitive cost - each infusion dose (of T cells) currently runs between $373,000-475,000 (Choi et al., 2022, pp. 296-297). It is reasonable to infer that an inflammatory immune response and a high price tag are issues that could accompany the BBB-opening platform proposed in this paper.

An ethical consideration that is only pertinent to my capstone project's therapeutic platform (and not NPTs) relies on the idea that there is an inherent value in being human, and we have a duty to preserve this value (Roache & Clarke, 2009, pp. 1-2). This school of thought is known as bioconservatism, and it posits that biotechnology should not be used to enhance humans in any manner. Bioconservatives argue that there is a propensity for human enhancement/modification through technology to backfire, as a result of either an irreversible change or simply because humans possess limitations that cannot be overcome (Browne & Clarke, 2019, pp. 246-248). The overall public opinion towards genetic modification of any sort is hesitation- this can be clearly seen through how genetically modified foods for human consumption are distrusted. According to a 20-public global survey conducted by the Pew Research Center between 2019 and 2020 of adults 18 and older, 48% of people are distrustful of genetically modified foods (Kennedy & Thigpen, 2020). However, there are many who view it their ethical responsibility to conduct research on genetic modification for human health. In late 2019, the National Institute of Health (NIH) awarded $89 million in funding to researchers in the United States and Canada to support genome editing research (*NIH Awards $89 Million for Additional Projects to Advance Genome Editing | National Center for Advancing Translational Sciences*, 2019). A grant providing such a large sum of money clearly illustrates that there are many proponents for genetic modification for the betterment of human health. This paper will look at genetic modification through virtue ethics, assessing whether the benefits outweigh the costs (or vice versa).

Individuals with AD and related dementias experience a significant loss of autonomy, putting them at high risk of losing their sense of dignity. A meta-analysis found that AD patients felt embarrassed, a lack of freedom, and powerless, all of which eroded their sense of dignity (Torossian, 2021, pp. 2906-2910). Both NPTs and DREADDs as treatment methods have the potential to impact the level of autonomy afforded to AD patients and, by extension, their sense of dignity.

Methods

In the section that follows, I will describe deontology and utilitarianism in the broad field of healthcare and briefly go over their shortcomings in this specific application. I will then follow up with a description of virtue ethics, and how it is able to compensate for the other theories' limitations in the context of healthcare.

Deontology is an ethical framework where our actions are bound by a set of moral laws, or duties. The morality of an action is dependent solely on the nature of the action itself- regardless of potential consequences (Gaus, 2001, p. 28). This framework is prevalent in the field of healthcare. A physician has a duty to uphold their patient's right to privacy, even if there may be consequences that might harm the patient's family - the consequences are not relevant. A physician is also obligated to do no harm to the patient. It is seen as the physician's duty to minimize harm to their patient, even if they may benefit from it in the long-term or it may benefit a larger group of people. As such, duty towards patients (and by extension, deontology) plays a large role in the doctor-patient relationship. Applying this framework as a physician places undue emphasis on the individual, irrespective of the consequences to society (Mandal et al., 2016, p. 6).

Utilitarianism lies on the opposite end of the spectrum as deontology. This framework determines the morality of an action based solely on the consequences of that action. The nature of the action itself is of no importance- all that matters is that more people benefit than suffer in the end (Stuart Mill, 1863, p. 16). Utilitarianism is very present in healthcare, especially in times of crisis. A relevant example is the COVID-19 pandemic. For example, in April of 2020, 38 states and Washington, D.C. issued state-wide mask mandates to minimize transmittance of the virus (Huang et al., 2022, p. 446). Many US citizens felt their autonomy (one of the core principles of deontology) was being stripped away with the mask mandate. The principles of utilitarianism were clearly applied in this scenario, in that greater emphasis was placed on society than on the needs of the individual. For a physician, this framework has the opposite effect as deontology- the emphasis is solely on society/maximizing the greater good, regardless of the consequences to individuals (Mandal et al., 2016, p. 5).

Virtue ethics, unlike the previous action-based theories, is character-based. It argues that to be ethical, there are specific moral traits humans should cultivate in their lives (Vallor, 2021, p. 78). However, these moral traits are not absolute, even in the face of duty (an important distinction from deontology). For example, courage, a virtuous trait, should generally be embodied by an ethical person, even when there is a risk for embarrassment as a result. However, virtue ethics dictates that this trait doesn't need to be exhibited in severe scenarios. A non-healthcare example of the limits of virtue ethics (in this case, referencing courage) includes attempting to retrieve a hat out of courage in the middle of a tornado (Darwall, 2005, p. 589). In the context of healthcare, virtue ethics shows how a healthcare provider's moral character can allow them to best serve their patients and community (Kotzee et al., 2017, p. 17). Edmund Pellegrino, a prominent bioethicist with a clinical background, theorized that virtue is a necessity in medical ethics (Pellegrino & Thomasma, 1993, p. xii).

One specific and more uncommon virtue is *observantia*, the virtue of acknowledging human dignity, which was coined by Thomas Aquinas (Jones, 2015, p. 87). This is especially relevant in healthcare, where people are often at their most vulnerable. The way a patient is cared for can preserve, or very easily damage their sense of dignity and subsequently, impact their recovery (Ekpenyong, et al., 2021, pp. 518-519).

Proponents of virtue ethics' application in medicine generally base their argument on three reasons. One, that action-based theories like deontology and utilitarianism are too abstract and vague to apply in medicine (Pellegrino & Thomasma, 1993, p. 19). Context is necessary to apply these rules in a practical manner. Two, that rules resulting from these action-based theories only put forward the minimum standard and, unlike virtue ethics, are not 'excellence-oriented' (Barilan & Brusa, 2013, p. 5). Lastly, the values that virtue ethics promotes are in line with clinical judgement, a skill that takes a patient's goals of care and ethical considerations into account (Kienle & Kiene, 2011, p. 621; Kotzee et al., 2017, pp. 2-3).

Analysis

In this section, I will synthesize the information listed above to conclude that in the context of NPTs and other nonstandard treatments for AD (like that of my capstone project), virtue ethics is an ideal ethical framework to use for analysis.

The first ethical consideration we will view through virtue ethics is impact on quality of life (QoL) and subsequent effect on caregiver burden. As stated previously, the lack of robust research on NPTs and the novelty of DREADDs as a therapeutic platform mean their effects, good or bad, have not been fleshed out. Both the use of DREADDs and NPTs have the potential to improve quality of life and ameliorate caregiver burden. The virtue of compassion for both the patient and caregiver indicates that these are favorable outcomes. However, I also reviewed the potential for off-target effects with NPT use (e.g. frustration and drop in self-esteem due to reality-oriented training) and with DREADDs (unintended immune response). Side effects of these off-target effects could include a drop in QoL and increase in caregiver burden, neither of which extend compassion to the patient or caregiver. Virtue ethics is an ideal framework to use in this scenario because it can cater to the circumstances of the patient and their family. Clinical judgement, which meshes well with virtue ethics, should be exercised.

As an example, if a caregiver has a patient with advanced Alzheimer's who has lost basic cognitive function, and they suggest NPT for their patient, a physician practicing virtue ethics would exercise their clinical judgement in reaching a decision. If the loss of cognitive function is severe enough, recommending a regimen of NPT would not be a compassionate decision, as it would put the patient at risk of becoming severely frustrated with their limited abilities, lowering their QoL, and increasing the burden on their caregiver. If another patient is presenting with much milder symptoms, it might be a better idea to recommend NPT for this patient. In this scenario, the potential for benefit to both the patient and caregiver outweighs the potential cost.

Another consideration for these treatments is price. NPTs have been shown to lower healthcare costs, while DREADDs could lower research costs by allowing existing drugs to be repurposed for AD treatment. A reduction in cost increases access to these treatments, promoting the virtue of fairness. The reduction of treatment costs also moves away from the belief that healthcare is a commodity, and towards its treatment as a basic human right. Virtue ethics clearly supports this shift; Edmund Pellegrino argued that healthcare is not a commodity and treating it as such is a violation of the ethics of patient care (Pellegrino, 1999, pp. 244-251). However, due to the personalized treatment of DREADDs, the cost for individual patients might be prohibitive. Here, the value of using virtue ethics is apparent. While a prohibitive price tag for treatment is by no means ideal, virtue ethics does not require the immediate dismissal of DREADDs solely because it isn't completely accessible. If any treatment option were to be banned if its distribution couldn't be equitable, insulin (as an example) would not be produced anymore due to its potentially prohibitive cost for those without insurance (8.4% of Americans in 2022, according to the National Health Interview Survey) (Cohen, 2022, p. 1). In situations like this, the virtue of prudence can be very valuable. Applying reason and good judgement to this situation makes it clear that while the high price tag of DREADDs shouldn't be brushed aside, it shouldn't impede the treatment option from being offered.

A large ethical concern specific to DREADDs is the use of genetic engineering. Because there is not much research that explores non-germline genetic engineering through a virtue ethics framework, this paper will consider a broader type of genetic engineering than specifically used in my capstone project. Virtue ethics approaches genetic engineering from a different perspective than bioconservatives. Celia Deane-Drummond, a theologian at the University of Oxford, hypothesized that if the four cardinal virtues of prudence, justice, fortitude and temperance are taken into account, genetic engineering is not inherently morally wrong (Deane-Drummond, 2003, p. 225). However, it is important to acknowledge/consider as best as possible the unintended consequences different forms of genetic engineering may engender in people/objects outside of the direct scope of the genetic manipulation. An example of such a form of genetic modification is human germline genome editing. The DNA that is passed onto future generations is manipulated, raising a litany of questions surrounding informed consent. It can be argued through virtue ethics that this is a violation of justice. My capstone project utilizes non-germline genetic engineering, where there is no risk for other people to be directly affected. If the patient does not object on religious or other duty-based grounds, using DREADDs is not unjust or morally reprehensible.

If a physician practicing virtue ethics were considering whether DREADDs and/or NPTs were a viable treatment option for an AD patient, they would likely take their respect for human dignity, or *observantia*, into account before making a decision. If DREADDs were to improve the bioavailability (and thus, increase efficacy) of a drug, there is a chance that a patient would be able to maintain some level of autonomy in their daily life. This argument rings especially true for the usage of NPTs. These treatment methods, many of which healthy people perform in their day-to-day lives, have the potential to increase a patient's autonomy and maintain/restore their sense of self. Performing these seemingly mundane tasks could restore a sense of dignity back to the patient. If a virtuous physician carries esteem for their patients and acknowledges their dignity, they will view both treatment options as being strongly in line with virtue ethics.

The above section highlights how virtue ethics approaches these alternate treatment methods. I believe virtue ethics is an open-minded way to appraise both options, providing a wide range of options depending on the context of the situation.

Conclusion

This paper analyzed non-standard treatments for Alzheimer's disease (AD), including nonpharmaceutical treatments (NPTs) and the use of designer receptors exclusively activated by designer drugs (DREADDs) as a therapeutic platform. Considerations discussed in this paper included how these treatment options would affect patient quality of life (QoL), caregiver burden, potential off-target effects, ease of access (due to cost), and patient dignity/sense of self. These considerations were viewed through the lens of virtue ethics. Utilitarianism and deontology are the two most prevalent frameworks in healthcare (Tseng & Wang, 2021, p. 2). I briefly defined these in the context of healthcare and explained why I thought they were not comprehensive enough to be used ubiquitously. A deeper analysis of these two frameworks in healthcare (and in the context of AD treatment) is beyond the scope of this paper. I delved deeper into virtue ethics and why I believe it is a thorough and flexible framework that can be used in the field of healthcare. The next section synthesized information I previously presented to explain why virtue ethics should be used in the context of deciding on non-standard treatments for AD. Prudence and compassion rise to the forefront in regard to virtues that should be considered when deciding on a treatment plan for someone with AD. Aristotle, one of the forefathers of virtue ethics, declared practical wisdom to be one of the central virtues. Practical wisdom is the ability to make decisions regarding practical, daily issues in peoples' lives (Caniglia et al., 2023, p. 493). I omitted practical wisdom from this discussion of virtue ethics, but it is a rich topic that could be the basis of another paper delving deeper into virtue ethics in AD treatment.

Criticisms of virtue ethics often center around it being a character-based theory rather than action-based, claim it does not have a basis upon which to state justified moral beliefs, and by extension, cannot be codified (Timmons, 2020, p. 256). While this paper did not address these arguments directly, doing so in a future paper could be valuable.

Through this paper, I have argued that virtue ethics is an exceptional ethical framework for analyzing the consequences of non-standard therapies for Alzheimer's, including NPTs and DREADDs.

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