How Has the Safety and Efficacy of Donepezil and Aducanumab Impacted Alzheimer's Disease and Progressed in The Last Century?

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Humans have experimented with neuromedicine for hundreds of years. Early civilizations relied primarily on natural remedies and stimulants. In recent decades, the neuromedical research landscape has exploded with novel treatments from pharmaceuticals to diagnostic techniques. The improvement of neuromedicine from ancient times to now has altered the landscape of medicine altogether. It will focus on two major drugs to alleviate Alzheimer's being primarily Donepezil and Aducanumab. The paper will cover how these drugs operate and effectively work to eradicate or assist in combatting Alzheimer's. The efficacy rates of treatments such as Donepezil and Aducanumab will also go into the study in this paper. The safety of these drugs as well as the side effects will be taken into account and provided from research. By the end of this paper, the reader will develop the historical build-up of the neuromedical field while summarizing the current investigational landscape to project where the field is heading.

Introduction

The brain is an essential organ that has allured society for centuries from the time of the ancient Egyptians to modern society[1]. From studying the brain at a functional and superficial level to studying the intricate neural networks of the brain, neuroscience has changed quickly over time, especially in the last century during an age of discovery and innovation. Compared to other medical fields of study, neuroscience is tremendously new with fields such as cardiology being traced back to the "early 1800s"[2]. However, advancements in the medical field have increased

the life expectancy of humans from "less than 40" in the 19th century to an average of 80 in the modern day[3]. In fact, the life expectancy from the year 2000 itself has gone up by more than 6 years per the average person[4]. Currently, in the United States the life expectancy is reaching 80, however, the life expectancy is projected to reach "mid-80s later in this century"[5]. This represents the competence of modern medicine in society. While these medical advancements have contributed to extended lifespans, greater longevity has likewise carried an increased incidence of illnesses, including neurological diseases such as Alzheimer's. To combat this neuromedicine was created after long periods of testing and experiments. In this research paper, the progression of the efficacy and safety of Aducanumab as well as Donepezil will be examined against Alzheimer's.

History of Neuromedical Drugs

While neuromedical drugs have just recently begun to be in use, treatments to assist neurological conditions date back to ancient civilizations and help combat the neurological diseases present in the status quo. Starting as far back as ancient civilizations, medicine, especially in neuroscience has evolved rapidly. Interestingly, findings from ancient civilizations are still used today to inform modern neuromedicine and neurologist practices. One of these practices is Trepanation where a hole used to be drilled through one's head to alleviate pressure or assist with one's head trauma, often done "with a stone tool"[6]. This practice is still used today for examinations and to access the brain for certain surgeries.

Ancient Solutions to Neurological Disease

In the past, civilizations had many treatments for illnesses in the brain. Although the technology was not nearly as advanced as it is now, people still made efficient cures. Circa 5000 B.C. Ancient Indians used the "Ayurveda text" which is a book filled with various types of medical diseases[7]. The practices of Ayurveda are ancient and have been recorded since the 2nd Century B.C.E.[8] These include "Apasmara (Epilepsy), Kampavata (Parkinson's Disease), and Shiroruk (Headache)". 7 This book allowed many learned Indian scholars to perform various surgeries that had surprisingly high rates of efficacy, curing many patients. Ancient Indians also utilized "herbal medicine" or remedial medicine which would benefit many people[7]. While ancient Egyptians did not have explicit protocols, there is clear evidence of experimentation to better understand the brain[1]. For example, archeologists discovered evidence of biopsies as well as references to common neuromedical phrases including the "skull, brain, vertebrae, spinal fluid, and meninges"[9]. Evidence shows that Ancient Egyptians made research on the nervous system, most likely signifying an attempt for remedial medicine

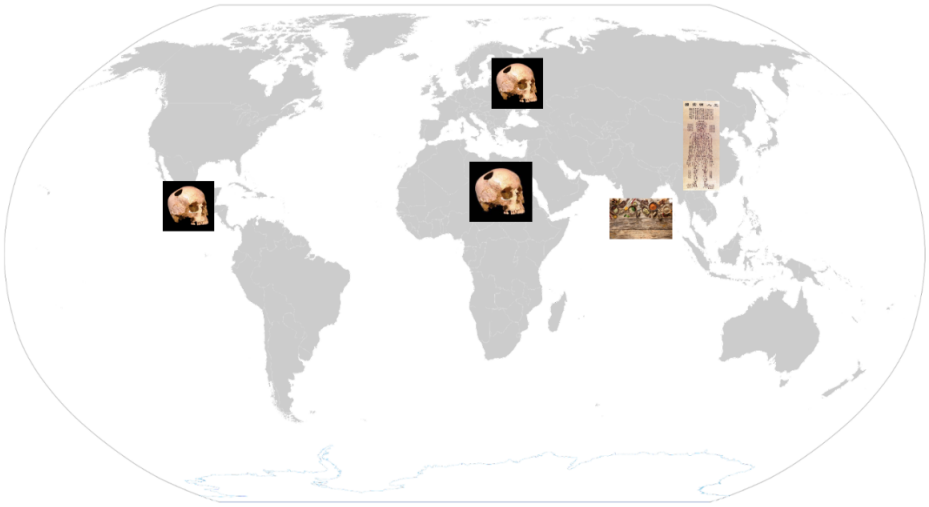

Fig. 1 The figure illustrates notable neuromedical practices used in different areas of the world by ancient civilizations. Techniques include herbal medicine, acupuncture, and Trepanation.

or treatment protocols to cure people of their disorders [1]. Similar to this, throughout history remedial and native medicine was practiced in various areas of the world.

The History of Modern Neuromedicine

Moving forward, modern neuromedicine has grown with the traditional medicine of the ancient world and has built upon the basis of traditional medicine. Modern neuromedicine emerged "in the late 1950s and early 1960s" and had begun its rapid acceleration as a prominent field of medicine [10]. While true neuromedicine was not knowingly founded until the 1950s, neuromedical treatments have existed since the 19th century [11]. Morphine was "the first modern, pharmaceutical medicine [which] was invented in 1804 by Friedrich Sertürner, a German scientist" [11]. Morphine eases pain by disrupting the connection between nerve cells and the pain receptors, ultimately blocking the transmission of pain signals to the brain. The finding of Morphine as well as future medicine was inspired by herbal medicine such as that used by ancient Indians and was practiced with the help of findings by processes such as Trepanation.

When Morphine was first implemented globally, it was found to contain many "traditional products" used in cultural medicines [12]. This revolutionized the medical field far more than imagined, benefitting thousands of people throughout the world.

The Efficacy of Neuromedical Drugs

As time progressed, the advent of medicine grew rapidly. Various types of medicine were distributed by healthcare systems to combat various diseases that globally affect people. Specifically, one neurological disease that massively affects millions of people called Alzheimer's causes memory loss, cognitive decline, and behavioral changes in a person's brain. This neurological disorder is the "sixth leading cause of death in the United States" [13].

Efficacy of Donepezil

As a result, a particular drug that is commonly used to combat Alzheimer's is Donepezil. This medical drug was approved for prescription use in the US in 1996 by the FDA. It has been used by millions of patients with Alzheimer's and multiple experiments have been tested to show its safety and efficacy as a medical drug. Donepezil is shown to be substantially better than placebos which are given drugs that contain no real effect on humans, however, allows for comparative data against the authentic drug to provide results. Donepezil itself, after being tested was shown to tremendously improve "cognitive functions" in patients' minds [14]. Through clinical trials of patients who experimented with Donepezil, neurologists found a significant amount of "less deterioration [or] improvement" in cognition [15]. This development or improvement in cognition is mostly a "short to medium term" benefit for patients experimented under clinical trials [15]. Long-term effects of Donepezil on Alzheimer's Disease are shown to improve cognition and other outcomes; however, it does not make a major impact on the overall function of an organism with the disease. This can be seen in an experiment conducted with 565 people who had Alzheimer's [16]. Some of the people were given placebos and some were given 5 mg and 10 mg doses of Donepezil. After a long-term period of 12 weeks, all subjects were made to take an MMSE (mini-mental state examination) and a BADLS (Bristol Activities of Daily

Living Scale) which is a questionnaire that tests the progress of someone with dementia to complete daily activities which tests daily functional skills[16]. The results showed 0.8 MMSE points higher with Donepezil and 1.0 points higher on the BDSL[16]. Although there is improvement through the use of Donepezil, in the long-term the drug has no explicit benefit in daily function.

Efficacy of Aducanumab

To add on, another neuromedical drug for Alzheimer's is Aducanumab. "On 7 June 2021, the US FDA approved aducanumab" as a neuromedical drug to treat Alzheimer's[18]. Aducanumab works by denaturing β-amyloid proteins or breaking them into specific amino acids for future protein building[19]. Studies have demonstrated that B-amyloid proteins have been linked to Alzheimer's disease. Aducanumab had been shown to have a "modest impact on the cognitive decline" of patients experimented on while the drug was being tested[19]. Although this was very recent and people hoped for the drug to work, it generated much controversy. After being released by the FDA and due to controversy over its efficacy, more experiments were run by many recognized universities and medical labs. One specific experiment examined the cerebellum of patients with Alzheimer's. The patients were administered a high dose of Aducanumab and scientists waited 78 weeks. The "week 78 cerebellum SUVR (standardized uptake value ratio) change and week 78 CDR-SB change was quite small" and lacked credibility with efficacy rates[12].

CDR-SB is the Clinical Dementia Rating Scale Sum of Boxes which measures the severity of one's dementia such as in this experiment where the decrease in severity was very little with Aducanumab. Another experiment testing the MCID or the consensus of benefits from patients themselves has yielded "no consensus"[19]. More suspicions were raised about the effectiveness of Aducanumab. Another experiment showed a population of mice who received Aducanumab and another population who received a placebo. The results showed that there was a "48% reduction in the number of Aβ plaques, while control mice showed a 14% reduction in Aβ plaques".

Although this shows promising results. After more experiments were conducted the results were much more contrary[14]. "Inconsistent results" have resulted in more doubt about the drug's usefulness and whether consumer spending is being exploited by doctors and trained personnel similar to patients' doubts about placebos as prescription drugs. 19 Many patients not only had inconsistent results but also had "amyloid-related imaging abnormalities" or ARIA, which means that the patients had abnormal differences when their brains were scanned by MRIs or sonar[19].

ARIA is a term to explain a "spectrum of image related abnormalities" and is specifically used in neurological case studies to assess the difference of a population of brains from another[20]. ARIA is a known side effect within many people for not only Aducanumab but many other neurological diseases which are detected by MRI scanning. From an experiment detailing the symptoms of participants with ARIA yielded that complications of the imaging abnormality are "headache, confusion, and visual disturbance"[20]. The causes for these unknown and undiscovered abnormalities raise a very serious safety concern associated with Aducanumab which resulted in major distrust of the drug itself in many states and countries that used it as treatment.

The Molecular Science of Alzheimer's

Apart from their efficiencies against Alzheimer's, to truly understand both drugs, it is necessary to delve into the molecular studies of the disease itself. Scientists have been studying molecular science for a long time through specific technology that allows them to experiment and view cellular processes that occur inside the body. The molecular science of neuromedicine is very complicated due to its difficulty in targeting a disease in the brain. The brain is a sensitive organ, that if tampered with can cause dramatic effects which is why neuromedicine is tested extensively before being approved for a broad prescription.

The Effects of Donepezil on Alzheimer's

Furthermore, to understand how Alzheimer's is combatted it is necessary to understand the impacts of drugs on the disease. Specifically, Donepezil improves cognition and memory loss in the brain. Acetylcholine is a compound that relays information from one neuron to another through synapses. "Acetylcholinesterase" is an enzyme that breaks down or "hydrolyzes acetylcholine (ACh), a naturally occurring neurotransmitter" into acids[21]. Acetylcholine degradation continues throughout time by Acetylcholinesterase. However, as time progresses, acetylcholine levels reduce a process that is driven further by acetylcholinesterase. Donepezil is an inhibitor of acetylcholinesterase and acts as both a "competitive and noncompetitive" inhibitor where it changes the function of the enzyme as well as competes against a substrate[21]. A competitive inhibitor competes for the space of a substrate in an enzyme, thus delaying or completely preventing the function of the enzyme until it is removed[22]. A noncompetitive inhibitor is an inhibitor of an enzyme that binds to another site of the enzyme called the allosteric site which in turn decreases enzyme function efficacy[23]. This makes reactions less efficient, which in this case is breaking down acetylcholine. This way of attacking the enzyme is very efficient, providing efficacy rates of cognition improvement through multiple clinical trials and experiments.

	Short-Term Improvements	Long-Term Improvements	Implications
Global	Substantial	Visible Improvements	Donepezil has great accuracy with global outcomes shor term improvements.
Cognition	Substantial	Visible Improvements	Donepezil has great accuracy with cognition outcomes shor term improvements.
Function	Little	Little to None	Donepezil has little accuracy at improving daily functions of the patients.
Behavior Mood	Little	Little to None	Little accuracy in benefiting the behaviour.

Table 1 Results of clinical trials on the short vs long-term effects of Donepezil on patients through different variables [17].

Aducanumab's Molecular Effect on Alzheimer's

In contrast, Aducanumab's molecular effect on Alzheimer's disease is much different from that of Donepezil. Historically, neurological-funded research in genealogy was conducted which led to the "discover[y] in 1987" of the Alzheimer gene [24]. Through this research, there was a strong positive correlation between beta-amyloid proteins and people having the neurological disease. Usually, these proteins help with neuronal growth and repair, however, "a corrupted form can destroy nerve cells" [25]. Pathogenesis or disease development studies showed that "the protein [accumulated] in clumps" in the brains of people with Alzheimer's disease [26]. These clumps were found to come together and form Amyloid plaques which create tangles inside the neurons. The tangles speculatively interrupt cellular processes within the neurons such as communication, the firing of neurons, or the connection of these neurons across synaptic membranes that are the spaces between two neurons which allow them to efficiently transport information. Eventually, the neurons die from the plaques which consist of beta-amyloid protein causing Alzheimer's.

However, Aducanumab breaks these Amyloid proteins and targets them for removal from the brain system. Through this removal of damaged and ineffective proteins, neuronal pathways can be conducted and completed efficiently resulting in a recovery of memory, cognitive function, and areas responsible for reasoning in the brain.

Safety of Neuromedicine

Despite molecular works and constant testing of neuromedicine, safety has shown to be a significant problem as a whole. While some diseases may be cured through neuromedicine, there could be side effects that have not been revealed in clinical trials, but instead several years later, after FDA approval.

A View of the safety of Donepezil

To continue, Donepezil has been studied intensely by neurologists and examined very closely by pharmaceutical companies. The results of Donepezil against placebos are mostly in favor of the drug over various placebos. In a "12-24 week treatment" from a clinical trial, drop-out rates ranged only from "0% to 8.4%" with Donepezil. 18 However, many side effects with this drug have been recorded which did not appeal to many patients that have Alzheimer's disease. Common side effects noted from a "72-month observational study" with people of Chinese descent were "nausea, vomiting, loss of appetite, insomnia, and mild muscle cramps" [27]. The symptoms in all patients were not immediate and had no sudden effect on the patients. Of the participants who had negative side effects, the symptoms were recurring within the population being those listed above. In some cases, side effects may develop into incredibly intense or sensitive problems that cause the participants to stop from continuing with the experiment. In the study above, "only nine out of 273 patients withdrew from Donepezil treatment because of side effects [which include] gastrointestinal problems, drowsiness, and insomnia" [27]. Donepezil, thus benefits the majority of the population opposing the minority where the side effects outweigh the medicine. Through this experiment, it is reasonable to conclude that Donepezil is efficacious in the short to medium term and statistically benefits cognition and memory more than other placebos.

Safety of Aducanumab

Comparatively, Aducanumab is a more recent FDA-approved drug that has raised safety concerns in patients. Via extensive clinical trials, Aducanumab has been shown to "substantially increase the incidence of amyloid-related imaging abnormalities (ARIA) with brain effusion or hemorrhage" in patients [28]. Most doctors prescribe the highest dose of Aducanumab to achieve the maximum efficacy in cognitive improvement. This is because Aducanumab attacks B-amyloid proteins, though recent studies have shown that "up to 40% of patients diagnosed with early AD do not have amyloid pathology when studied with amyloid imaging" [28]. This proves that Aducanumab needs to have certain criteria which is having a large presence of B-Amyloid proteins to even be registered as efficacious in improving the cognition and memory of a majority of patients, which renders Aducanumab as inefficient.

Current Understanding of Alzheimer's

Although scientists and researchers actively work to create safe and improved medicine for Alzheimer's our current understanding of the disease is limited. Many researchers have tried finding correlations with "beta-amyloid and tau proteins" however a lot of them have come with non-conclusive findings to its upcoming

and prevention[29]. Especially, in the brain which is an extremely complex organ, research is difficult to conduct and find correlation and conclusive evidence, thus preventing much scientific discovery. In addition, many complexities occur during times of research. Examples of this include ethnic issues that arise such as cultural normalities and practices that interfere with studies of patients who have AD. Ethical questions also arise as to whether the research done on patients with Alzheimer's is safe for the patient. Complications such as these arise and limit the study possible on AD and other neurological diseases. Despite these complications, researchers and neurologists are still making breakthrough discoveries such as more effective neuromedicine for treating AD.

Conclusion

Neuroscience has been experimented with and practiced informally for thousands of years. Through experimentation, people in ancient civilizations began to learn about neuroscience and develop their understanding of the brain. In ancient times processes such as Trepanation and Ayurveda text were used to heal the brain and the rest of the body. From ancient civilization to modern globalization, research collaboration helped the world enhance its knowledge of neurology worldwide. As time went on, advancements in technology increased as well as neuromedical drugs came into the world which increased the lifespan of humans and continues to do so. One drug designed to do so by battling Alzheimer's, Donepezil was put through multiple experiments. One experiment was where 565 people were split into being given either a placebo or real Donepezil treatment. After the MMSE and BADLS exams, it was clear that Donepezil did benefit the majority of the people who took the real medication than those who didn't.

Aducanumab is another drug that is very recent and has the potential to eliminate Amyloid B proteins, but it yields inconsistent results and little proof of cognition growth to help cure Alzheimer's. Through experimentation, this has been seen with the SUVR experiment where patients had tested their cerebellum after 78 weeks of being treated with Aducanumab. The change in the severity was too little to be counted as efficacious in the trial period of this experiment, thus showing inconsistency. This is why it is necessary to continue research on neuromedical drugs to find more long-term solutions. By increasing funding for neuromedical research, neurological diseases could also be eradicated much quicker and the discoveries about an essential organ, the brain, can be actively made. Through the use of brain organoids as well as pluripotent cell research, diseases like Alzheimer's in the future could also be solved. Organoids act as organs to help bodily functions complete their tasks and have been used in various parts of the body. Currently, extensive research is going into using this in neurological diseases which could intensively benefit research and advancement in the area. Pluripotent cells are stem cells that can be genetically modified to become neurons or another type of cell. Further research and advancement into this area would incredibly benefit neurological diseases since neurons cannot reproduce asexually in the way stem cells can. If these aspects are looked into, in the future neurological Alzheimer's major advancements will be made in neurology. Achieving these milestones would massively benefit neurological diseases such as Alzheimer's and save millions of lives. Given more time and resources to the field of neuroscience, children will one day be able to step into this world unburdened by the shackles of confinement on neuroscience and be able to break the limitations of research on neurological disorders such as Alzheimer's forever.

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