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Treatments of Alzheimer's Disease: A Review

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ABSTRACT

Alzheimer's Disease (AD) affects about 24 million people worldwide and costs Americans billions of dollars every year.[1] With the prevalence of AD, treatments are needed to combat the disease and reduce its effect. In the past, cholinesterase inhibitors were used to treat the symptoms of the disease. In recent years, however, a new type of drug, monoclonal antibody, has been used for the treatment of AD. The purpose of this paper is to review the old and new Alzheimer's treatment through the lens of affordability and accessibility, and provide insight into the future of the treatment options. In the end, innovative treatments such as vaccines and targeting different mechanisms of action are the next step in Alzheimer's treatment. Access to these treatments should be more readily available and affordable to low-income families. To support this, the FDA should modify its accelerated approval program to reward rigorous scientific research.

Key Terms

ChEI therapy: Cholinesterase-inhibitor therapy

AD: Alzheimer's disease

Acetycholine (ACh): A neurotransmitter

Acetylcholinesterase (AChE): An enzyme that catalyzes the breakdown of ACh

Butyrylcholinesterase (BuChE): Butyrylcholinesterase is a backup for AChE

Cholinergic neuron: A nerve cell which mainly uses the neurotransmitter acetylcholine (ACh) to send its messages

Reversible inhibitor: An inhibitor that allows the enzyme to work again after unbinding.

Pseudo-irreversible inhibitor: A pseudo-irreversible does not bind covalently to the enzyme but has a high affinity for the receptor.

Introduction

Alzheimer's Disease (AD), a neurodegenerative disorder, affects close to 24 million people worldwide.[1] The prevalence of the disease has steadily increased, and 7.2 million people aged 65 and up are projected to have AD by 2025, an 11% increase from 6.5 million in 2022.[2] Currently, Alzheimer's costs Americans an estimated 305 billion dollars a year, and is expected to rise as the population grows older.[3]

AD is characterized by amyloid deposits and neurofibrillary tangles that are caused by buildups of the tau protein in neurons.[4] These buildups cause lesions in cholinergic nuclei, which reduces cholinergic neurotransmission resulting in neuronal death. Cholinergic neurons rely on the neurotransmitter Acetylcholine (ACh), and reduced cholinergic neurotransmission results in a decrease in ACh.

Access to the newest treatment, Aduhlem, which targets the amyloid plaques in the brain and costs $26,000, is comparatively expensive to the current standard of care, cholinesterase inhibitors (ChEIs), which target acetylcholinesterase (AChE) and/or butyrylcholinesterase (BuChE) to prevent the breakdown of the neurotransmitter ACh.

Old AD Treatments

The first treatments developed to treat Alzheimer's disease were known as cholinesterase inhibitors (ChEIs). Lowered levels of Acetylcholine (ACh) were found in the cholinergic neurons in patients with Alzheimer's Disease (AD). Reversible inhibitors, such as Tacrine, bind to the enzyme acetylcholinesterase (AChE) and/or butyrylcholinesterase (BuChE). Pseudo-irreversible inhibitors, like rivastigmine, bind to the enzymes directly and permanently alter the function of the enzyme. AChE breaks down ACh, with BuChE aiding AChE with its function.

Figure 1 shows the timeline of major treatments approved by the US Food and Drug Administration (FDA), which are discussed in the next sections.

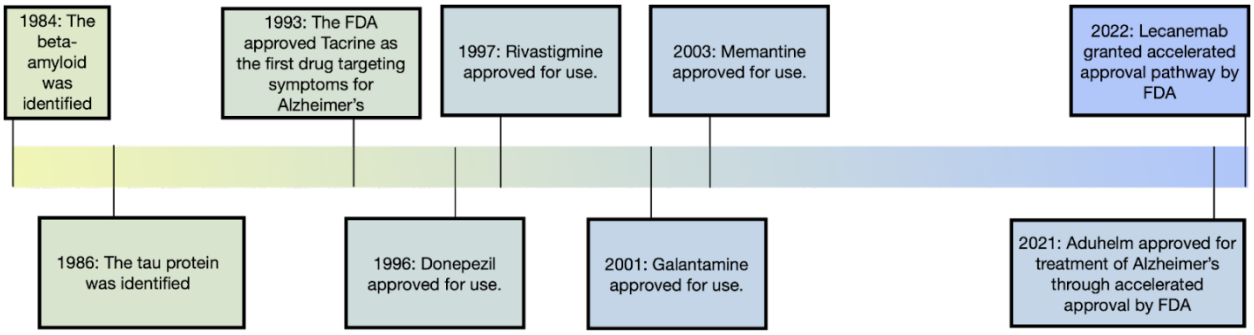

Figure 1: Timeline of major advancements in Alzheimer's understanding and treatment. Note the 18-year gap between Aduhelm approval and the previous treatment

Tacrine

Tacrine (tetrahydroaminoacridine) is a ChEI, and was the first drug approved to treat AD by the FDA in 1993 (see Figure 1).[5] Tacrine is a reversible inhibitor of the AChE and BuChE enzymes, and has a plasma half-life of two to four hours, meaning that it must be administered two to four times a day.[6] In a 30-week study with 663 patients, fifty-five percent of Tacrine-treated patients dropped out due to adverse effects.[7] Tacrine costs $200 a month.[8] It is rarely used to treat AD now.[9]

Donepezil

Donepezil is a selective, reversible ChEI of the AChE enzyme, and was approved by the FDA in 1996.[4,6] Donepezil has a plasma half-life of 80 hours, allowing for once-per-day administration.[10] In a clinical study comparing donepezil and another ChEI, rivastigmine, more patients were able to complete donepezil trials, with fewer patients dropping out due to adverse effects.[4] Donepezil can cost up to $73 a month without insurance.[11] As a result, donepezil is widely used because of the once-per-day administration and reasonable efficacy.[6]

Rivastigmine

Rivastigmine is a pseudoirreversible ChEI of AChE and BuChE in the cerebral spinal fluid (CSF), and decreases the enzyme activity directly.[6] In the study comparing donepezil and rivastigmine, it was found that patients who did not benefit from donepezil were more likely to benefit from rivastigmine. The plasma half life of rivastigmine is 1.5 hours, and is administered twice daily.[12,13] The cost of rivastigmine without insurance is a $473 a month.[14]

Galantamine

Galantamine is a selective, reversible inhibitor of AChE, and is used to treat mild to moderate Alzheimer's disease.[15,16] Galantamine has a different mechanism of action compared to the other ChEIs, where it increases the intrinsic action of ACh on nicotonic receptors, which increases cholinergic neurotransmission.[17] The plasma half-life of Galantamine is 7 hours and is administered twice daily.[18,19] Galantamine costs $59 a month.[20]

Memantine

Memantine is an NMDA-antagonist therapy approved by the FDA in 2003.[4] Memantine lowers glutamate levels and prevents it from killing nerve cells without disturbing the normal transmission of nerve cells.[21] It demonstrated an ability to delay cognitive and functional deterioration.[4] Memantine has a plasma half-life of 60-80 hours and is taken once or twice a day.[22,23] Memantine ranges from $32-$477 a month, depending on the brand.

Non-FDA-approved treatments

There have also been several treatments that have not been approved by the FDA, including physostigmine, metrifonate, eptastigmine, and idebenone.

New AD Treatments

Figure 1 shows an 18-year gap in FDA approval of AD treatments. The treatments approved or expected to be approved after 2021 are considered as new treatments which are discussed below.

Aduhelm

Aduhelm (aducanumab) is a monoclonal antibody used to treat Alzheimer's disease and was approved by the FDA in 2021 through the accelerated approval program.[24,25] Aduhelm directly targets the clumps of beta-amyloid plaque seen in Alzheimer's patients by stimulating the immune system to target and break down the plaques in the brain.[26] Aduhelm has a plasma half-life of 24.8 days and is administered through an IV infusion every 4 weeks.[27] Aduhelm started at $56,000 a year for treatment, but then halved the price to $28,000 a year.[28]

However, Aduhelm did not demonstrate clear benefits in the treatment of Alzheimer's disease. Although a council of senior agency officials from the FDA agreed that the drug needed another clinical trial, the FDA approved the drug anyway.[29] Two late-stage trials of the drug were shut down because the drug did not demonstrate any benefits to the patients. Later, it was demonstrated that patients receiving the highest dose of Aduhelm benefitted slightly. However, the trials also demonstrated that Aduhelm can cause brain swelling or bleeding.

Lecanemab

Lecanemab is a monoclonal antibody used to treat Alzheimer's Disease. Lecanemab selectively binds to toxic amyloid-beta plaques which are believed to cause AD.[30] Lecanemab has a half-life of 7 days and can be administered biweekly.[30] Lecanemab is currently on the accelerated approval pathway with the FDA and the FDA's decision on approval is expected in January 2023.

FDA approved AD treatments discussed above are summarized in Table 1.

Table 1. Treatments of AD and their characteristics**.**

Treatment	FDA Approved?	Plasma half-life	What it inhibits	Percentage (%) of people who dropped out due to adverse effects
Aduhelm	Yes[31]	24.8 days[27]	beta-amyloid plaques in the brain	6 - high-dose participants [32]
Tacrine	Yes[31]	2-4 hours[6]	AChE, BuChE enzymes	55[6]
Rivastigmine	Yes[31]	1.5 hours[12]	AChE, BuChE enzymes	29-43 - high-dose 7-15 - low dose [6]
Donepezil	Yes[31]	80 hours[10]	AChE enzyme	---
Galantamine	Yes[31]	7 hours[18]	AChE enzyme	---
Memantine	Yes[31]	60-80 hours[22]	Pathologic Neural Toxicity	---

Cost and Access of AD Treatments

The costs of treating AD are expected to rise, as our population gets older, with healthcare costs for Alzheimer's expected to reach over $1 trillion in the future.[3]

With prices of monoclonal antibodies such as Aduhelm reaching over $28,000 a year, the cost of treating Alzheimer's with new medications may be unaffordable. Furthermore, Medicare limited the coverage of monoclonal antibodies to patients in clinical trials, making future treatments even more inaccessible for low-income families.[33]

Lacking access to disease-slowing drugs can accelerate nursing home placement, with a negative impact on life expectancy, with an estimated 47-month loss of life expectancy without health state controls.[34] Furthermore, in 2015, the average cost of dementia care over a 5-year period was $287,038, which amounts to around $57,000 a year.[35]

The people that will suffer the most from Alzheimer's are people who are near-poor, in which they are not poor enough for Medicaid, but do not have enough money for long-term care out of pocket.[36] Additionally, low levels of education and low socioeconomic status are individually linked to a higher risk of AD.[37]

Discussion

The increasing age of the population paired with the projected costs of Alzheimer's care has led to the consideration of preventative treatments.[6] A preventative treatment would have to be safe to use for everyone at risk without harming

those who will never develop AD. One preventative treatment option would be vaccines. There are currently no active immunotherapies approved for clinical use for AD and other neurodegenerative diseases. However, peptide-based vaccines have shown promise for neurodegenerative diseases, and the cooperation of the FDA is needed to take this research further.

As shown with Aduhelm, the usage of the FDA's accelerated approval pathway yielded limited benefits. The FDA should focus on greater regulation within the pathway that will reward companies doing rigorous sciences, which reduces uncertainty toward investing in pipeline candidates.[38]

Finally, researchers could target a different mechanism of action for Alzheimer's treatment. Researchers could target Choline Acetyltransferase (ChAT), an enzyme responsible for the synthesis of ACh.[39] With combination therapy, doctors could develop a treatment plan that not only inhibits AChE but also catalyzes the function of ChAT, increasing cholinergic neurotransmission.

Conclusion

Recent breakthroughs in AD treatment have shown promise, but need adjustments to avoid future controversies. The impact and benefits of monoclonal antibodies need to be further investigated and developed. Therapeutic approaches should focus on disease prevention, due to the increasing prevalence of the disease. The development of these approaches will depend on creating more innovative treatments that prevent AD or target different mechanisms of action.

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