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REVIEW ARTICLE

Potential Treatment for Alzheimer's Disease: CRISPR/Cas9

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ABSTRACT: Alzheimer's disease (AD) is a multifactorial neurodegenerative disease caused by a combination of risk factors such as increasing age, genetic factors, vascular diseases, diabetes, infections, and air pollution. AD is a concerning disease as it is the leading cause of dementia and currently lacks a cure. It affects approximately 50 million individuals around the world. Up to 70% of early-onset Alzheimer's disease (EOAD) cases had genetic factors that were related to the disease. Mutations in Amyloid precursor protein (APP), Presenilin-1 (PSEN-1), and Presenilin-2 (PSEN-2) were linked with the development of familial AD. Currently approved drugs are effective only in treating the symptoms of AD, facilitating the synaptic function; they do not cure or prevent the disease. In this paper, we detail the current clinical treatments for AD and biomarkers such as cerebrospinal fluid (CSF) used to detect the formation of beta-amyloid, which are highly related to mutations. This paper aims to evaluate the availability of CRISPR/Cas9 as a treatment for familial Alzheimer's disease (FAD), exploring the technological challenges involved in its implementation. An understanding of potential treatments for AD and their limitations can contribute to the future development of a treatment involving CRISPR/Cas9 that cures AD.

KEYWORDS: Cellular and Molecular Biology, Genetics, Alzheimer's Disease (AD), CRISPR/Cas9, Gene editing, Mutations, Disease Treatment and Therapies.

Introduction

One of the most concerning types of dementia is Alzheimer's disease (AD).[1] AD is a chronic neurodegenerative condition characterized by neuronal death, which affects memory and cognition.[2] Around the world, an estimated 50 million people suffer from AD, and projections show that by 2050, the number of patients with AD will go up to 150 million. The estimated annual cost of AD rises to US$1 trillion, considering the individuals affected, their families, and the economy.[1,3] A major concern is that the causes of AD are multifactorial, with increasing age, vascular diseases, and diabetes being major risk factors for developing the disease. Most AD cases start after 65 years of age; however, in early onset AD (EOAD), genetic factors were related to 70% in the inheritance of it. AD can be divided into early-onset AD (EOAD), which is around 1-6% of cases, with a range of 30-60 years old, where most cases are related to familial AD. Most FAD cases are inherited in an autosomal dominant pattern, with mutations in the dominant genes such as Amyloid precursor protein (APP), Presenilin-1 (PSEN-1), and Presenilin-2 (PSEN-2). Late-onset AD (LOAD) presents more frequently after 65 years old, the multifactorial risks were highly related to AD, and less than 1% of LOAD cases were related to mutations in the apolipoprotein E (ApoE) gene, making gene editing with CRISPR/Cas9 irrelevant. AD lacks a cure, and the current available treatments for it are limited to just improving the symptoms, including side effects such as depression, dizziness, and diarrhea.[3-5] In AD, the neurons die because of structural and functional damage in the central nervous system (CNS), leading to a decrease in the brain size (Figure 1b). The Amyloid beta and Tau hypothesis pathways were suggested to explain the most common hallmarks of AD. In amyloid beta hypothesis structural damage is caused by neuritic plaques that generate due to the accumulation of amyloid-beta peptide's (Aβ) (Figure 2a), which gathers abnormally outside nerve cells; and neurofibrillary tangles (NFT) made up of tau protein, which normally stabilizes the microtubules in healthy neurons, but in AD phosphorylated Tau protein detaches from the microtubules and forms tangles that blocks the neurons communication system and cause their posterior death. (Figure 2b).[1,6] Each current potential treatment for AD faces challenges, but some treatments are more likely to become a cure for AD. A potential treatment that could be used for AD is the early detection of mutations with biomarkers and the subsequent design of a single-guide RNA that recognizes mutated DNA. This will be corrected via clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9 (CRISPR/Cas9). Although there are some limiting factors for this tool, like the safe delivery methods that currently exist. Viral and non-viral methods are used to deliver CRISPR/Cas9 with a lack of efficiency.[3] CRISPR/Cas9 is a revolutionary tool that targets the mutations that relate to AD; it provides a pathway for treating diseases with limited or scarce treatment options, such as AD and Huntington's disease (HD).[3] Currently, CRISPR/Cas9 has not yet been successfully used to cure AD, although it has been used successfully in other diseases, indicating potential for future applications in AD.

In this paper, we first summarize what Alzheimer's disease is, mutations of the presenilin-1 (PSEN1) gene, presenilin 2 (PSEN2) gene, and amyloid precursor protein (APP) that are highly linked with AD. The symptomatic treatments used for AD as cholinesterase inhibitors and N-methyl d-aspartate (NMDA) antagonists. We discuss the potential use of CRISPR/Cas9 and its challenges as brain delivery via non-vi-

DOI: 10.36838/v7i10.60

ral vectors, brain delivery via viral vectors, immunogenicity, blood-brain barrier (BBB), and reticuloendothelial system (RES). This paper aims to discuss whether CRISPR-Cas9 is a viable treatment that could be used for FAD, as this tool has been used to cure other diseases, and current technological challenges could be addressed in the future by research, bringing a way that alleviate the symptoms of FAD.

Discussion

Aβ and Tau protein processing:

Neuritic plaques (NPs) and neurofibrillary tangles (NFTs) are highly involved in several neuronal processes, such as alteration in the permeability of the blood-brain barrier (BBB), mitochondrial disturbance, neuroinflammation, neurovascular unit dysfunction, oxidative stress, and synaptic alteration.[1]

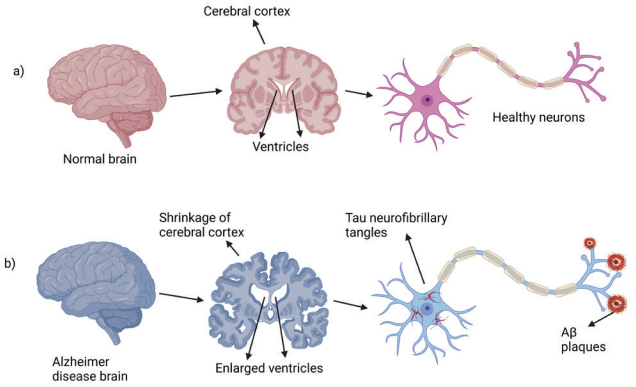

Figure 1: Structure of a healthy brain in (a) and structure of a brain with AD in (b). The AD brain shows significant atrophy, especially in areas responsible for memory and cognition. (Created by author).[2]

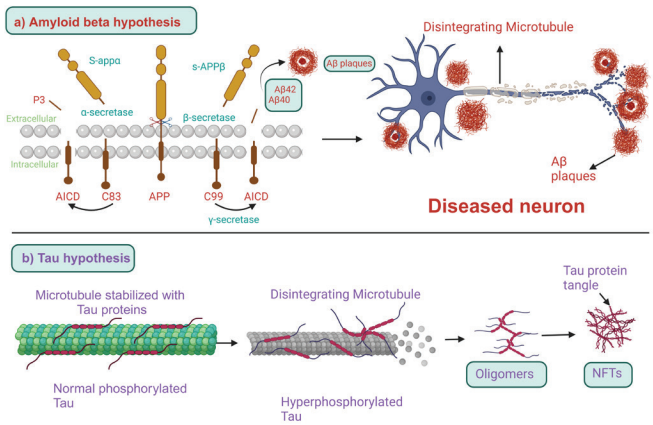

Figure 2: Hypothesis of Aβ relation with AD in (a) and hypothesis of tau protein misfolding related to AD in (b). These figures show how abnormal protein accumulation contributes to neuronal damage and cognitive decline. (Created by author)

NPs and NFT have been postulated to act as endogenous "damage signals" because Aβ oligomers activate microglial cells. Once activated, these cells release proinflammatory cytokines that contribute to neuronal damage. Tau protein is released when neurons die, which can further activate microglial cells, perpetuating a cycle of inflammation, tau hyperphosphorylation, and subsequent aggregation. This self-reinforcing cycle leads to progressive neurodegeneration.[1]

Mutations that cause Alzheimer's disease:

- ***Presenilin-1 (PSEN1) gene:***

A main causative factor of early-onset Alzheimer's disease (EOAD) is the presenilin-1 (PSEN1) gene. The PSEN1 gene codes for the core protein presenilin-1, which is responsible for cutting longer proteins. Presenilin-1 interacts in this way with the amyloid precursor protein (APP), Notch, nicastrin, and the modifier of cellular adhesion (MOCA), beta-catenin. PSEN1 activates the y-secretase complex that plays a role in the production of beta-amyloid from amyloid precursor protein.1 Mutations of PSEN1 were confirmed to impact long amyloid (Aβ42) production and reduce the production of short amyloid (Aβ40); these mutations increase the ratio of Aβ42/Aβ40.[8]

Mutations in the PSEN1 gene provoke the overproduction of long amyloid Aβ42, which tends to aggregate and deposit as plaque in the brain. The cerebrospinal fluid (CSF) is in direct communication with the brain, and when there is an overproduction of Aβ42 and deposition into plaques, the CSF concentration of Aβ42 drops. A low concentration of Aβ42 in the CSF is an indicator of AD.

- ***Presenilin 2 (PSEN2) gene:***

Presenilin 1 and Presenilin 2 share the catalytic core of the y-secretase complex, the enzyme responsible for the generation of beta-amyloid peptides.[9] Presenilin 2, as Presenilin-1 cuts longer proteins. Mutations on PSEN 2 are less common than in PSEN 1. About 300 mutations for PSEN 1 have been described, and only 58 mutations in PSEN 2, which are described as rare and playing a minor role in beta-amyloid production.[1,9] Nevertheless, any mutation in PSEN 2 has severe effects on the Ab42/Ab40 ratio level, increasing the production of Ab42, building up in the brain and forming amyloid plaques as Aβ42 is a protein fragment and is more likely to aggregate than Aβ40, and reducing the concentration of Aβ42 in the CSF.[1-9] Mutations in PSEN 1 and PSEN 2 affect the production of beta-amyloid, leading to the irregular production of long amyloid (Aβ42), which forms amyloid plaques in the brain.

Amyloid precursor protein (APP):

The APP gene is encoded on chromosome 21. It is a type 1 transmembrane protein cleaved by y-secretase to release beta-amyloid and other proteins. Mutations on the APP gene are less common than in PSEN1 and PSEN2; around 25 mutations cause beta-amyloid production and accumulation in the brain.[1] One protective mutation on the APP gene has been identified with the name Icelandic mutation (A673T), decreasing beta-amyloid Ab40 and Ab42 secretion into the brain, reducing the chance of plaque deposition. Another important mutation on APP is A673V, which demonstrates the presence of NFTs and overproduction of beta-amyloid that contribute to neuronal loss.[1] Tables 1, 2, and 3 (see Annex) summarize key mutations in APP, PSEN 1, and PSEN 2 genes, including codon positions and associated clinical relevance for potential gene editing using CRISPR/Cas9.

Current Treatments for Alzheimer's:

The current treatments for AD are reduced to only two classes of drugs, one being inhibitors to cholinesterase enzymes and antagonists to N-methyl-d-aspartate (NMDA).

One of the multiple factors verified to contribute to the development of AD is the reduction in acetylcholine (ACh) biosynthesis. The therapeutic strategy used to address this is by inhibiting cholinesterase enzymes, also known as acetylcholinesterase (AChE), with cholinesterase inhibitors (ChE-Is). The inhibition of AChE stops the degradation in synapses. The increase in ACh results in its continuous accumulation, which activates cholinergic receptors. This treatment was considered to increase the cognitive and neural cells' functions.[1,6] NMDA is the other drug approved to treat AD and is believed to have an important role in the pathophysiology of the disease. NMDA is a membrane receptor that participates in the transmission of electric pulses into the CNS. The stimulation of NMDA results in the formation of long-term potentiation (LTP), which is important for synaptic neurotransmission, plasticity, and memory formation. Verified side effects are caused by the over-activation of NMDAs, which release abnormal levels of Ca2+ signaling and overstimulation of glutamate. This overstimulation results in excitotoxicity, synaptic dysfunction, neuronal cell death, and a decline in cognitive functions. In clinical trials, several NMDA non-competitive antagonists have been tested, but most of them have failed due to low efficacy and the major concern of the side effects, which worsen the disease.[1,6] The first drugs licensed for symptomatic treatment of AD were ChE-Is, but currently, four drugs (donepezil, memantine, galantamine, rivastigmine) are approved. Table 4 (see Annex) outlines the mechanism of current AChE inhibitors and NMDA receptor antagonist drugs for Alzheimer's disease.[6]

Potential of CRISPR/Cas9 for treating AD:

CRISPR/CAS9 is a potential treatment that could be used for AD by gene-editing the mutations that cause it, potentially clearing patients from the disease. CRISPR/Cas9 utilizes two components for gene editing, one being the Cas9 enzyme and single-guide RNA (sgRNA). The sgRNA recognizes the desired DNA sequence to be modified, and the Cas9 protein acts as a pair of scissors, breaking the double strands of DNA. After this break, two pathways can be chosen to repair it, one resulting in the inactivation of the gene and the other in the replacement of a mutated sequence with the correct one. Homology-directed repair (HDR) utilizes a donor DNA template to replace a mutation with a correct sequence. As non-homologous end joining (NHEJ) leads to premature stop codons and DNA frameshifts, resulting in gene inactivation.3 As shown in Figure 3, CRISPR/Cas9 enables precise gene editing using guided RNA and Cas9 protein, and is delivered using viral or non-viral vectors.

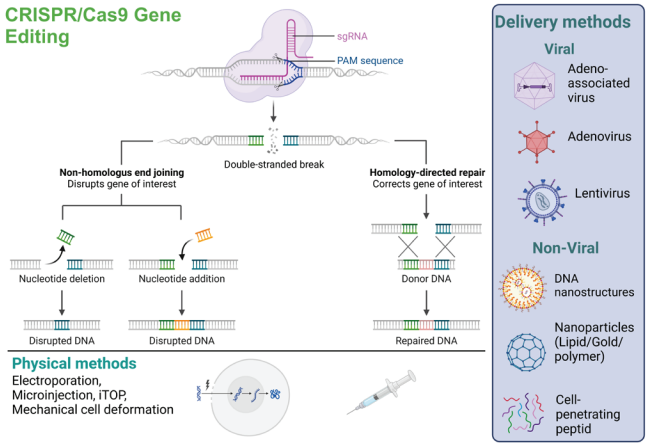

Figure 3: CRISPR/Cas9 gene editing tool. This figure illustrates the gene editing mechanism of CRISPR/Cas9 and the methods used for its delivery into cells, including viral and non-viral vectors. (Created by author).[10]

Treatment with CRISPR/Cas9 might not be as viable as other treatments because most AD cases are sporadic, and they involve unknown causes. Only less than 1% of familial cases of AD (FAD) account for genetic mutations and have negligible effects in sporadic AD (SAD). However, CRISPR/Cas9 might be considered as a therapeutic option to regulate beta-amyloid metabolism in FAD and SAD, reducing the overproduction of beta-amyloid, reducing the progression of the disease, or stopping it.[3] Personalized CRISPR has been used successfully to treat sickle cell disease (SCD) by gene editing hematopoietic stem cells.[11] Although possible, the major challenges for CRISPR/Cas9 in treating both AD and SCD are the low editing efficiency and the high off-target. However, if these challenges for CRISPR/Cas9 are resolved, the application of this tool could open new pathways for curing various diseases, such as AD and SCD.[12] CRISPR/Cas9 opens a pathway to reduce the progression or stop AD, but does not prevent it, by targeting the mutations that cause the accumulation of beta-amyloid or Tau protein. The modification of these genes comes with challenges that are discussed in this paper, as the methods of delivery of CRISPR/Cas9. To target the mutations that cause AD, a guide RNA that specifically binds to the region of DNA containing the mutation needs to be created. The codon where the mutation is can be corrected with HDR or deactivated the mutation with NHEJ.

Limitations of CRISPR/Cas9:

CRISPR/Cas9 lacks efficient and safe delivery methods to date. Currently, viral and non-viral methodologies are used for the delivery of CRISPR/Cas9. For viral methodologies, a concerning point is that they may incorporate mutations that have adverse effects on patients.

Viral methodologies:

Adeno-associated viruses (AAV) are frequently used vectors because of their high infectivity and low integration into the human genome, addressing the problem but lacking in efficiency due to the small amounts of genetic code that can be modified. Lentivirus is another type of virus that incorporates

DOI: 10.36838/v7i10.60

long DNA inserts, allowing bigger modifications but with lower brain dissemination efficiency. The negative factor for lentiviruses is the difficulty in the production of large quantities, and they cannot be incorporated into the human genome as easily as AAV, provoking immune reactions that are not desired.[3] Adenoviruses can't trespass the blood-brain barrier (BBB) by their size; on the other hand, non-viral methodologies are preferred to target the brain as they are smaller and easier to deliver.

Non-viral methodologies:

Non-viral methodologies are more promising to deliver CRISPR/Cas9 due to better cost-effectiveness and flexibility. They address the problem of mutations better because they are less immunogenic than viral vectors, which predispose to more immunogenic reactions. The formation of nanocomplexes by combining positively charged CRISPR/Cas9 peptides with negatively charged nucleic acid cargo doesn't present a huge challenge for the non-viral methodologies. The problem arises in the delivery methods of nanocomplexes in the brain, as they are unable to cross the blood-brain barrier (BBB) that protects the CNS from chemical substances in the blood and limits the chance of therapeutic drugs.[6] Another important factor is the reticuloendothelial system (RES), which actively removes nanocomplexes from the blood. Therefore, other delivery methods are used for nanocomplexes, such as intracerebroventricular and intrathecal injections. These direct infection methods require multiple injections for the proper distribution of nanocomplexes across the brain, which results in a complicated application.[3] Given current technology, it remains very difficult to utilize viral and non-viral methodologies to deliver CRISPR/Cas9 into the brain. There is a need to develop better technology that can facilitate the application of non-viral vectors, presenting a promising treatment for AD.

Conclusion

CRISPR/Cas9 is a novel tool that allows gene editing of specific gene sequences. It allows the elimination or replacement of unwanted mutations in genes that contribute to the development of diseases. CRISPR/Cas9 is present as a potential treatment for all diseases that have mutations in their genes involved such as FAD, a type of AD. AD lacks a cure, and the current treatments used for it only center on improving the cognition that is affected by AD. Independent of genetic factors in SAD and FAD, an altered amyloid beta metabolism is present, which leads to the accumulation of amyloid plaque in the brain that reduces synaptic function and causes the progressive deterioration of the brain. The causes of AD are multifactorial and mainly not related to genes. Mutations that provoke AD are only present in FAD, which represents 6% of all AD cases. CRISPR/Cas9 allows the modification of these mutations, presenting them as a potential treatment for 6% of AD cases, and establishing them as a new treatment that will clear the disease in all the patients who suffer from FAD. CRISPR/Cas9 could edit mutations that are linked with the development of FAD, such as mutations in the APP, PSEN-1, and PSEN-2 genes. CRISPR/Cas9 faces challenges such as efficient and safe delivery methods to edit mutations in humans. Viral and non-viral vectors are used to deliver CRISPR/Cas9 for potential therapy use in humans. Non-viral vectors are preferred because of their easier delivery methods and safer interactions with the receptor system, which do not include immunogenic reactions as viral vectors do. The main challenge of non-viral vectors is their small capacity to store genetic material and deliver it correctly, resulting in an inefficient therapy to cure the disease. For the future it is highly important to resolve the challenges that present for CRISPR/Cas9 when gene-editing for AD, the resolution of the challenges that limit this therapy will bring an effective treatment not only for AD but also for other diseases due that the challenges that present with CRISPR/Cas9 are not exclusive to AD, and present in general when gene-editing modification is applied for human therapies.

Acknowledgments

The author thanks Hamidreza Shaye, Lauren Tetz, and the IRIS program for their guidance in the research process.

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Iván, a sophomore at Tecnológico de Monterrey with an interest in biomedical engineering.

Annex

Table 1: Variants in APP associated with familial Alzheimer's disease.
This table lists key mutations in the APP gene associated with familial Alzheimer's disease. Several variants, such as the Swedish and Flemish mutations, increase amyloid-beta production or aggregation, contributing to early disease onset.

Variant ID	Position	Amino Acid Change	Clinical Significance	dbSNP	Citations (Substitute SNP in link with dbSNP) (https://www.ncbi.nlm.nih.gov/snp/)
VAR_000015	670-671	KM>NL	In AD1; Swedish mutation; highly increases hydrolysis by BACE1 and amyloid-beta protein production	rs28186516	Yes
VAR_044424	678	D>N	In AD1	rs63750064	Yes
VAR_000016	692	A>G	In AD1; Flemish mutation; increases the solubility of processed amyloid-beta peptides and the stability of peptide oligomers	rs63750671	Yes

DOI: 10.36838/v7i10.60

VAR_014215	693	E>G	In AD1	rs63751039	Yes
VAR_000019	713	A>T	In AD1	rs63750066	Yes
VAR_032277	714	T>A	In AD1	rs63750643	Yes
VAR_014218	714	T>I	In AD1; increased amyloid-beta protein 42/40 ratio	rs63750973	Yes
VAR_010108	715	V>M	In AD1; decreased amyloid-beta protein 40/total amyloid-beta	rs63750734	Yes
VAR_000020	716	I>V	In AD1	rs63750399	Yes
VAR_000023	717	V>F	In AD1; increased amyloid-beta protein 42/40 ratio	rs63750264	Yes
VAR_000022	717	V>G	In AD1; increased amyloid-beta protein 42/40 ratio	rs63749964	Yes
VAR_000021	717	V>I	In AD1; increased amyloid-beta protein 42/40 ratio	rs63750264	Yes
VAR_014219	717	V>L	In AD1	rs63750264	Yes
VAR_010109	723	L>P	In AD1	rs63751122	Yes

Table 2: Variants in PSEN 1 are associated with familial Alzheimer's disease.
This table summarizes mutations in the PSEN1 gene linked to familial Alzheimer's disease. Many of these variants increase the Aβ42/Aβ40 ratio, disrupt protease activity, and are highly pathogenic.

Variant ID	Position	Amino Acid Change	Clinical Significance	dbSNP	Citations (Substitute SNP in link with dbSNP) (https://www.ncbi.nlm.nih.gov/snp/)
VAR_075260	35	R>Q	In AD3; uncertain significance; decreased protease activity with APP	rs63750592	Publications
VAR_006413	79	A>V	In AD3; also found in late-onset Alzheimer disease; impaired protease activity with APP; altered amyloid-beta production and increased amyloid-beta 42/amyloid-beta 40 ratio; no effect on GFAP	rs63749824	Publications
VAR_006414	82	V>L	In AD3; decreased protease activity with APP; no effect on GFAP	rs63749967	Publications
VAR_075261	83	I>T	In AD3	-	1 Publication
VAR_081228	85	L>P	In AD3; spastic paraparesis and apraxia; loss of protease activity with APP; altered amyloid-beta production and increased amyloid-beta 42/amyloid-beta 40 ratio	rs63750599	Publications
VAR_081229	89	V>L	In AD3; decreased protease activity with APP; increased amyloid-beta 42/amyloid-beta 40 ratio	rs63750815	Publications
VAR_016214	92	C>S	In AD3; loss of protease activity with APP	rs63751141	Publications
VAR_081230	94	V>M	In AD3; uncertain significance; reduced protease activity with APP; no change in amyloid-beta 42/amyloid-beta 40 ratio	rs63750831	Publications

Table 3: Variants in PSEN 2 associated with familial Alzheimer's disease.
This table outlines rare PSEN 2 mutations associated with familial Alzheimer's disease. Some of these variants affect calcium regulation and amyloid-beta production.

Variant ID	Position	Amino Acid Change	Clinical Significance	dbSNP	Citations (Substitute SNP in link with dbSNP) (https://www.ncbi.nlm.nih.gov/snp/)
VAR_006461	62	R>H	In AD4; likely benign	rs58973334	Publications
VAR_070027	71	R>W	In AD4; uncertain significance	rs140501902	Publications
VAR_009214	122	T>P	In AD4	rs63749851	Publication
VAR_081261	122	T>R	In AD4; increased mitochondrion-endoplasmic reticulum membrane tethering resulting in increased calcium transfer to mitochondria	rs28936380	Publications
VAR_081262	126	E>K	In AD4; uncertain significance	-	1 Publication
VAR_064903	130	S>L	In CMD1V and AD4; uncertain significance	rs63750197	Publications
VAR_006462	141	N>I	In AD4; results in altered amyloid-beta production and increased amyloid-beta 42/amyloid-beta 40 ratio; loss of function as calcium-leak channel;	rs63750215	Publications

			calcium overload in the ER		
VAR_081263	141	N>Y	In AD4	rs61761208	Publication
VAR_007958	148	V>I	In AD4; late-onset Alzheimer disease	rs63750812	Publication
VAR_009215	239	M>I	In AD4	rs63749884	Publication
VAR_006463	239	M>V	In AD4	rs28936379	Publication

Table 4: Drugs used for Alzheimer's disease.
This table summarizes the mechanisms of current treatments that focus on symptom management rather than disease modification.

Drug Name	Drug Type	Target	Mechanism/Effect
Donepezil	Acetylcholinesterase Inhibitor	Acetylcholinesterase (enzyme)	Inhibits acetylcholinesterase, increasing acetylcholine levels in the synaptic cleft; enhances cholinergic function.
Memantine	NMDA Receptor Antagonist	NMDA Receptor (N-methyl-D-aspartate receptor)	Blocks excessive glutamate activity at NMDA receptors, preventing excitotoxicity associated with neurodegeneration.
Galantamine	Acetylcholinesterase Inhibitor	Acetylcholinesterase; Nicotinic receptors (allosterically)	Inhibits acetylcholinesterase and modulates nicotinic receptors, increasing acetylcholine and enhancing neurotransmission.
Rivastigmine	Acetylcholinesterase and Butyrylcholinesterase Inhibitor	Acetylcholinesterase and Butyrylcholinesterase (enzymes)	Inhibits both acetylcholinesterase and butyrylcholinesterase, increasing acetylcholine levels to improve cognition and behavior.

DOI: 10.36838/v7i10.60