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Journal of
Mental Health and Psychiatry Research

Review Article

A Road Map of Dementia and its Hereditary Forms

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Received: 2024 Feb 29 **Accepted:** 2024 Mar 19 **Published:** 2024 Mar 28

Abstract

Dementia is not a particular condition, but rather a broad term for the reduced ability to recall, reason, or make decisions, which interferes with daily activities. Alzheimer›s disease is the most prevalent type of dementia. Memory loss, forebrain cell death, and cognitive impairment are hallmarks of Alzheimer›s Disease (AD), a neuro degenerative disease that primarily affects the elderly. The main cause of Alzheimer›s disease is the buildup of tau angles within cells and the release of Aβ outside of them, resulting in neuro-inflammation and oxidative stress. A single genetic mutation accounts for less than 5% of cases of Alzheimer›s disease (AD). It is not uncommon for members of these families to start exhibiting symptoms in their 30s or 40s, and they often do so well before they reach the age of 65. Abnormalities in the neurological system, such as neurodegenerative disorders, can be caused by even little mitochondrial dysfunction. Unfortunately, effective neuronal protective medications to prevent AD are few . Therefore, effective medications that target molecular pathways are desperately needed to combat the massive growth of this disease.

Keywords: Alzheimer's Disease, Familial Alzheimer's Disease, Global Scenario and Drug Development.

1. Introduction

Alzheimer's disease (AD) is a severe senile dementia in which neurons and memory are gradually destroyed. This type of dementia, known as Alzheimer's disease, develops to cognitive decline and amnesia. Alzheimer's disease affects a large proportion of the elderly population and grows at an exponential rate after the age of 60. According to the 2010 World Report on Alzheimer's disease, Alzheimer's disease has the same societal cost as cancer, heart disease, and strokes. AD can be classified as Early-onset AD (EOAD) or Late-onset AD (LOAD) based on the age of onset. The most frequent type of Alzheimer's disease is LOAD, which affects people over the age of 65; EOAD is less common, affecting people under that age [1].

Although familial Alzheimer's disease (FAD) makes up just 5% of cases, it offers vital insights into the etiology of sporadic illness. All variants exhibit autosomal dominant inheritance with strong penetrance. Early-onset Alzheimer's disease is typically diagnosed before the age of 65. Most occurrences of familial Alzheimer's disease are caused by mutations in one of three key genes involved in amyloid processing [2].

1.1. Global Scenario

Alzheimer's disease affects approximately 50 million people and is expected to increase by 152 million by 2050, doubling every five years worldwide. The Alzheimer's disease impact on the financial system, families, and individuals is projected to be $1 trillion every year worldwide. Alzheimer's disease and associated dementias (ADRD) are anticipated to affect more than 75% of the global population by 2050, particularly in low- and middle-income nations. It affects around 6.7 million Americans over the age of 65.

This figure could rise to approximately 13.8 million by 2060 if medical improvements prevent, postpone, or cure Alzheimer's disease. According to death figures published in 2019, Alzheimer's disease caused 121499 fatalities, ranking sixth among leading causes of death in the United States. Between 2020 and 2021, the COVID-19 pandemic was one of the top ten major causes of death, and Alzheimer's disease rose to seventh place. Alzheimer's disease continues to be the fifth leading cause of mortality among Americans over the age of 65. Between 2000 and 2019, the number of deaths from heart disease, stroke, and HIV decreased but Alzheimer's increased by more than 140% [3].

The most common is Alzheimer's disease, a type of dementia. This is because mild memory loss progresses to a lack of speech and reactivity to our surroundings. This condition affects the language, cognition, and memory parts of the brain. Alzheimer's disease can significantly impair a person's capacity to undertake daily tasks [4]. For example, Ardekani et al. found that women are more likely than men to acquire both structural and functional nervous system abnormalities [5]. Women, on the other hand, are twice as likely as men to develop psychiatric issues, particularly depression. All

of the disorders listed above increase the likelihood of developing Alzheimer's. Furthermore, female brains are more susceptible to Alzheimer's disease because to the influence of sex hormones [6]. Furthermore, studies have connected severe SARS-CoV-2 infection with cognitive decline and an increased risk of developing Alzheimer's disease.

According to Siu et al. and Xia et al., this may be caused by an acute viral infection in the central nervous system and long-term accumulation of pro-inflammatory cytokines [7, 8]. These cytokines act as a catalyst, hastening or initiating neurodegenerative processes. As a result, patients are more likely to develop Alzheimer's disease due to their pathogenic mechanism. There are two types of front temporal dementia: familial and sporadic. Familial FTD occurs when many members of a family suffer from FTD or a comparable illness in consecutive generations. Multiple people are usually closely connected to one another, such as a grandparent, parent, and adult kid, and they all come from one side of the family or the other, but not both. Sporadic FTD is when only one member of a family has FTD.

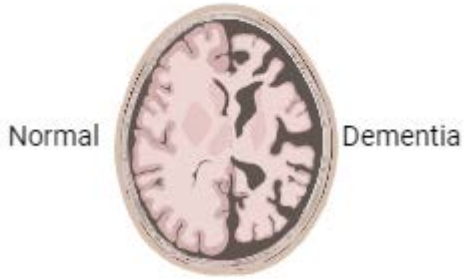

Figure 1: The Normal Brain and the Dementia Affected Brain.

1.2. Molecular Bases of Familial Alzheimer's Disease

Autosomal dominant Alzheimer's disease (ADAD) is caused by gene mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2) genes, which are highly penetrant and disease-causing (Sheppard and Coleman). However, mutations in these genes can only explain a small proportion of all FAD instances, implying the presence of other, inherited, disease-predisposing genes. Some familial FTD cases have no recognized cause. Some cases of familial FTD result from a single genetic etiology. This is referred to as genetic FTD. Genetic FTD accounts for around 10- 20% of all FTD cases. Genetic FTD is caused by a single gene mutation. Genetic FTD is primarily caused by a mutation in one of three genes: C9ORF72, MAPT, or GRN. Mutations in TARDBP, VCP, CHMP2B, SQSTM1, UBQLN1, or TBK1 can occasionally cause sickness [9].

FTD is inherited in families in a dominant pattern. This indicates that the kid of someone with an FTD causing gene mutation has a 50 %, or one in two, chance of inheriting the same mutation. With a few exceptions, almost every individual with an FTD-causing gene mutation will develop FTD or a similar illness if they live to their eighth decade. The age at which the first symptom appears varies according to the FTD-causing gene mutation present. It is not rare for the first symptoms to appear in people aged 50 to 60. However, the first symptom appears between the ages of 30 and 40 and continues until the seventh decade of life. Because FAD often progresses clinically from pre-dementia to dementia, it is critical to identify and diagnose it before symptoms appear in order to begin therapy as soon as feasible [10]. As a result, a greater knowledge of FAD molecular bases, specifically the identification of causal genes, may improve the care and clinical outcomes of these patients and their families.

1.3. Genes Associated with Familial Alzheimer's Disease

Only a small percentage of FAD cases are explained by mutations in the APP, PSEN1, and PSEN2 genes, as well as the APOE ε4 risk allele. This suggests that other genes may also play a role. In recent years, NGS-based research, which analyzes vast pedigrees, have enabled the discovery of novel genes likely associated to FAD. Guerreiro et al. found a harmful mutation in the NOTCH3 gene while studying a Turkish FAD family. Interestingly, the same mutation has previously been linked to a dementia problem comparable to Alzheimer's disease, and the proband comes from a consanguineous family with a complex history of neurological disorders. NOTCH3 (OMIM# 600276, chromosome) is a transmembrane receptor that regulates cellular signalling and embryonic development [11]. More than 130 mutations in this gene have been found, and they are linked to the rare syndrome cerebral arteriopathy autosomal dominant with subcortical infarctions and leukoencephalopathy; a role in FAD has recently been hypothesized [12].

Pottier et al. conducted WES on 29 probands from FAD families, revealing negative mutations in the three main FAD genes, including 7 in the SORL1 gene [13]. The p.G511R mutation reduces the protein's capacity to bind Aβ peptide, leading to its buildup [14].

Interestingly, genome-wide association studies found approximately 30 additional risk factors/alleles for late-onset AD [15, 16]. Variants affecting CLU (APOJ) or CR1 (complement component 3b/4b receptor 1), implicated in Aβ clearance, have been associated with AD. Additionally, heterozygous missense mutations in TREM2 (triggering receptor myeloid 2 cells) have been shown to raise the risk of AD thrice. It has been postulated that these genes could possibly be responsible for FAD instances.

Clusterin (CLU, OMIM# 185430, chromosome), a protein involved in synapsis turnover, has been found to have a higher incidence of uncommon coding mutations in AD patients. These mutations primarily affect the β chain. Most of the CLU variations reported thus far can enhance CLU degradation, hence lowering its activity [17].

1.4. The Interaction of Neurotransmitters

Neurotransmitter-mediated signals across synapses are critical for the preservation of synaptic and cognitive functioning in mammals, including humans [18]. Neurotransmitters are endogenous chemical messengers that enable neurotransmission. Neurotransmitters convey signals across neuromuscular junctions and synapses [19]. When the appro-

priate signal is received at the synapse, neurotransmitters are released from their regular storage within synaptic vesicles located beneath the membrane in the axon terminal. The released neurotransmitters explain how they function by attaching to the appropriate receptors and connecting across the synaptic cleft. The body produces these neurotransmitters spontaneously from amino acids. NMDA is derived from D-aspartic acid and arginine, acetylcholine (ACh) from serine, dopamine from L-phenylalanine/L-tyrosine, GABA from glutamate via decarboxylation, serotonin from L-tryptophan, histaminergic from L-histidine, and GABA from glutamate.

Except dopamine, these are the principal neurotransmitters involved in the pathophysiology of AD. Other neurotransmitters that may contribute to oxidative stress but play no significant role in AD pathogenesis include glutamate, glycine, norepinephrine, epinephrine, melatonin, gastrin, oxytocin, vasopressin, cholecystokinin, neuropeptide Y, and enkephalins. According to reports, these chemical messengers have a function in synaptic processes such as producing the action potential required for synaptic vesicles to spread via exocytosis. To potentially trigger synaptic transmission, released neurotransmitters diffuse across the synaptic cleft and bind to the appropriate receptors on the postsynaptic cell membrane. The postsynaptic membrane contains neurotransmitter receptors that are both ionotropic and metabotropic. Ionotropic receptors are ligand-gated channels, whereas metabotropic receptors are membrane receptors that communicate with the secondary messenger [20].

1.5. Cross Talk Signalling Pathways in Alzheimer's Disease

There are different views about the causes of Alzheimer's disease (AD). These comprises oxidative stress, cholinergic dysfunction, the amyloid cascade, tau protein abnormalities, and neuro inflammation. The hypotheses of neuro illness and tau protein play an important role in understanding AD. Investigation has shown that neurodegeneration is a major risk factor for Alzheimer's disease. Both animal models and patients with AD exhibits neuro inflammation, particularly increased activation of microglia around senescent plaques in brain regions like the hippocampus and cerebellum.

Additionally, there are higher levels of inflammatory markers in AD characteristics complete genome studies have demonstrated a notable decrease in antioxidants and an increase in inflammation-related genes. The severity of Alzheimer's disease is closely linked to the inflammatory response initiated by activated microglia against Aβ. Furthermore, the production of tau protein, which plays a major role in AD pathogenesis, is induced by GSK-3β expression [21]. The Akt signalling pathway also plays a significant role in the development and progression of AD by regulating innumerable cellular functions such as survival, gene expression, cell proliferation, and metabolism through phosphorylation of downstream substrates triggered by Akt activation. Moreover, disruption of the Akt signal has been involved in pathogenesis of AD.

1.6. Drugs for AD

Immunotherapies: The complex structure of Alzheimer's disease (AD) pathogenesis remains a significant barrier to medication development. Immunotherapies have been developed to prevent amyloid plaque formation by blocking BACE, oligomer aggregation, and Aβ peptide reduction [22-24]. Many therapeutic intervention trials failed due to significant side effects or ineffectiveness, while new immunotherapies are being studied. DYRK1A kinase inhibitors have been shown to improve cognitive performance in animal models of DS and AD [25]. RCAN1 has been identified as a potential target for treating Alzheimer's disease and dementia, but no medicines have been developed to inhibit it [24]. Observed that fish oil supplementation reduced levels of this protein in mice. Compounds that inhibit calcineurin may have immunosuppressive effects, which should be investigated. Using calcineurin/NFAT inhibitors for organ transplantation can have substantial side effects.

The mTOR pathway is another possible therapeutic target for Alzheimer's disease. Research shows that mTOR inhibitors, like as rapamycin, can lower tau pathology, Aβ levels in the blood, and cognitive impairment in AD rats. However, these inhibitors have not been studied in humans because to the negative effects they have on mTOR's function in protein synthesis, metabolism, and cell growth and proliferation. Tau poisons cells and contributes to Aβ toxicity. Reducing tau pathology may help minimize the main hallmark, which is currently being evaluated in phase II clinical trial; (ii) kinase inhibitors, such as the small-molecule NSAID salsalate and the CDK5 inhibitors flavopiridol and roscovitine, which have not been tested in clinical trials in patients with AD; tideglusib, which does not show improvements in the AD population; lithium chloride; and a GSK3β inhibitor, which stabilized the cognitive sym Methylene blue and curcumin, both tau aggregation inhibitors, did not enhance clinical outcomes in Alzheimer's disease. Despite the efficacy of several techniques for suppressing tau expression in preclinical models, such as small interfering mRNAs (siRNA), no therapy studies have been conducted in the Alzheimer's population.

Drugs that target tau protein changes include (i) phosphatase inhibitors such as sodium selenium and memantine, an NMDA receptor antagonist that aids Alzheimer's patients [26]. Several medications, including melatonin, MitoQ, Skulachev (SkQ1), and the Sezto-Shiller (SS) tetrapeptide SS31, diminish the neurodegenerative characteristics of AD mouse models and are promising candidates for human studies. One fascinating treatment strategy for Alzheimer's patients has been proposed: reducing neuroinflammation. Consistent use of NSAIDs (nonsteroidal anti-inflammatory drugs) has been linked to a lower risk of Alzheimer's disease, and long-term use of naproxen or ibuprofen slows the progression of mild cognitive impairment to AD. NSAID. NSAIDs may only benefit ApoE4 carriers, even though ibuprofen treatment lowers tau and amyloid formation in these people. To minimize neuroinflammation in Alzheimer's patients, converting microglia into phagocytic cells can improve Aβ clearance from the brain. Jujuboside A is one medicine that has shown this impact in Alzheimer's mouse models [26-28].

Urolithin A (UA): Urolithin A (UA) is generated from ellag-

itannin phytochemicals and has been shown to improve mitochondrial function and homeostasis by inducing mitophagy in animals and mammals [29]. Numerous in vivo studies using AD replicas have demonstrated the favourable effect of UA, with significant increases in pathogenic characteristics following the introduction of mitophagy [30]. UA treatment in C. elegans models of APP/PS1 and Aβ1-42 mice decreased cognitive failure and sickness by activating Parkin/PINK1-dependent mitophagy. Furthermore, UA was discovered to maintain mitochondrial functional and structural abnormalities despite increasing synapse count. Furthermore, UA reduced mitochondrial impairment in microglia, reversed inflammatory actions, and improved phagocytic consent for Aβ symptoms. UA treatment improved cognition and dramatically reduced Tau hyperphosphorylation in mice with 3xTgAD [31].

The first human clinical experiment used UA (0.5-1 g per month) in healthy deskbound older persons and showed that it was safe and effective in regulating mitochondrial genetic changes.NAD+ Boosters serve as cofactors for a wide range of molecules, including those from the Sirtuins family (SIRT1, 3, 6, and 7), which can promote widespread mitophagy and autophagy via many pathways [29, 32]. Both NMN (nicotinamide mononucleotide) and NR (nicotinamide riboside) are excellent mitophagy stimulants [33]. NMN improved memory impairments in an animal model (C. elegans expressing Aβ1-42) via activating mitophagy pathways, including PINK1/Parkin-dependent ones.NR promotes mitophagy, reduces proteotoxic stress and Aβ levels, and improves longevity and health. Furthermore, NR increased OXPHOS, LC3, and PINK1 mRNA levels, reduced cortical Aβ deposits, and enhanced cognitive function in mice with APP/PS1 [34]. Several clinical trials are presently underway to look into the effects of NR on brain health, OS, cognition, and CSF pTau levels in MCD (mild cognitive damage) and AD patients.

Approaches such as NAD+ level restoration in brain tissues via amplification of NAD+ precursors such as NR and NMN may increase mitophagy inspiration and have the potential to be used as anti-AD drugs. Natural compounds like Actinonin (AC) have a variety of biological actions, including antibacterial and anticancer properties [32]. AC treatment in an AD nematode model can decrease memory errors, Aβ burden, and APP-CTF load. AC enhanced mitochondrial architecture, function, and synaptic density in APP/PS1 mice by inducing mitophagy [35]. AC increased mitophagy in microglia by boosting Aβ inscription and lowering neuroinflammation, which was surprising. In AD, AC showed moderate defensive benefits against APP- and mutant Aβ-induced mitochondrial dysfunction and synaptic toxicity [36].

Resveratrol: Resveratrol (3,5,4′-Trihydroxy-Trans-Stilbene; RES) is a naturally occurring phenolic compound that acts as a strong ROS inhibitor, an iron chelator, and a mitophagy and autophagy stimulator. Prolonged oral administration of phenolic substances in APP/PS1 mice improved mitochondrial function and memory, activated AMPK and SIRT1 pathways, and lowered Aβ levels. Sun et al. found that prolonged oral administration of melatonin to PS1 mice increased mitochondrial assembly and functionality while also demonstrating extreme mitophagy as indicated by a decrease in mitophagy indices (LC3-II/LC3-I, Parkin, PINK1) and the number of autophagic vesicles [28]. Melatonin was discovered to aid spatial learning and alleviate memory impairments by down-regulating APP expression. Numerous studies have shown that RES has a favourable effect on AD. RES enhances mitophagy pathways in PC12 cells, protecting against Aβ1-42-induced OS, apoptosis, mortality, and mitochondrial damage [37]. However, this fragment has a significant therapeutic disadvantage because it is metabolically unstable, resulting in low water bioavailability.

The researchers stated that employing the RES nanoform will improve bioavailability and therapeutic efficacy for Alzheimer's disease. Other drugs have been widely utilized to increase mitophagy. A machine learning system recently identified RES (stilbenoid) and Kaempferol (flavonoid) as mitophagy stimulators, which have been authorized in both vivo and in vitro studies. These medicines reduced APP-CTF, pTau, and Aβ levels in AD models (cells, larvae, and mice). Xie et al. found that RES and Kaempferol decreased memory loss in AD trial models, namely in Aβ and Tau [33].

AD treatment has made extensive use of a wide range of natural medicines. However, there are few long-term applications for these soluble and bioavailable compounds. Nanocarriers helped scientists to solve these issues by boosting therapeutic absorption, increasing circulation, and having the ability to bypass or surpass biological barriers. The treatment of Alzheimer's disease in rats has been extensively studied using several nanoforms, including resveratrol-loaded nanoliposomes (RLNB) and luteolin nano-blossoms (LNB) (50 mg/kg) [38]. Researchers discovered that mice administered RLNB and LNB had considerably lower levels of IL-6, COX2, Tau, and Aβ compared to medicine suspensions containing luteolin or RES [38] . El-Nashar et al. found that administering mice artichoke extract or a chitosan-coated artichoke-loaded nanoform improved memory and cognition while significantly lowering β-Tau and Aβ levels. Finally, these findings indicate that blossomed-coated natural compounds may be a unique delivery approach with the potential to improve bioavailability and stability.

Since 1901, when Dr. Alzheimer first recognized senile dementia in 'Auguste Deter', there have been no metabolic-based treatments to prevent it, but some may temporarily relieve symptoms. The FDA has approved three AChEIs, a single NMDA antagonist, and an AChEI/NMDA antagonist combo. The sigma-2 receptor (S2R) is an endoplasmic reticulum (ER) transmembrane protein with a binding site called TMEM97, a biomarker for rapidly proliferating cells that is over expressed in a variety of lymphoma types. The difference between agonists and antagonists at the S2R is unknown, however agonists appear to be effective anticancer agents. S2R antagonists in animal models have been proposed as potential Alzheimer's disease treatments due to their capacity to block oligomer attachment to neurons and their impact on neuro degeneration, synapse loss, and

cognition. Kargbo found that selective S2R ligands based on a nor benzomorphan scaffold are effective in mice models of Alzheimer's disease [39].

Nuclear Receptors (NRs): Nuclear receptors (NRs) are a superfamily of ligand-activated transcription factors that regulate the expression of many genes involved in various biological processes, including energy and lipid metabolism, in response to environmental and dietary changes. Many studies completed over the last decade have shown that pharmaceutical targeting of multiple NRs is advantageous in AD animal models, notably the liver X receptor (LXR), PPARs, the retinoid X receptor (RXR), and, to a lesser extent, the retinoic acid receptor (RAR). LXR, PPARs, and RAR are members of the type II NR family, which also includes non-steroid NRs that form necessary hetero dimers with RXR. The heterodimeric receptors bind to sequence-specific DNA sequences in the enhancers and promoters of their target genes, therefore directly directing gene transcription. Regardless of their ligand binding site, heterodimeric receptors remain in the nucleus [40].

Importantly, LXR and PPAR heterodimers with RXR are classified as "permissive," which means that ligating either component of the receptor pair activates the heterodimer, and when ligated simultaneously, it can respond in an additive or synergistic way. RAR-RXR heterodimers, on the other hand, are "conditionally permissive;" they are not activated by RXR ligands alone; rather, binding a RAR ligand activates the dimer, which then allows the binding of RXR ligands, therefore enhancing RAR's transcriptional potential. Other "non-permissive" RXR heterodimers, such as the thyroid hormone receptor, respond solely to nonpermissive binding partner ligands and not RXR ligands [41]. Importantly, in the absence of ligand interaction, RXR heterodimers bind to DNA and operate as transcriptional repressors, inhibiting gene expression. This repression strategy uses an interaction with corepressor complexes that include the NR corepressor (NCoR), the silencing mediator of retinoic acid thyroid hormone receptors (SMRT), and HDAC3.

When a ligand is bound, the heterodimer changes conformation, disabling the corepressor complex and forming an association with transcriptional coactivators such as p300 and members of the steroid receptor coactivator (SRC) subfamily, which catalyzes the assembly of large protein complexes that regulate gene transcription. Furthermore, alternative repression mechanisms mediated by these NRs that do not require direct DNA binding (transrepression) have been discovered in macrophages. PPARγ and LXR monomers bind to their ligands, preventing NCoR corepressor complexes from leaving chromatin. This method decreases genes activated by NF-κB in response to inflammatory signals, namely in immune cells [42].

Although animal studies have yielded good results, it is too early in the AD treatment process to determine whether activating nuclear receptors (NR) is beneficial. According to Gold et al., rosiglitazone, a PPARγ agonist, was not effective as a monotherapy for mild to severe Alzheimer's disease, perhaps due to inadequate brain penetration [43]. Takeda and Zinfandel Pharmaceuticals are undertaking a phase III study to assess the efficacy of pioglitazone, a PPARγ agonist, for Alzheimer's disease.

Furthermore, established a neuroprotective effect in a 6-year analysis of data from the German health insurance registry, discovering that chronic pioglitazone treatment of diabetic patients lowered dementia risk by 47% [44]. Cummings et al. conducted a small phase II study on Alzheimer's disease patients to evaluate the RXR ligand bexarotene [26]. A 30-day study of mild to severe Alzheimer's disease patients found that APOE4 non-carriers had significantly lower brain amyloid load and higher serum Aβ(1-42) levels, indicating that Aβ was successfully evacuated from the brain to the periphery. Amyloid burden was not different amongst APOE4 carriers [45].

2. Conclusion

Alzheimer's cases, frequency, and mortality rates increased considerably globally throughout that time period. According to GBD 2019 and 2022 forecasts, the global incidence in 2050 is expected to be 152.8 million. Over the 30-year study period, both the ASIR and ASPR (per 100,000 population) demonstrated a continuous upward trend. Trends indicate that the proportion of the population over 60 years old will grow the quickest, reaching 22% by 2050. Healthcare costs for Alzheimer's disease and other types of dementia are expected to rise in the future, owing to factors such as an aging population and an increase in disease incidence.

Women are twice as likely as men to suffer from mental health issues such as depression, and they are also more prone to develop neurological disorders. All of these disorders may be precursors to Alzheimer's disease. Furthermore, sex hormones make female brains naturally more susceptible to Alzheimer's disease. Women have a longer life expectancy than men, and they make up a large share of the senior population. Alzheimer's therapy and prevention, as well as treatments aimed at female patients, should be supported.Multiple research studies have discovered that COVID-19 patients are predisposed to Alzheimer's disease, which is concerning given the virus's rapid spread in recent years. This could be because some people are more likely to develop Alzheimer's disease (AD) due to direct viral involvement in the central nervous system and long-term accumulation of pro-inflammatory cytokines, which either causes or accelerates the neuro degenerative process.

Addressing the relative risk factors is the greatest way to prevent disease emergence. Alzheimer's disease incidence has decreased in various European countries.Because of the recent success of medications designed to improve aspects of dementia such as cardiovascular health, metabolism, cognitive, and lifestyle.Numerous hurdles have delayed the development of new Alzheimer's treatments, including high failure rates in costly and time-consuming preclinical and clinical trials. Because of AD's complicated and poorly understood genesis, variable clinical presentation, and numerous associated comorbidities, developing new treatments

for the illness has been particularly challenging.

Because of these problems, researchers are looking for novel ways to treat Alzheimer's disease. Despite recent setbacks, therapeutic repurposing remains an attractive area of Alzheimer's disease (AD) research, with considerable potential for expanding the variety of possible AD treatments beyond those that target amyloid beta. However, future drug repurposing studies will need substantial validation to narrow the alternatives. It is an interesting method for researching potential Alzheimer's treatments because it offers several advantages over new drug research, including reduced costs, faster development schedules, and, most importantly, a better guarantee of medication safety.

Because of AD's complex and poorly understood etiology, diverse clinical presentation, and various associated comorbidities, creating new treatments for the disease has been extremely difficult. Because of these challenges, researchers are seeking for new approaches to treat Alzheimer's disease. Despite recent setbacks, therapeutic repurposing remains an intriguing field of Alzheimer's disease (AD) research, with great promise for broadening the range of possible AD treatments beyond those that target beta amyloids

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