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REVIEW ARTICLE

Emerging Horizons in Alzheimer 's disease: New Frontiers in Treatment and Care

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ABSTRACT
Alzheimer's sickness (AD) is an ongoing, gradually moderate neurodegenerative issue and generally normal in old patients. It is quite possibly the most moderate types of dementia, eventually prompting passing in matured population. The significant signs of Alzheimer's disease incorporate deposition of extracellular amyloid feeble plaques and intracellular neurofibrillary tangles in mind neuronal cells. In spite of the fact that there are old style helpful choices accessible for the treatment of the sicknesses, notwithstanding, they give just a suggestive alleviation and don't change the sub-atomic pathophysiological course of the infection. Late examination propels in Alzheimer's disease have featured the expected job of hostile to amyloid, anti-tau, and calming treatments. Nonetheless, these treatments are as yet in various periods of pre-clinical/clinical trial. Moreover, drug repositioning/repurposing is one more fascinating and promising way to deal with investigate justified choices for the treatment of Alzheimer's disease. This survey talks about the various parts of the pathophysiological component engaged with the movement of Alzheimer's disease alongside the limits of current treatments. It also includes two methodologies, specifically; dynamic immunotherapy and latent immunotherapy. Dynamic immunotherapy approach includes the organization of antigen to invigorate the actuation of arrival of antibodies. Moreover, this survey additionally features arising investigational drugs alongside ongoing medication repurposing approaches for Alzheimer's disease.
Keywords: *Alzheimer 's disease; Immunotherapy; Clinical trial; Dementia; Antigen-antibody*

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INTRODUCTION

Dementia is progressively being perceived as one of the main clinical issues in more seasoned individuals with a commonness ascending from 1% at 60 years old to a minimum 35% at 90 years old [1]. Inside the range of dementias, Alzheimer's disease (AD) is the most common subtype, representing around 60% of all dementias. It is portrayed clinically by moderate memory and direction misfortune and other intellectual shortages, including hindered judgment and navigation, apraxia and language aggravations. These are ordinarily joined by different neuropsychiatric manifestations (for example gloom, detachment, nervousness, tumult, fancies, and mental trips). The proceeding with development of future, prompting a quickly developing number of patients with dementia, especially AD, has prompted a tremendous expansion in research zeroed in on the disclosure of medications for essential, auxiliary or tertiary counteraction of the illness. Notwithstanding all logical endeavors, right now there are no successful pharmacotherapeutic choices for anticipation and treatment of AD.

Until this point, set up medicines are just indicative in nature, attempting to offset the synapse unsettling influence of the infection. Three cholinesterase inhibitors (CIs) are endorsed for the treatment of gentle to direct AD [2]. A further helpful choice accessible for moderate to extreme AD is meantime [3]. Simultaneously antipsychotic and energizer medicines are utilized for the social manifestations of the illness [4]. Medicines under research remember intensifies that represent the obsessive substrate of the infection: extracellular amyloid β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs).

Promotion was once viewed as an uncommon issue yet as of late it is considered as an incredible danger and hazard component to the old local area [5]. In one among nine individuals old enough 65 and above has Alzheimer's disease [6]. AD is liable for most dementia cases revealed worldwide and is checked by the deficiency of memory and accumulation of Amyloid beta-peptide (AßP) and Neurofibrillary tangle (NFT) [7]. Dementia is utilized to depict an expansive arrangement of manifestations like loss of memory and challenges in critical thinking just as thinking. It involves concern in light of the huge level of populace succumbing to the condition and the absence of successful consideration gave to the enduring patients [6, 8]. As indicated by World Health Association (WHO) information, it has been assessed that 50 million individuals experience the ill effects of dementia. Strangely, Alzheimer's infection (AD) is liable for right around 60- 70% of the complete instances of dementia [9]. Most later World Alzheimer Report 2016 has seen that as just half of patients in created nations get legitimate finding and the conclusion rate in center just as low pay nations fall as low as 10% [10]. The way that appropriate clinical consideration and treatment is unreachable for a huge number of patients even in profoundly created nations involves incredible concern. The neuropathological normal for AD is set apart by intracellular neurofibrillary tangles (NFT) and extracellular accumulated amyloid fibrils and amyloid-β plaques, this pathology increments with maturing [11, 12]. The Neuropsychiatric indications (NPSs) are a trademark element of AD and can end up being troubling for both the patients just as the guardians. These indications show in three stages; the primary stage is set apart by discouragement and peevishness, second stage set apart by uneasiness and unsettling followed by visualization and daydream in third stage [13]. The indication and movement of the illness have been subject of different examinations throughout the long term, in demonstrate hatred for of this reality, the indications, movement and the way in which people react to the treatment stays as an issue of discussion [14]. The current and generally utilized remedial system endorsed by United States Food and
Drug Administration (U.S.F.D.A) comprises of the utilization of N-methyl D-aspartate (NMDA) receptor adversaries, what's more Cholinesterase Inhibitors (ChEIs) to mitigate the side effects [15, 16, 17]. The disappointment of these treatments is halfway because of them being only indicative and the utilization of ChEIs has not given any persuading proof regarding neuroprotective impact in patients with AD.

Flow indicative ways to deal with Alzheimer's disease

Cholinesterase inhibitors

The cholinergic speculation of AD infers that cholinergic frameworks in the basal forebrain are impacted from the get-go in the infection interaction, including loss of acetylcholine neurons, loss of enzymatic capacity for acetylcholine amalgamation and debasement, bringing about cognitive decline and disintegration of other intellectual and noncognitive capacities, for example, neuropsychiatric manifestations [18, 19]. A system to upgrade the cholinergic transmission by utilizing CIs to postpone the corruption of acetylcholine between the synaptic parted has been proposed. Until this point, three CIs are endorsed for the treatment of gentle to direct AD: donepezil (Pfizer, New York, NY, USA), rivastigmine (Novartis, Basel, Switzerland) and galantamine (Janssen, Beerse, Belgium) [20]. These medications have been viewed as the norm and first-line treatment for AD. Foundational audits including some twofold visually impaired, randomized, fake treatment controlled preliminaries (RCTs) of these three CIs all showed benefit on intellectual capacities, exercises of day by day living (ADL), and worldwide capacity for patients with gentle to direct AD; there was no huge contrast of viability between individual CIs [20, 21]. Likewise, donepezil is currently additionally endorsed for the treatment of extreme AD in the USA [22]. Despite the fact that tacrine (First Horizon Pharmaceuticals, Alpharetta, Georgia, USA) was the primary CI medication endorsed for AD in 1993, it is not generally utilized because of hepatotoxicity [23]. Related foundational audits showed that the frequency of gastrointestinal unfriendly impacts, like queasiness, spewing, looseness of the bowels and stomach cramp, was lower with donepezil than with rivastigmine and galantamine [24]. The frequency of unfavorable impacts was related with higher remedial portion. Notwithstanding, it could be that galantamine and rivastigmine might be equivalent to donepezil in decency assuming a cautious and steady titration routine of over 90 days is utilized. The dermal type of rivastigmine gives a lower portion less antagonistic impacts however equivalent adequacy, and is was liked by certain guardians [25]. Utilization of CIs is likewise answered to be related with expanded paces of syncope, bradycardia and pacemaker inclusion. The danger of these unfavorable occasions should be weighed cautiously against the medications' advantages [26].

Surveys and meta-investigations on CIs that have as of late been distributed showed that they defer the decrease in intellectual capacity as estimated by the AD Assessment Scale – intellectual subscale (ADAS-gear-tooth), worldwide clinical rating, conduct and ADL more than 6 year time frames. These advantages appear to be relevant to gentle, moderate and serious AD [27, 28]. Contrasted and those on fake

treatment, patients on CIs for the most part show an underlying gentle improvement in intellectual capacities over the initial 3 months. From there on, the mean decrease in intellectual capacities was additionally less quick over the ensuing 3–9 months. At a half year, the intellectual improvement (versus fake treatment) was 2.7 focuses over the Mid scope of ADAS-pinion [27]. Indications that were worked on included consideration, thinking, memory, praxis, language understanding and correspondence [28].
Inception of CI treatment in the beginning phases of AD is liked. A 52-week investigation of the adequacy of rivastigmine in patients with gentle to decently extreme AD detailed that patients with AD who began the CI a half year after the fact accomplished lower intellectual execution than the individuals who began the medication following the conclusion [29]. Protected intellectual capacity was likewise seen following a year of treatment with rivastigmine in patients with gentle AD in contrast with untreated patients who notably deteriorated in cognizance during a similar period [30].

N-methyl-D-aspartate antagonist

Memantine is another treatment option for moderate to severe Alzheimer's disease (Lundbeck, Valby, Denmark). This medication is an N-methyl-D-aspartate (NMDA) antagonist with a modest affinity that protects neurons against excitotoxicity. McShane et al. [31] conducted a systematic analysis of double-blind, parallel-group RCT studies of memantine and found that it improved cognition, ADL, and behaviours in patients with moderate to severe AD after 6 months of usage. Memantine may improve behavioural and psychological symptoms of dementia, according to a systemic review that comprised six RCT studies [32]. Dizziness, headache, and disorientation were the most commonly reported side effects in memantine trials. Agitation may occur in a small number of patients [33].

Combination therapy

RCT studies on patients with moderate to severe Alzheimer's disease found that combining memantine and donepezil improved cognitive function, language, ADL, behaviours, and overall health compared to the placebo group (memantine and placebo) [34, 35, 36]. However, no such effect was seen in people with mild to severe Alzheimer's disease [37].

Treatment of behavioral and psychological symptoms of dementia in Alzheimer's disease

Noncognitive neuropsychiatric symptoms, also known as behavioural and psychological symptoms of dementia (BPSD), are common in all stages of Alzheimer's disease (AD), including amnestic mild cognitive impairment (MCI) (the pre-dementia stage of AD), and their prevalence increases as dementia progresses. They are the primary determinants of increased caregiver strain and patient institutionalisation. According to a large observational study, BPSD can be classified into four major symptom clusters with high prevalence: psychosis (38 percent of patients, e.g. delusions), affective symptoms (59 percent, anxiety and depression), hyperactivity (64 percent, e.g. aggression, disinhibition), and apathy (65 percent) [38].
Other antidepressants commonly used in this demographic include mirtazapine, venlafaxine, and duloxetine, which are SNRIs (selective noradrenalin and serotonin inhibitors), as well as bupropion. A few small RCTs and meta-analyses show their efficacy in treating depression in Alzheimer's disease [39]. SSRIs may also be used to treat agitation and psychosis in Alzheimer's disease dementia [38]. However, a recent randomised, multicenter, double-blind, placebo-controlled trial of sertraline or mirtazapine for depression in dementia (HTA-SADD) found no effect and increased the risk of side events when compared to placebo. The trial found that the existing practise of utilising these antidepressants in conjunction with standard care for depression in Alzheimer's disease patients should be reassessed [40].

The amyloid hypothesis

Amyloid plaques, NFTs, and neuronal loss are the major histopathologic lesions of Alzheimer's disease pathogenesis. Mature plaques have a central amyloid core surrounded by degenerating neurons that are damaged by the Aβ toxic effect. [41] NFTs are made up of hyperphosphorylated tau protein in a double helical filament shape.
Secretase (BACE1) in the extracellular domain and secretase in the transmembrane region sequentially proteolyze the amyloid precursor protein (APP) to produce the Aβ.
According to the 'amyloid theory,' A production in the brain starts a chain of events that leads to Alzheimer's dementia [42]. A is a protein that comes in two different forms: A40 and A42. A42 is the most soluble type, and it has a proclivity for aggregating into fibrils, which make up the majority of amyloid plaques. It is the most common kind detected in the brain parenchyma of Alzheimer's sufferers. As part of 'cerebral amyloid angiopathy,' A40 is predominantly found in the cerebral vasculature. A has a proclivity for forming oligomers. Oligomers can combine to produce A-fibrils and protofibrils, which will eventually

form benign amyloid plaques. The formation of amyloid oligomers is what causes neurotoxicity and starts the amyloid cascade. Local inflammation, oxidation, excitoxicity (excess glutamate), and tau hyperphosphorylation are all components of the cascade. Tau proteins fold into intraneuronic tangles as a result of this process, resulting in cell death. The lack and imbalance of numerous neurotransmitters (e.g., acetylcholine, dopamine, serotonin) caused by progressive neuronal death leads to the cognitive deficits evident in Alzheimer's disease [42, 43].

Strategies in Drug Discovery for Alzheimer's
Biomarkers

A biomarker is an objectively assessed measurable sign of some biological or pathological state or condition used to evaluate normal biological or pathological processes. They can be used to diagnose as well as track the progress of a treatment (Figure 1). Magnetic resonance imaging (MRI) or positron emission tomography (PET), invasive cerebrospinal fluid (CSF) biomarkers, genetic markers, and serum myloid with significant specificity and reactivity are currently available diagnostic methods for Alzheimer's disease [44]. However, while neuropsychological analysis is regarded the "best standard" for pre-mortem detection of Alzheimer's disease [45], the screening process is time-consuming and may require multiple assessments.

The majority of AD drug development relevant biomarkers currently used are brain imaging, plasma and cerebrospinal fluid (CSF) measurements; microarray and spectroscopic examination of multiple genes, proteins, lipids, and metabolites; and microarray and spectroscopic examination of multiple genes, proteins, lipids, and metabolites. Florbetapir-PET pictures (an imaging agent with a high binding selectivity for amyloid) show a link between amyloid burden and cognitive function [46]. Another biomarker, A amyloid, can be evaluated using a commercially available imaging agent (AV-45) for future research into Alzheimer's disease; however, no imaging agent for tau is currently commercially accessible. However, Victor Villemagne's research group is working on developing 18F-THK523 as a tau imaging agent in Alzheimer's patients [46], and Jeff Kuret is working on biomarkers for tau imaging for early analysis, differential analysis, and monitoring response to various treatments, but selectivity and binding potential are the primary challenges in the development of tau imaging agents. Enhanced sensitivity of a TDP-43 was demonstrated during Cerebro Spinal Fluid (CSF) testing in frontotemporal dementia [27]. The importance of the heterogeneity of the definition of neuronal injury is demonstrated by neuroimaging and CSF measures of -amyloid and neuronal injury, which has major implications for therapeutic trials using biomarkers as replacement endpoint endpoints [47].

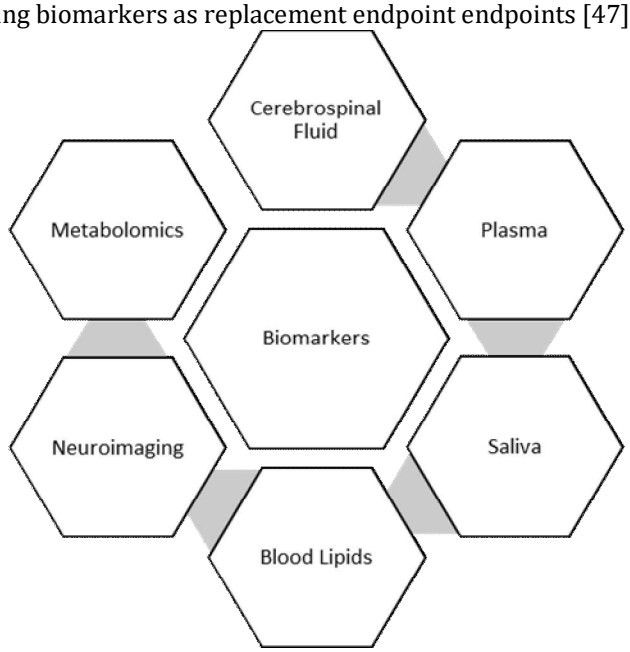

Figure 1: Various biomarkers used in diagnosis of AD

Multi-Target-Directed Ligand (MTDL) Design Strategy

Multi-target-directed-ligands (MTDLs), which are chemicals that influence two or more biological targets and processes, have been discovered to be a new kind of polypharmacology. This method has evolved rapidly in recent years, primarily in the setting of multifactorial disorders like Alzheimer's disease.

Chemical fragments responsible for interaction with desirable biological targets have been used to develop and manufacture a number of promising multifunctional anti-AD compounds. MTDL for Alzheimer's disease has also been produced with multifunctional features such as antioxidant activity, blood-brain barrier penetration, biometal chelation, A aggregation control, and neurotrophic and neuroprotective effects. It also indicated the multiplication of hippocampal cells in adult mice who were still alive. ASS234 has been found as a multi-targeted molecule for Alzheimer's disease. The cholinergic system is now the most effective therapeutic strategy for medication development for Alzheimer's disease. The reduction of acetylcholine (ACh) levels is thought to be the cause of cognitive and memory problems. As a result, blocking cholinesterase's (ChEs), which govern the hydrolysis of ACh, is important for the treatment of Alzheimer's disease. There are two forms of ChEs: acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) (BuChE). Because AChE is the governing element for ACh metabolism (80%), acetylcholinesterase inhibitors (AChEIs) can effectively limit ACh hydrolysis and provide effective therapeutic effects. In Alzheimer's disease patients, the level of AChE drops to 90%, resulting in the loss of AChEI function. BuChE, on the other hand, remains at a constant level or is upregulated for ACh metabolism. BuChE is a promising target for therapeutic development in advanced Alzheimer's disease [48].

Targets and Small Molecules against Tauopathies

Tau accumulation's link to neurodegeneration in Alzheimer's disease and other tau-positive neurological illnesses, commonly known as tauopathies, points to tau aggregates' participation in neurotoxicity (Figure 2). Delrieu et al. have begun planning Expedition 3, a new third phase 3 clinical trial for solanezumab in individuals with mild AD and signs of amyloid buildup. Solanezumab, a previously developed medication, appears to be more effective when taken in the early stages of amyloid accumulation, demonstrating the necessity of identifying AD as early as feasible and undertaking clinical trials at this period [48, 49]. Gibbons et al. discovered new tau monoclonal antibodies (mAbs) that allowed for the selective detection of AD tau pathology by binding to a tau conformation specific to AD [50].

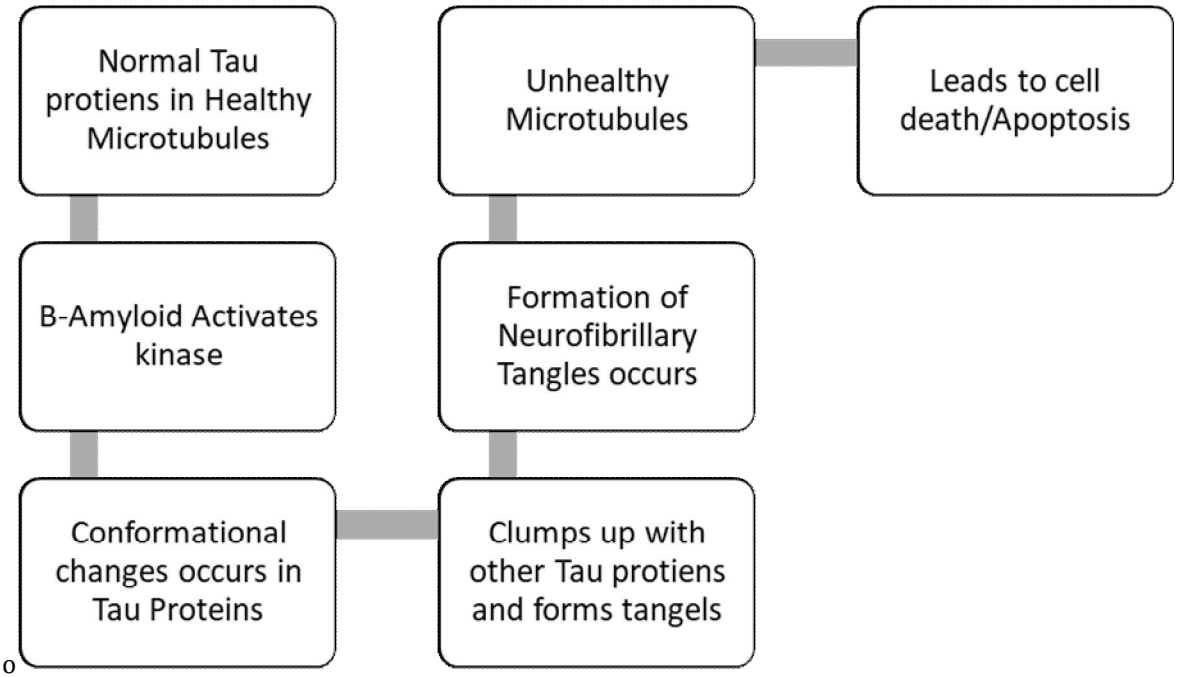

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Figure 2: Tau pathology

Azure C (AC) was created by Lo et al., and it is capable of controlling tau oligomer formation pathways at low concentrations while also releasing tau oligomer-induced toxicity in cell culture [51]. Surprisingly, AC reduced toxicity by converting oligomers into groups of aggregates with non-toxic conformations.

Other Strategies

Ginsenosides have been shown to have significant inhibitory effect against AChE, BChE, and BACE1, as well as ONOO and nitrotyrosine production, in a variety of in vitro enzyme studies. The blossoms of Inula japonica, a member of the Asteraceae plant family, have been utilised in traditional Chinese medicine and

as a nutritious tea. Two new sesquiterpenes and 10 recognised terpenes were discovered in the flowers of I. japonica by Liu et al. [52]. Their studies demonstrated that the blossoms of I. japonica are a nutritious tea that may be beneficial for Alzheimer's disease and other neuroinflammatory illnesses. Anti-inflammatory and neuroprotective effects of baicalin are well recognised. Chen et. al. colleagues investigated the neuroprotective effects of baicalin and discovered that its anti-inflammatory properties increased A (1-42) protein-related pathology and cognitive dysfunction [53].

Astrocytes have been proven to serve a critical role in maintaining CNS homeostasis and neuronal function. Tg astrocytes showed a number of notable effects, including increased reactivity and expression of the inflammatory cytokine interleukin-1 beta (IL-1), stimulation of the hexose monophosphate shunt, and the initiation of hypoxia inducible factor-1 alpha (HIF-1), which helps to protect against A toxicity [54]. Pantethine, a vitamin B5 precursor with neuroprotective and anti-inflammatory properties, alleviated the pathogenic pattern in both Tg and WT astrocytes treated with A.

Compounds with a benzofuran ring have been identified as playing a critical role in decreasing A-induced toxicity, but only synthetic benzofurans have been examined to date. González et al. investigated the neuroprotective characteristics of fomannoxin (Fx), a natural benzofuran derived from the Andean-Patagonian fungus Aleurodiscus vitellinus cultures, in vitro [55], and found that it protected against A peptide toxicity. Paley et al. suggested that tryptophan metabolites cause neurotoxicity and neurodegeneration in Alzheimer's disease patients [56]. Shikimate pathway is known to produce tryptophan (SP). Human cells do not contain SP; instead, human gut bacteria use it to produce aromatic amino acids (AAA). This group of researchers has conducted a gene-targeted analysis of human gut microbiota in AD faecal samples.

Current Advancement in the treatment of Alzheimer's disease (AD)

Aβ-targeting strategies

The appearance of senile plaques in the hippocampus, which are predominantly produced from the extracellular deposition of Aβ, a 40-42(3) amino acid polypeptide, is one of the hallmarks of Alzheimer's disease. By sequential proteolysis of two proteases, and -secretase, at the N- and C-terminus of the Aβ sequence, the Aβ is removed from a large transmembrane protein, the amyloid precursor protein (APP). Alternatively, within the Aβ sequence, APP can be processed by -secretase, preventing the synthesis of Aβ peptide while also generating a soluble neurotrophic sAPP. A is a neurotoxic, according to many experiments; it aggregates and creates deposits, which eventually lead to neural dysfunction. The abnormal accumulation of A in the brain causes oxidative stress, neuronal death, and, eventually, clinical signs of Alzheimer's disease. According to this idea, secondary prevention of AD can be achieved by reducing Aβ production, stimulating Aβ clearance, or preventing Aβ aggregation into amyloid plaques [57].

Immunotherapy

Following promising results from in vitro and animal research, both active (vaccination) and passive (monoclonal antibodies) immunisation are being investigated in AD patients. Morris water maze trials revealed that active immunisation against A42 in transgenic mice resulted in fewer plaques and improved cognitive performance. These promising findings prompted clinical immunisation trials in Alzheimer's disease patients. A phase II clinical trial with the synthetic Aβ peptide AN1792/QS-21 in individuals with mild to moderate AD was started, however it was eventually stopped because roughly 6% of the vaccinated AD patients (18/300) experienced meningoencephalitis [58]. Furthermore, the study found a link between brain volume decrease and cognitive performance in AN1792/ QS-21 antibody responders, as determined by MRI scanning. Furthermore, the study found a link between brain volume decrease and cognitive performance in AN1792/ QS-21 antibody responders, as determined by MRI scanning. Only individuals with meningoencephalitis had enhanced T-cell activation after being treated with AN1792/QS-21. As a result, it was hypothesised that a T-cell response was required for the development of meningoencephalitis. Although immunisation with Aβ(42) resulted in amyloid plaque clearance in patients with Alzheimer's disease, this clearance did not prevent increasing neurodegeneration, according to a recently completed clinical experiment [59].

HMG-CoA reductase inhibitors (the "statins")

Statin users have a lower risk of Alzheimer's disease, according to epidemiological studies. In vitro research revealed that a high-cholesterol diet boosted APP-secretase processing, but a low-cholesterol diet lowered Aβ synthesis. The idea that high cholesterol levels enable Aβ production while statin treatment reduces Aβ production led to the idea that statins could be a promising treatment for Alzheimer's disease. In Alzheimer's patients, a one-year clinical trial using atorvastatin showed some

therapeutic effect. The level of plasma Aβ was reduced after treatment with lovastatin. Other research, on the other hand, found no evidence of lower plasma Aβ levels.
The disagreement between these studies is difficult to explain; it could be due to the diverse cognitive tests utilised, the treatment period, the experiment design, the discrepancy across studies, and the fact that different stages of the illness respond to statins differently. Another key consideration is that the statin dosage utilised in clinical trials may be significantly lower than that used in in vitro culture, resulting in significantly different findings in human trials than in in vitro experiments. Although the effect of statins on Aβ production is unknown, many research indicate the link between cholesterol and Alzheimer's disease. Aβs a result, there is a need for larger clinical investigations that track cholesterol and APP metabolism both before and after treatment.

Monoamine oxidase inhibitors
Deprenyl, an MAO inhibitor, is an anti-Parkinson medication that prevents dopamine breakdown in the brain. In addition, as a Deprenyl, a neuroprotective drug, has been used to halt the progression of Alzheimer's disease. The progression of neurodegenerative disorders like Alzheimer's disease for a long time despite the fact that certain clinical trials are contentious, Deprenyl has been shown in trials to help with a variety of ailments. Indications of Alzheimer's disease Deprenyl can modulate APP processing through PKC, according to an in vitro experiment. Signaling by mitogen-activated protein kinase (MAPK) mechanisms could explain its late clinical effect stage of the illness Another MAO-B inhibitor has been discovered. Rasagiline, another MAO-B inhibitor, is a bifunctional chemical that also inhibits acetylcholinesterase. Its neuroprotective mechanisms, which include APP processing regulation, activation of the PKC and MAPK signalling pathways, inhibition of cell death markers, and upregulation of neurotrophic factors, justify its use in the treatment of Alzheimer's disease, but clinical trial data has yet to be published. In vivo, Ladostigil is a dual acetylcholinebutyryl cholineesterase and brain-selective MAO-A and-B inhibitor that has been proven to counteract scopolamine-induced spatial memory impairment. It may also activate PKC and MAPK and affect APP processing. Its use as an anti-AD treatment is justified by its inhibition of neuronal death indicators, prevention of a drop in mitochondrial membrane potential, and overexpression of neurotrophic factors and antioxidative activity [60].

Non-steroidal anti-inflammatory drugs (NSAIDs)
Microglial cells, which are closely connected to the peripheral macrophage series of cells, grow in size and number in the brain as Alzheimer's disease progresses. The concept of complement was born out of this finding and the presence of complement in amyloid plaques. Alzheimer's disease has been identified as an inflammatory disease. a lot more There are 20 epidemiological studies, some of which are follow-up studies. providing a reasonable estimate of NSAID prescription use Pharmacist research has revealed that the prolonged NSAID use has been linked to a lower risk of Alzheimer's disease [61]. With the incidence of CIND (mild coronary artery disease) increasing in a 10-year population-based cohort study in Canada, It was discovered that cognitive impairment (not dementia), Alzheimer's disease (AD), and all-cause dementia are linked. There is a link between NSAID use and a lower risk of cancer. However, due to gastrointestinal damage, clinical trials with powerful NSAIDs (indometacin) resulted in significant withdrawal rates. Some studies have found no benefit from COX-2 selective (celecoxib and rofecoxib) or unselective (naproxen) NSAIDs or other anti-inflammatory medicines such dapsone, hydroxychloroquine, and prednisone. Further NSAID trials have revealed that NSAIDs have a deleterious effect in the later phases of AD pathogenesis, although asymptomatic people treated with traditional NSAIDs like naproxen have a lower AD incidence after 2 to 3 years. As a result, therapy effects vary depending on the stage of the disease.

Estrogen
Estrogens have been shown to protect the brain from oxidative stress, excitatory neurotoxicity, and ischemia. Estradiol injection dramatically reduces the neurodegeneration associated with Alzheimer's disease in an experimental rat model, according to studies. This could be due to its potent antioxidant, antiapoptotic, neurotrophic, and antiamyloidogenic properties. Estrogen can stimulate matrix metalloproteinases-2 and 9 to enhance beta amyloid breakdown, according to Merlo et al. [62]. Within the forebrain, receptors are situated on the same neurons as cholinergic receptors that are specifically affected by pathologic alterations in Alzheimer's disease. Within the forebrain, receptors are situated on the same neurons as cholinergic receptors that are specifically affected by pathologic alterations in Alzheimer's disease. It is thought that the absence of oestrogen in postmenopausal women causes a susceptibility to Alzheimer's disease. Hormone replacement therapy (HRT) using oestrogen has also been

proposed as a neuroprotective treatment for Alzheimer's disease. Hormone therapy appears to be effective in the treatment of mild to moderate Alzheimer's disease, according to several small short-term randomised clinical trials and epidemiologic research [63]. Short-term hormone therapy with transdermal estradiol enhanced cognition in postmenopausal women with Alzheimer's disease in a randomised controlled trial [64]. However, research by Shumaker and colleagues found that postmenopausal women taking oestrogen and progestin had a higher incidence of dementia [57].

Nicotine

Nicotine is a cholinergic agonist that works both postsynaptically and presynaptically to release acetylcholine, an alkaloid found in tobacco plants' leaves (Nicotiana tabacum and Nicotiana rustica). Nicotinic receptor density is further reduced in the elderly with age-related neurodegenerative illnesses such as Alzheimer's disease [65]. Numerous in vivo and in vitro studies have shown that nicotine can improve neuron survival in the face of a variety of neurotoxic insults. In a rat model of Alzheimer's disease, nicotine elicited improvements in learning and memory via neuropeptide Y Y1 receptors [66].

Cell transplantation and gene therapy

Cholinergic innervation in the cortical and subcortical regions is reduced as the cholinergic neurons in the nucleus basalis of Meynert degenerate. Reduced neurotransmitter transduction is linked to the clinical and pathological severity of Alzheimer's disease and can be treated. Transplantation of cholinergic-rich tissue or peripheral cholinergic neurons improves aberrant behaviour and cognitive function in the AD rat model. However, no clinical trials in Alzheimer's patients have been started using this approach. Endogenous nerve growth factor (NGF) deficiency can cause memory problems, whereas NGF injection protects neurons from injury-induced cell death and improves memory [67], making NGF a good candidate for gene therapy.

Other pharmacological therapies in clinical AD trials

Docosa-hexaenoic acid (DHA)

Increased consumption of the omega-3(n-3) polyunsaturated fatty acid DHA has been linked to a lower risk of Alzheimer's disease. In the brain, DHA is the most prevalent omega 3 fatty acid. Animal studies support the idea that DHA, through antiamyloid, antioxidant, and neuroprotective processes, could be an effective treatment for Alzheimer's disease. In a 12-month RCT with 204 individuals with mild to moderate AD, omega-3 fatty acid administration revealed no delay in the pace of cognitive loss as measured by the MMSE or the cognitive section of the AD Assessment scale. However, in a small group of patients with extremely mild Alzheimer's disease, beneficial effects were seen [57].

Clioquinol

In a pilot investigation with 36 patients with Alzheimer's disease, metal chelation with clioquinol was found to lessen the rate of cognitive loss in a double-blind, placebo-controlled phase 2 clinical trial [68]. The ability of clioquinol to chelate zinc and copper associated with amyloid plaques is responsible for its efficacy in this preliminary investigation. The therapeutic effect is thought to be based on the mobilisation and elimination of brain amyloid. Clioquinol has been shown to diminish zinc buildup in neuritic plaques and block the amyloidogenic process in the brain of APP/PS1 transgenic mice [69].

CONCLUSION

Because the development of Alzheimer's disease is a complex process including both hereditary and environmental variables, developing effective disease-modifying medications is proving difficult. Current treatments for Alzheimer's disease patients may help to alleviate symptoms by offering brief relief and slowing the rate of cognitive impairment. The development of therapies that significantly delay the start or affect the progression of AD can be expected, given the large range of possible molecular targets and the rapid progress in identifying prospective therapeutic agents.

Alzheimer's disease is characterised by a rapid accumulation of -amyloid, neurodegeneration, and cognitive impairment. It is the most common age-related neurodegenerative disorder, affecting millions of people around the world. As a result, finding an appropriate intervention and therapy is critical. For the treatment of Alzheimer's disease, medications are urgently needed, however practically all previous clinical trials of AD therapeutic candidates have failed or have become obsolete. For the development of clinical trial simulators, a variety of tools such as mathematical, computational, or statistical tools can be used to aid in the advancement of trial design and thus aid in the success of possible breakthrough therapeutics. Drugs that target several targets may be able to lessen the excessive influence on the intricate nerve network, and this process, known as multi target-directed ligands (MTDLs), may lead to

the identification of new therapies for Alzheimer's disease. Dual binding AChE and BACE1 inhibitors, AChE inhibitors and antioxidants are examples of previously developed multitarget compounds.

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CONFLICT OF INTEREST
The authors declare no conflict of interest, finically or otherwise.

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