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Latest Intervention Strategies for Treatment and Management of Alzheimer's Disease: A Review

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Abstract: The recent years of Alzheimer's therapy provides interim improvement for the symptoms- memory loss and complications with reasoning and thinking processes. These treatments boost performance of the signaling molecules of the brain that carry information from one neuron to another. Although, these treatments are unable to stop the fundamental reasons for the reduction and death of the neurons. As more frequently these cells die, Alzheimer's disease continues to advance. Experts are cautiously hopeful about developing Alzheimer's treatments that can stop or significantly delay the progression of Alzheimer's. A growing understanding of how the disease disrupts the brain has led to potential Alzheimer's treatments that short-circuit basic disease processes. Here we highlight the use new vaccines targeting specific components of Aβ and tau protein, anti-microbial therapy, Symbiotic strategies, mesenchymal stem cells, epigenetics and the introduction of medical devices for detection, and diagnosis for the treatment of Alzheimer's disease.

Index Terms **– Alzheimer's disease, antimicrobial therapy, epigenetics, mesenchymal stem cells**

I. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease and is the most common cause of dementia. Dr. Alois Alzheimer declared that Alzheimer's disease is an aggressive form of dementia, manifesting in memory, language, and behavioral deficits [1]. This disease worsens with increasing age. It is neuropathologically described by the amassing of accumulated amyloid beta (Aβ) and tau. Accumulated Aβ stores in the vasculature and the parenchyma, shaping congophilic amyloid angiopathy (CAA) and extracellular amyloid plaques. Hyperphosphorylated tau aggregates intraneuronal to frame neurofibrillary tangles (NFTs) [2], [3]. Two factors that contribute to the difficulty in establishing accurate incidence rates of AD: determining the age at onset; and defining a disease-free population. The rapid rise in the frequency of AD with advancing age, combined with the relatively long duration of the illness, accounts in large part for the high prevalence of the disease worldwide. Improvement and standardization of diagnostic methods have provided a means to compare estimates of the frequency of AD across various populations [4]. The inheritance pattern typically exhibited in AD is an autosomal dominant inheritance pattern that is related to mutations in genes that lead to alteration in beta-amyloid (Aβ) protein production or metabolism, including presenilin-1 (PSEN1), amyloid precursor protein (APP), and presenilin-2 (PSEN2) [2].

Researchers are investigating therapeutic options to treat this disease. Recently new vaccines have been introduced which intend to target specific components of Aβ and tau protein. New medical devices are being constantly developed to tackle the main issue in AD i.e., cognitive decline. These medical devices help in the enhancement of cognitive functions. Medical devices either use two strategies: invasive, non-invasive [2]. Invasive techniques such as DBS were found fortunately upon conducting a study of DBS on candidates afflicted with obesity. Noninvasive techniques such as transcranial direct current stimulation, visual sensory stimulation, electroconvulsive therapy, and photobiomodulation have shown promising results in the enhancement of cognitive function [2], [3].

II. Latest Trends of Therapeutic Merit in Alzheimer's Disease

2.1 Vaccines

2.1.1 Active and Passive Immunotherapeutics Targeting Aβ and Tau Proteins for AD

Genetic mutations in the amyloid precursor protein (APP) and enzymes necessary for APP cleavage (presenilin 1 and 2 [PS1 and PS2]) lead to autosomal dominant forms of early-onset AD (EOAD) [5] . The start of early-onset AD provides strong support for the amyloid cascade hypothesis [6]. Targeting tau may also be necessary, especially considering that individuals with extensive plaque burden can have normal cognition and the presence of neurofibrillary tangles has correlated better with disease progression [7]. By targeting tau, we can accomplish the task of inhibiting cognitive decline, which is predominantly seen in AD patients. Active and passive immunizations have been the most optimal way to treat AD by directly targeting Aβ and tau by the production of specific antibodies. Active immunization provides long-term immunity, by the production of antibodies. There are some concerns regarding active immunization: First, in immune-compromised individuals or elderly individuals. It may not elicit a good and fast immune response. Secondly, it may trigger adverse reactions like an inflammatory response, which may be very hazardous to the patients.To tackle this issue, passive immunization was developed. It elicits immune response even in old individuals with showcasing the adverse effect. Precise concentrations of antibodies can be administered. Currently, clinical trials are being carried out to develop active and passive immunotherapeutics targeting specific parts of the Aβ protein and pathological components of tau. Tables 2.1 and 2.2 summarize the active and passive immunizations for Aβ and tau proteins in AD treatment.

Table 2.1: Active Immunizations for Aβ and Tau Proteins

Name of the vaccine	Drug Candidates	Clinical trials	Therapeutic Target	Patient Population	Outcome	Complications
AN1792 *[8]–[11]*	full length Aβ42 in QS-21 adjuvant	A phase IIa immunotherapy trial - terminated	fibrillized Aβ	patients with mild to moderate Alzheimer disease	reduces Aβ plaque burden and preserves cognitive function	autoimmune toxicity in the form of T-cell-mediated meningoencephalitis in 6% of patients caused by an Aβ-specific T-cell response (TH1-type CD4
CAD106(Novartis) *[12], [13]*	CAD106 coupled to the bacteriophage coat protein as an adjuvant carrier	Phase IIb study November 2015- Phase II/III trial Conclusion date - May 2024.	Bcell epitope found in the N-terminus of the Aβ peptide	Alzheimer's disease cognitively unimpaired APOE ε4/ε4 individuals between the ages of 60 to 75.	Preclinical trial - Preclinical testing of CAD106 showed anti-Aβ titres without activating a T-cell response and treatment reduced Aβ accumulation. Clinical trial- elicited an Aβ specific immune response.	Amyloid related imaging abnormalities (ARIAs) There was a larger decline in Mini-Mental State Examination (MMSE) in individuals eliciting a strong Aβ-specific immune response to CAD106.
ACC-001 *[14]*	contains a six amino acid sequence Ab1–6 connected to a carrier protein by the use of a surface-active saponin adjuvant QS-21	Phase 2 trials- terminated in 2014	fibrillized Aβ	Mild-moderate Alzheimer disease patients	Reduce brain Aβ plaques	An extreme strong autoimmune response
Affitope AD-02 *[15]*	a synthetic peptide of six amino acids that mimic the N-terminus of Aβ+B cell epitope	Phase 2 trials-	N-terminus of Aβ	early AD as diagnosed by episodic memory deficit and hippocampal atrophy	production of anti-Aβ antibodies while minimizing a pro-inflammatory TH1 response.	No complications
ACI-24 (AC Immune SA) *[16]*	an array of Aβ1-15 sequences adopting an aggregated β-sheet structure once attached to the surface of liposomes	Phase I/II study – completed in 2009 – results not published AC immune began dose-escalation Phase I trial for 24 months – completed, results not published	aggregated/fibrillized Aβ	mild-to-moderate AD. test in adults with Down Syndrome	Preclinical testing – reduced levels of insoluble Aβ40 and Aβ42, improvement in cognitive testing, and the generation of high anti-Aβ titers.	
ABvac40 (Araclon Biotech) *[17]*	multiple repeats of a short C-terminal fragment of Aβ40 conjugated to	Phase I trial - completed in 2015 Phase II trials from October 2017 - Ongoing	C-terminus of Aβ40	Alzheimer's disease	specific anti-Aβ40 antibody immune response	No complications.

	the keyhole limpet cyanine carrier protein with aluminum hydroxide as the adjuvant.					
UB-311 (United Neuroscience) *[18], [19]*	two Aβ 1-14 peptides, each coupled to a different helper T-cell epitope and packaged into a Th2-biased delivery system.	Phase I, open-label, uncontrolled trial-completed in 2011. 78-week Phase II trial – completed in 2018 – Terminated results not published	aggregated Aβ	Mild AD	Pre-clinical Testing - good immunogenicity in small animals, baboons, and macaques. Clinical Studies – The vaccine was well tolerated. high anti-Aβ antibody response. Improved cognition in patients with mild AD safety and immunogenicity with a 96% response rate. All secondary endpoints - including Amyloid PET burden, CDR-SB, ADCS-ADL, ADAS-Cog, and MMSE	Insignificant sample size
Lu AF20513 (H. Lundbeck, Otsuka Pharmaceutical Co., Ltd.) *[20]*	three copies of the Aβ1-12 (B-cell epitope) peptide separated by two different T-helper cell epitopes from tetanus toxoid.	Phase I trial in 2015 – completed in 2018 It is terminated and the results are not published	Aβ	Mild AD	enhances anti-Aβ antibody production by B-cells. aid immune response in an elderly population with reduced immune function. In preclinical testing, Lu AF20513 induced strong humoral responses in guinea pigs, Tg2576 mice, and monkeys.	
AADvac1 (Axon Neuroscience SE) *[21]*	tau fragment (amino acids 294-305) coupled to keyhole limpet hemocyanin (KLH)	Phase 1 trial completed Phase 2 trial completed-no results posted	Pathological tau regions	Mild-moderate AD	It produced high antibody titres specific for pathological tau and elicited a Th2 immune response.	It caused a higher rate of cortical atrophy and ventricular volume expansion in the AADvac1 treated groups. This raised safety concerns.
ACI-35 (AC Immune SA, Janssen) *[22]*	16 copies of a tau fragment containing phosphorylatio	Phase 1b trial-completed but results not yet posted.	Phosphorylated Tau	Early AD	It depicted strong antibody response to phosphorylated tau.	No complications

	n at residues Ser396 and Ser404 + adjuvant MPLA					

Table 2.2: Passive Immunization for Aβ and Tau Proteins

Name of the vaccine	Drug Candidates	Clinical trials	Therapeutic Target	Patient Population	Outcome	Complications
Bapineuzumab *[14], [23]–[25]*	humanized form of murine monoclonal antibody 3D6	Phase 1 trial – completed Phase 2 trial – completed Phase 3 trial-discontinued as it did not showcase significant change.	targets the N-terminal region of fibrillar and soluble Aβ	mild-to-moderate Alzheimer disease	lower plaque burden, improve measures of synaptotoxicity, and improve performance on mouse behavioral assays. Reduction in phosphorylated tau and fibrillar cerebral Aβ	Microhaemorrhage, ARIA-E, back pain, anxiety, paranoia, Deep-vein thrombosis, syncope, seizures, vomiting, hypertension, weight loss, skin laceration, gait disturbance, muscle spasm, and pulmonary embolism
Solanezumab *[26]–[28]*	humanized monoclonal IgG1 antibody	Phase 2 trials-completed Phase 3 trials-completed Dominantly Inherited Alzheimer's Network Trial -completed on Feb 10 2020-terminated	The mid domain of soluble monomeric Aβ	Mild-moderate AD	By sequestering Aβ, shifting equilibria between different species of Aβ, and removing small soluble species of Aβ that are directly toxic to synaptic function. Reduced cognitive decline in phase 3 trials. In phase 3 trial with patients with mild dementia, showed no significant change in cognitive decline.	As a result of phase 2 trials, no clinical benefit was observed. In later studies, No significant change in cognitive decline. It did not decrease the levels of brain atrophy. The DIAN trials failed because it did not show any significant change.
Donanemab *[29]*	humanized IgG1 monoclonal antibody combination therapy with N3pG and the BACE inhibitor LY2811376	Phase1 trial-completed Phase 2 trial-completed	Aβ(p3-42), a pyroglutamate form of Aβ that is aggregated in amyloid plaques.	Mild AD	It cleared more than 80 percent of cored and diffused amyloid from the brains of PDAPP-transgenic mice. It reduced the load of Aβ plaques	During the phase 1 trial, patients developed ARIA-E.
BAN2401 (Biogen, Eisai Co., Ltd.) *[30], [31]*	Humanized IgG1 version of the mouse monoclonal antibody mAb158	Pre-clinical study-completed Phase 1 trial – completed Phase 2 trial-completed Phase 3 trial – will be completed by 2024	large, soluble Aβ protofibrils	Mild-moderate AD	Preclinical study: It reduced Aβ protofibrils in the brain and CSF of Tg-ArcSwe mice Phase 1 clinical trial: The drug was well tolerated even at high doses. Phase 2 clinical trial: It reduced the Amyloid beta plaque burden and	Some of the patients developed ARIA-E.

					showed a reduced cognitive decline.	
SAR228810 *[32]*	monoclonal antibody engineered on an IgG4 backbone	Phase 1 trial - completed but no results are posted	soluble protofibrillar and fibrillar species of Aβ	Alzheimer's disease	prevented brain amyloid plaque formation and plaque-related inflammation	No complications
Crenezumab (AC Immune SA, Genentech, Hoffmann-La Roche) *[33]*	a humanized antibody with an IgG4 backbone	Phase 1 trial- completed Phase 2 trial – completed Phase 3 trials - halted	Multiple forms of aggregated Aβ, including oligomeric and fibrillar species and amyloid plaques with high affinity, and monomeric Aβ with low affinity.	mild to moderate AD	It cleared all forms of aggregated Aβ. The phase 2 trial did not showcase significant results. It was suggested to test higher doses in early AD patients	There was a significant increase in CSF β-amyloid1-42 levels. One case of amyloid-related imaging abnormalities indicative of vasogenic edema or effusions Phase 3 trials were halted as the study did not reach the primary endpoints.
Gantenerumab *[34]*	fully human IgG1 antibody	Phase 1 trial – completed Phase 2 trial- completed Phase 3 trial -	conformational epitope on Aβ fibrils Parenchymal and vascular aggregated brain Aβ	Alzheimer's disease	It disassembles and degrades amyloid plaques by recruiting microglia and activating phagocytosis. In APP/PS-1 transgenic mice, gantenerumab binds to cerebral Aβ, reduces small plaques by recruiting microglia, and prevents new plaque formation.	The phase 3 trial was halted due to many cases of asymptomatic ARIA.
Aducanumab *[35], [36]*	high-affinity, fully human IgG1 monoclonal antibody	Phase 1 trial- completed Phase 2 trial- completed Phase 3 trial - 221AD301 ENGAGE study -terminated as it did not meet the primary endpoints. 221AD302 EMERGE study - completed	a conformational epitope of Aβ aggregated forms of Aβ	Prodromal and mild AD	In a preclinical study, it was able to reduce levels of soluble and insoluble Aβ in a dose-dependent manner. It depicted a slower cognitive decline. It caused a dose-dependent reduction in brain amyloid and some CSF phospho-Tau reduction.	ARIA-E, headache, diarrhea, and dizziness
Gosuranemab *[37], [38]*	humanized IgG4 monoclonal anti-tau antibody	Phase 1 trial- completed Phase 2 trial – terminated as it did not meet the primary endpoints of the study.	Extracellular, N-terminal fragments of tau (eTau)	patients with progressive supranuclear palsy (PSP), Alzheimer's disease	Reduce and neutralize the toxicity of extracellular tau	No complications
ABBV-8E12(AbbVie) / C2N 8E12(C2N Diagnostics) *[39]–[41]*	humanized IgG4 antibody	Phase 1 trial – completed Phase 2 trial – ongoing – will be completed	aggregated, the extracellular form of pathological tau	Early AD	In P301S tau-transgenic mice, it was reported to reduce brain neurofibrillary pathology, insoluble tau, microgliosis, seeding	No complications

		by October 2020			activity by the lysate of the treated brain, brain atrophy, and deficits in the conditioned fear response	
RG7345 *[42],[20], [43]*	humanized monoclonal antibody	Phase 1 trial - discontinued	tau phosphoepitope pS422	AD	It will decrease levels of insoluble p422S tau. It will reduce the accumulation of tau.	No complications
Semorinemab *[44]*	anti-tau IgG4 antibody	Phase 1 trial – completed but results not posted yet. Phase 2 trial – completed by 2021	Extracellular tau	Mild-moderate AD	It reduced inflammation and reduced levels of extracellular tau.	No complications
BIIB076 (Biogen) *[45]*	Human recombinant, monoclonal anti-tau antibody	Phase 1 trial – Completed but results not posted yet	monomeric and fibrillar forms of tau	Mild AD	CSF tau and free tau is highly reduced	No complications
Zagotenemab	humanized anti-tau antibody derived from the mouse monoclonal antibody MCI-1	Phase 1 trial – completed but results not posted yet Phase 2 trial – ongoing, will be completed by 2021	neutralizes soluble tau aggregates.	Mild-moderate AD	It showcases low levels of aggregated tau.	No complications
JNJ-63733657 *[46]*	monoclonal antibody	Phase 1 trial – completed but results not posted yet	mid-region of tau	prodromal or mild Alzheimer's disease	Eliminate and inhibit the spreading of tau.	No complications

Currently, many potential treatments have been developed to treat AD, with active and passive immunotherapies being constantly developed. If a particle drug is being terminated during a clinical trial, the drug is not discarded. Instead, it is being repurposed. The researchers are trying to impart a better immune response by a combination of one or more drugs.

Both active and passive immunotherapeutics are both essential, but passive immunotherapeutics are more suitable and beneficial. Since AD is a progressive neurodegenerative disorder, it gradually worsens with increasing age. Due to this, the therapeutics being developed must be compatible with elderly individuals. Active immunotherapeutics cannot be used as they are coupled with strong adjuvants and might evoke adverse side effects that are not favorable to all age groups. Active immunotherapeutics provide a long-lasting response and are affordable to the majority of the population. Many plant-based vaccines are also being developed are under clinical study.Therefore, in the long run, immunization might be the ultimate cure for the prevention of AD.

2.2 Antimicrobial Therapy for Alzheimer's disease

Bearing in mind the antimicrobial hypothesis of AD, many antibiotic therapeutics have been developed that could combat the insoluble plaques made by the Aβ peptides as well as targeting the bacteria-as the characteristic nature of an antibiotic. Table 2.2 illustrates different antimicrobial drug therapies for AD.

Table 2.3: Antimicrobial Therapy in AD

Candidate	Stage	Duration of treatment	Mechanism of Action	Outcome	References
Doxycycline	Clinical Trials	3 months	Interference and neutralisation of AβOs' action and/or a direct anti-inflammatory effect	Memory recovery associated with lower neuroinflammation; disassembly of amyloid-β fibrils	[47] [48] [49]
Propranolol	Preclinical Trials	6 months	Decreases responsiveness to CNS noradrenergic stimulation	Reduction in Aβ levels in brain	[50] [51]
Rifampicin	Clinical Trials	3 months	Inhibits toxicity of pre-aggregated amyloid peptides; prevents amyloid cell interaction	Improvement in memory, reduction in synapse loss	[52] [53]
Gingipain Inhibitors	Clinical Trials	~ 11 months	Ameliorate infection, reduce Aβ42 peptide production, protect neurons from gingipain toxicity	Blocked amyloid-β1-42 production; Reduction in neuroinflammation	[54]
Cycloserine	Clinical Trials	~ 1 month	Inhibition of cell wall synthesis for incorporation into the bacterial cell wall	Significant improvement in ADAS-cog	[55] [56]
Ceftriaxone	Preclinical Trials	2 months	Selective and irreversible inhibition of bacterial cell wall	Increase in the density of pyramidal neurons in the hippocampal CA1 area	[57] [58]
Erythromycin	Preclinical Trials	3 months	Alteration in APP processing	Reduction in the amyloid- β1-42 levels in the cortex	[59] [60]
Minocycline	Clinical Trials	4 months	Mitigation of cognitive impairment	Reduction in brain inflammatory parameter and reverse spatial memory impairment	[61] [62]
Amoxicillin	Clinical Trials	2 years	Transpeptidation led activation of autolytic enzymes in the bacterial cell wall	H. pylori eradication	[63] [64]
Clarithromycin	Clinical Trials	2 years	Triple eradication antibiotic regimen	H. pylori eradication	[65] [64]

2.3 Effects of Probiotics and Fecal Matter Transplant (FMT) on Alzheimer's disease

Association between the gut microbiota and AD has been conjectured because of the part of inflammation in this pathology[66][67].The effect of this microbiome can be posited by either microbial infection, antimicrobial protection hypothesis or by either impaired immune system[68]. Probiotic bacteria have beneficial effects on the health of the host and prebiotics are substances which function as the nutritional source for the probiotic bacteria[69]. Healthy diet along with the supplementation of prebiotics and probiotics can delay the weakening of the neurocognitive functions as well as reducing the possibility of AD as well[70]. This can be understood by realizing the restoration effects of these gut microbes by ameliorating the effects of oxidative stress which is one of the pathological effect in AD[71][72].Study has been shown to prove favourable effects aimed at neuropsychiatric disorders by controlling gut microbiota, however, its effect on AD remains unclear[68]. Recent studies have also demonstrated the neuroprotective effects of Fecal Matter Transplant (FMT) against the action of AD by improving cognitive insufficiencies, synaptic dysfunction, Aβ accumulation and neuroinflammation.[73][74][75].FMT renders its effects by reverse altering the gut microbiota and the metabolites associated, such as few Short Chained Fatty Acids (SCFAs)[76]. As SCFAs are one of the most important chemical mediators of the gut-brain axis, it can be hypothesized that SCFAs like propionate, butyrate and acetate may exert neuroprotective effect that can be modulated by the gut microbes [73]. Also, studies show that butyrate provides neuroprotective effects like, modulating the functioning and maturation of microglia in brain and also along with propionate can interfere in Aβ1-40 oligomerization [77][78]. This can recommend the probable benefits of these bacterial derivate SCFA. It has also been observed that Proteobacteria quantity increases in the gut microbiome all through aging[79]. Moreover, Proteobacteria is also related to inflammation, which was linked to AD pathogenesis and increases the risk of dementia. [80]

2.4 Role of Stem Cells in Alzheimer's disease

Stem cells are the cells that have a specific function with the ability of self-renewal, possess varied potency, and differentiate into multilineages [81]. Stem cells are divided into various types based on their origin into mesenchymal stem cells(MSCs), perinatal stem cells, neural stem cells(NSC), embryonic stem cells (ESCs), fetal stem cells, placental stem cells, umbilical cord stem cells, adult stem cells, induced pluripotent stem cells (iPSCs) [82][83].Based on their ability to differentiate they are classified as follows totipotent or omnipotent stem cells, pluripotent stem cells, multipotent stem cells, unipotent stem cells[82].Stem cells in general are useful in a plethora of diseases like Parkinson's Disease, Type 1 diabetes, amyotrophic lateral sclerosis, osteoarthritis, etc.MSCs, with their distinguishing properties of differentiation potential as well as their migration abilities, are a promising candidate for use in regenerative medicine. Bilateral delivery of murine BMSCs into the dentate gyrus of the hippocampus was tested on an acute mouse model of AD, induced by injection of Aβ aggregates. As a result, Aβ deposits were reduced, likely due to the activation of surrounding microglia. A signal of microglial phagocytosis was indicated by the change of cell morphology from ramified to amoeboid[84]. A neuroprotective effect against Aβ toxicity, using human, MSC treatments, both in vitro and in vivo experiments wherein reduced neuronal death was observed in Aβ- treated neuronal cultures and in the hippocampal region of mice in which Aβ was injected into cerebral ventricles and MSCs in the tail vein. Increased neuronal survival was correlated to enhanced autolysosome formation and clearance of Aβ[85]. The effect of MSCs on mouse models of AD pathology and cognition may be mediated through modulatory effects on neuroinflammation[86]. Also, enhanced neurogenesis via the Wnt signaling pathway in the hippocampus is playing an important role in the effect of MSC on mouse models of AD[87]. The transplantation of human NSCs targeted to the fimbria fornix is safe and improves behavioral and pathological phenotypes in the APP/PS1 model, partly via an immunomodulatory mechanism[88]. The presence of neurotrophic factors, the activation of immunomodulatory molecules, and the increase in the expression of synaptic proteins have been implicated[89]. An ongoing phase II clinical trial with autologous AD-MSCs administered intravenously did not show adverse effects after 3 years (NCT03117738). Similar results have been found in other clinical trials (NCT02054208, NCT01547689)[15]. When MSCs were transplanted into a tail vein in a rat model of vascular dementia and found that levels of autophagy proteins of LC3-II and Beclin-1 were significantly increased, which indicated autophagy was associated with AD. Upon MSC transplantation, synaptic damage, mitochondrial agglomeration, and damaged presynaptic area were reduced and the hippocampal expressions of brain-derived neurotrophic factor (BDNF) and N-methyl-D-aspartate receptor 1 were increased, leading to improved cognitive function[18]. BM-MSCs were transplanted into the cerebellum of a Niemann-Pick type C disease mouse model and corrected increased sphingosine-1-phosphate levels and decreased sphingosine accumulation were observed. Therefore, it could reduce apoptosis, restore calcium homeostasis, and prevent neuron loss[90]. MSCs can be differentiated into endothelial cells with differentiation media containing vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF), epidermal growth factor (EGF), ascorbic acid, and heparin[91]. The delivery of β-site APP-cleaving enzyme 1 (BACE-1) siRNA, which targets β-secretase, resulted in 60% of BACE-1 gene knockdown, thus leading to a 55% reduction of Aβ level in the animals[92]. Direct injection of hUC-MSCs into the carotid artery of APP/PS1 mice was able to reduce cognitive loss and Aβdeposits in the cerebral cortex and the hippocampus[93]. In aged rodent models, transplanted MSCs were shown to undergo differentiation into neural cell types, increasing local concentrations of acetylcholine neurotransmitter, BDNF, and NGF, and improving locomotor and cognitive function[94].Thus stem cell therapy can possess a great potential in alleviating AD.

2.5 Role of Epigenetics in Alzheimer's disease

Epigenetics is defined as the branch of biology that studies the causal interactions between genes and their products, which bring the phenotypical changes into the human being. It involves genetic control by factors other than an individual's DNA sequence and can switch genes on or off and helps to determine which proteins are transcribed. It is involved in many normal cellular processes. Epigenetic mechanisms mainly aided in treating AD are DNA methylation, histone methylation, chromatin remodelers, histone acetylation, and deacetylation, etc. Histone acetylation (and its counterpart, deacetylation; HATs and HDACs) is one of many epigenetic mechanisms now identified as playing a significant role in long-term potential (LTP) and memory formation, observable through fear conditioning and spatial memory exercises [95]. Fear conditioning training using APP/PS1 mice has demonstrated decreased contextual freezing performance could be restored to wild type levels via acute treatment with Trichostatin A (TSA), an HDAC inhibitor. APP/PS1 chimeric mutant mouse/human transgenes result in AD phenotypes with Aβ plaque deposits accumulating by 6 months of age [96]. A mercaptoacetamide-based class II HDACi and a hydroxamide based class I and II HDACi both decrease β-amyloids in vitro by reducing gene expression of components and increasing degradation enzyme gene expression, which ultimately rescued learning and memory defects in AD mice while decreasing tau [97]. It has been shown that HDAC2 can differentially bind and regulate the expression of several learning and neuroplasticity- related genes, but that its viral-mediated depletion or its specific pharmacological inhibition is sufficient for restoring the synaptic and cognitive deficits observed in p25/Cdk5 [98],[99]. When cortical samples of APP swe/PS1dE9 mice–harboring the Swedish APP mutation in combination with the deletion of the exon9 of the PSEN1 resulting in increases Aβ formation and immunoprecipitation of the DNA using DNA methylation-specific antibodies followed by the hybridization of the resulting DNA to promoter microarrays. Following this approach, around 10% of analyzed genes showed higher levels of DNA methylation in the APP swe/PS1dE9 mice than in the controls, and no hypomethylated genes were reported[100]. The co-localization of PTK2B with hyperphosphorylated and oligomeric tau in progressive pathological stages in the brains of AD patients and transgenic tau mice, which strongly indicates PTK2B as a genetic risk factor for AD likely involved in the pathophysiological processes implicating tau, further suggesting PTK2B as an early pathological marker that shows high correlation with progressive tau pathology in AD[101]. A study previously reported that the methylation of PS1 by S-adenosylmethionine (SAM) results in decreased Aß production, thus preventing Alzheimer's[102]. Global DNA changes in methylation and acetylation that correlated with the progression of the pathology from earlier onset to final stages of the disease in 5XFAD, including neuronal loss, gliosis, and the disturbances in cognition and behavior present in this animal model of AD[103]. Early targeted regulation of tau hyperphosphorylation, inhibition of NFT deposition, and formation in the locus coeruleus and raphe nuclei are especially important for the prevention of AD[104]. The transgenic mouse models that had increased amyloid deposits which mimicked the amyloid pathology that is characteristic of AD, studied the phosphorylation of serine-57 and threonine-58 on H3, a histone greatly regulated by phosphorylation. Data showed a 40% reduction in serine57 phosphorylation and a 45% reduction in threonine-58 phosphorylation in these transgenic mice compared to wild type. Additionally, there was a 30% reduction of the doubly phosphorylated serine-57 and threonine-58 sites. This decline in phosphorylation is likely thought to result in a more repressed chromatin structure, which in turn aligns with the epigenetic blockage exhibited in Alzheimer's[105]. PLD3 gene is downregulated in the hippocampus of AD patients. Moreover, PLD3 expression inversely correlates with the β-amyloid burden, which adds evidence to the hypothesis that PLD3 protein may contribute to AD development by modifying APP processing[106]. Thus, epigenetic switches can pave the way in the treatment of AD.

2.6 Intervention using Medical Devices in Alzheimer's disease

The use of medical devices is aimed to aid towards to enhancement of cognitive processes. Neuromodulation via the use of therapeutic entities have witnessed limited success. The strategy involved is in the interception of formation of tau and amyloid proteins, consequent neuroinflammation and oxidative stress. The constellation of effects caused by protein deposition in the brain results in altered mitochondrial biogenesis [107].

Medical devices either use two strategies: invasive, non-invasive. Invasive techniques such as Deep Brain Stimulation (DBS) were found serendipitously upon conducting a study of DBS on candidates afflicted with obesity. Noninvasive techniques such as transcranial direct current stimulation, visual sensory stimulation, electroconvulsive therapy and photobimodulation have shown promise in the enhancement of cognitive function [3].

Table 2.4: Medical Devices in AD

Candidate	Stage of development	Duration of treatment	Mechanism of Action	Outcome	Reference
DBS	Clinical (pilot study)	12 months 2,6,12 weeks	Increases neurotransmitter release, glucose metabolism, neurogenesis and increased vascularization in the hippocampus	Restoration of hippocampal volumes, bountiful hippocampal and entorhinla neural activity. Reduced atrophy of the hippocampus,	[108], [109]
Transcranial direct current stimulation	Clinical (pilot)	10 days	The excitability thresholds of neuronal membrane are modulated. Enhances neuronal activity, modifies polarity dependency and aids in oscillations that can alter brain activity. Modify connectivity patters that confer functionality in the brain	Improves visual memory and recognition. Increased CBF(cerebellar blood flow), enhanced declarative memory and implicit memory.	[110]–[112]
Sonocloud	Pre developmental stages-Phase I/II of clinical trial	Implanted in the brain	Ultra sound is emitted upon implantation in the skull of low intensity. This is capable of advancing the permeability of the Blood Brain Barrier (BBB). This enables the entry of anti Aβ antibodies which otherwise show low penetration (0.3%)	The openings so produced are reproducible and are capable of delivery of drugs upto 2000kDa. A rise of upto 700% is observed upon the administration of carboplatin.	[2], [113]
Transcranial alternating current stimulation(tACS)	Preclinical/ clinical phase I	2-4 weeks	The stimulation applied is in synchronization with the neuronal activity which mediates sensory, motor and cognitive components. This results in a synchrony of the oscillation in the brain network. tACS is capable of correlation between cognitive processes and brain oscillations.	Bountiful enhancement of cognitive function, better retrieval accuracy. Clinical trials are underway in human beings.	[114]–[116]
Electroconvulsive therapy	Preclinical/clinical	24-27 weeks 6 to 12 months	Cerebral seizures are induced	Increase in BDNF levels. Contradictory reports on APOE-ε4 and beta amyloid level. Increase in grey areas of the Hippocampal regions	[117], [118]
Transcranial magnetic stimulation	Clinical I, Approved by Food Drug Administration (FDA) for depression	2-4 weeks, 1-6 months	Neuroplastic effects mediated by long term potentiation and long term depression.	Improved accuracy in verbal response, enhanced language neuronal network enhanced comprehensive task completion.	[119]–[121]
Photobiomodulation	Preclinical	4 weeks-2months	Reduction in hyperphosphorylation of neurofibrillary tangles reduced amyloid load. Soluble AβPPα and lowered pTau, Bax/Bcl2	Improved memory when tested on Y maze and Passive Avoidance (PA) test.	[107], [122]

III. Conclusion

The presence of 134 candidates pending approval in the year 2020 for Alzheimer's disease acts as a litmus to display the outpouring of research into better understanding the neurodegenerative disease. It also shows rapid attrition rate indicative of the lacunas left unexplored. One of caveats in treatment Alzheimer's disease may be due to the conservative approach that is employed in its treatment. The research community has centralized its effects onto two major culprits: neurofibrillary tangles and amyloid plaques. Perhaps it's time the research community changes its narrative and identifies key elements at the grassroots' level that can forever change the approach of translational research. With 10 million cases worldwide there is a need to shed light on lesser known counterparts that confer therapeutic benefit.

The vaccine trials aims to tackle the debilitating disease and have gained momentum, if fruitful; it can provide the best therapeutic alternative that is highly compliant. The understanding of the gut brain axis is indicative of the essentiality of our commensal friends in maintaining mental health. This is further validated by antimicrobial therapy and FMT studies and can expedite the process of phytochemical identification that can aid in better management of the menagerie of symptoms. In due course with valid cohort studies on a massive scale the epigenetic factors that make an individual more susceptible may be identified that can be either treated or eliminated.

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