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Current and Future Strategies for AD Therapy

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Authors' contributions

This work was carried out in collaboration among all authors. Author AJ designed the study and wrote the protocol, wrote the first draft of the manuscript and also did the literature search. Author OOF managed the animals. Author HDM collected all data and performed statistical analysis. Author AO did proof reading of the manuscript.

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Review Article

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ABSTRACT

Alzheimer's disease is an insidious disease of the brain. It is a degenerative and intractable neurological disorder that causes deterioration of memory, judgment, and reasoning in the elderly. About 46.8 million people worldwide are suffering from AD; prevalence is expected to affect 131.5 million by 2050. It is also characterized by myriad of syndrome, diverse theories and multi-factorial causes. It is a syndrome rather than a disease. Pathological hallmarks include; deposition of GPR3 protein in the brain which augment toxic amyloid plaques, abnormal deposition of tau proteins in neurons and its hyperphosphorylation into NFTs, increased levels of toxic amyloid β (Aβ) oligomers, neuronal and vascular death due to oxidative stress, inflammation or excessive action of the brain's immune cells-glial, among others. Currently there is no cure for it and much of the treatments have only been able to delay the progression of the disease. However, this paper attempt to provide update information on available pharmacological regimens and their effectiveness in curtailing AD as well as future therapeutic target.

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1. INTRODUCTION

The etiology and pathogenesis of many neurodegenerative diseases are mostly vague and shrouded in mystery, so also is Alzheimer's disease (AD). AD is a progressive, neurodegenerative disorder that mostly affects elderly people and is considered to be responsible for about 65% of all dementia in older people. About 46.8 million people worldwide are now suffering from AD, and disease prevalence is expected to affect 131.5 million by 2050 [1]. The annual incidence worldwide is estimated at 4.6 million cases which is the equivalent of one new case every seven seconds. It is a disorder whose syndromes, hypotheses and theories are multifactorial with debilitating effects and recalcitrant pharmacological management. The significance of AD is further compounded as the number of identified cases is estimated to double or triple in 2050 [1]. AD is an intractable disorder and currently there is no cure for it and much of the available treatments have only been able to delay the progression of the disease. This article is aimed to holistically review the current pharmacological interventions in ameliorating the debilitating neurodegenerative disease called AD.

2. ALZHEIMER'S DISEASE AND ITS PHARMACOLOGICAL INTER-VENTIONS

2.1 Current Pharmacological Regimens

2.1.1 Cholinesterase inhibitors (ChEI)

Despite the impressive amount of progress in understanding the molecular mechanisms behind AD, ChE inhibitors such as tacrine, donepezil, rivastigmine and galantamine represent currently almost the only employed approach for the treatment of AD [2].

The selective degeneration of cholinergic neurons that emanate in the forebrain proceeds to the cortex and hippocampus, the two brain parts that are responsible for learning and memory and this account for the substantial loss of cholinergic markers, such as choline acetyltransferase (ChAT), acetyl-choline (ACh) levels and acetylcholinesterase (AChE). ACh is associated with learning and memory and it is the deficit of this neurotransmitter that contributes to cognitive decline. The degeneration of these cholinergic neurons is attributed to amyloid fibril-induced neuronal toxicity, tangle formation, and astrocyte phagocytic activity [3].

Having said that, potentiating or engaging in ACh reuptake at the synaptic cleft reduces amyloidogenic processing and reduce tau phosphorylation by reducing the activity of protein kinase which phosphorylates tau. Therefore, disorderliness of cholinergic signalling pathway may lead to a feedback loop that increases production of neurotoxic Aβ through altered APP processing, increasing phosphorylation of tau protein by kinase thereby contributing to the progression of AD pathology [4].

Corroborating the aforementioned statement, restoration of the central cholinergic function through cholinesterase inhibitors significantly improved cognitive dysfunction and may prevent AD progression in patients. Cholinesterase inhibitors (ChEI) act by inhibiting the enzymes (acetyl- and butyryl-cholinesterase) responsible for the breakdown of acetylcholine hence increasing its availability at the synaptic cleft. Three ChEI's are widely available and include; donepezil, rivastigmine, and galantamine. They are considered symptomatic treatments as they improve symptoms without modifying the course of the disease.

I. Donepezil: Donepezil is a piperidine derivative that reversibly inhibits acetylcholinesterase [5].
II. Rivastigmine: Rivastigmine is a carbamate derivative that reversibly inhibits both acetyl- (AChE) and butyryl- (BuChE) cholinesterase [6].
III. Galantamine: Galantamine is a tertiary alkaloid agent that reversibly inhibits AChE [7].
IV. Memantine: Memantine is a N-methyl-D-aspartate (NMDA) non-competitive glutatmate receptor antagonist [8].

2.1.2 Beneficial of anti-diabetic drugs in Alzheimer's disease state

With myriad of studies suggesting a possible relationship between diabetes mellitus and Alzheimer's disease, several clinical trials are

being expected to establish an effective diagnostic and treatment modalities for Alzheimer's disease. There are variant opinions and reports concerning the effects of insulin therapy on the cognitive functions of dementia patients. While some studies report that insulin therapies exacerbate the risk of dementia in diabetic suffers other reviews suggest that insulin therapy helps in slowing down the cognitive decline in Alzheimer's disease patients. Regarding the pathophysiological finding a combined treatments of insulin and oral hypoglycemic medications was found to have encouraging therapeutic outcomes. This was evidenced by robust reduction in the level of the neuritic plaques in diabetes patients who are placed on both insulin and anti-diabetic therapies.

Considering the possible intricate relationship between the two disorders, and with a reasonable number of studies suggesting a positive outcome of anti-diabetic medications on cognitive abilities, a common pharmacotherapy is expected to be effective in controlling the course and progression of these two disorders. Be that as it may, researchers could not exclude the possibility that the beneficial effects of some anti-diabetic medications could be due to their inherent properties that are unrelated to their sugar-controlling effects.

2.1.2.1 Insulin therapy for AD patients

Insulin can be administered through oral, vaginal and other parenteral routes like rectal and transdermal routes to avoid gastrointestinal enzymes degradation [9] Intranasal Delivery of insulin via intranasal route as well as other compounds, is enabled by the direct neuroanatomical connections between the olfactory nerves and brain. This route of access to the brain is advantageous because anatomical modifications of existing therapeutic compounds may not be needed, especially when they are minute molecules. Another reason is that medications which could be used to treat neurological and psychiatric disorders may have limited therapeutic outcomes not unconnected to inadequate penetrance across the blood-brain barrier and therefore restricted ability to reach the CNS. Intranasal therapy bypasses these barriers and at the same time reduces unnecessary systemic effects. The finding that nasal mucosa accentuates and can deliver insulin to the brain suggest that nasal-to-brain transfer of insulin is normal. In, intranasal treatment provides a practical and noninvasive approach for treating cerebrovascular, behavioral, neoplastic, and neurophysiologic diseases, and may also enable quick and safe delivery of neuroprotective medications. Since normal neuroanatomical connections between the olfactory and limbic systems mediate memory, cognitive function, and behavior, intranasal therapy could be used to target neurodegenerative and psychiatric diseases.

Administration of insulin through intranasal route provides an efficient means of supplying the brain with insulin to counteract shortfall in production, transport, and responsiveness, reproducing the effects of systemic insulin but with avoidance of untoward effects. Intranasal insulin improves cognitive ability with respect to attention, and verbal and hippocampal declarative memory.

Furthermore administration of insulin through intranasal route was demonstrated to change hypothalamic activity, which regulates homeostatic and reward-related functions [13]. These findings suggest that brain insulin resistance can differentially affect cognitive and metabolic signaling pathways.

Administration of insulin through intranasal route results in direct movement of insulin from the nasal cavity to the central nervous system through intra-neuronal and extra-neuronal pathways that circumvent the blood brain barrier and minimize systemic adverse effects [9]. It is now well established that defects in insulin signals correlates with dementia, particularly in AD. Evidence suggests that CSF insulin declines with AD progression [10]. Intranasal insulin therapy provides an efficient means of supplying the brain with insulin to overcome deficits in production, transport, and responsiveness, reproducing the effects of systemic insulin but with avoidance of adverse effects. Intranasal insulin improves cognitive function with respect to attention, and verbal and hippocampal declarative memory [11]. One example of success along these lines pertains to the use of the rapidly acting insulin analog, insulin Aspart, which when administered intranasal, enhances memory without altering plasma insulin and glucose levels [12].

So the main advantage of administration of insulin through intranasal route is that it offers unregulated movement of therapeutic agents to the brain or CSF making it possible for higher

local levels to be achieved for disease specific targeting [14].

2.1.2.2 Incretins

As a substitute to insulin, another sanguine method is therapeutic administration of incretins, such as glucagon-like peptide-1 (GLP-1). GLP-1 is a potent antihyperglycemic hormone that induces the beta cells of the pancreas to release the hormone insulin in response to rising glucose, while suppressing glucagon secretion. The time taken for the concentration or amount of GLP-1to reduce to half is only but a short period of time and is quickly degraded or broken down by a degrading enzymes known as dipeptidyl peptidase-4. GLP-1functions by lowering blood glucose in persons with noninsulin diabetes [15,16] and increases or augment insulin sensitivity. The insulin sensitivity action of GLP-1is one of the germane considerations for its use and other allied molecules in the treatment of insulin resistance in Alzheimer's disease.

GLP-1 stimulates growth of neurons in the CNS and offers neuroprotective actions against glutamate-mediated excitotocity, oxidative stress, nitrosative stress, trophic factor withdrawal and apoptosis [17,18]. Furthermore, prevention of the degrading enzymes, dipeptidyl peptidase-4, which degrades GLP-1, mitigates or decreased oxidative and nitrosative stress, inflammation, cognitive function, and AβPP-Aβ deposits in an AD transgenic mouse model [19]. GLP-1 can cross the blood-brain barrier, and may effectively reduce brain AβPP-Aβ burden in AD [14,15,20]. Having known that GLP-1 has a short half-life and therefore limited practical use for long-term therapy, synthetic long-lasting analogues of GLP-1 have been generated and proven to be effective in preserving cholinergic neuron function [21]. The development of GLP-1 receptor agonists, such as Geniposide or Exendin-4, which harbor the same neuro-protective and neuro-stimulatory properties as GLP-1 [22], but have longer half-lives [16,19, 23,24], may provide effective and standardized long-term options for treating brain insulin resistance diseases such as AD.

2.1.2.3 Anti-hyperglycemic agents

Metformin is in the biguanide class. It works by decreasing glucose production, marketed under the tradename Glucophage among others, is the first-line medication for the treatment of type 2 diabetes. This is particularly true in people who are overweight It is also used in the treatment of polycystic ovary syndrome. Limited evidence suggests metformin may prevent the cardiovascular disease and cancer complications of diabetes. It is not associated with weight gain, neither does it cause cognitive dysfunction and CVD [25]. Metformin medication was found to potentiate the generation of both intra- and extracellular AβPP-Aβ due to over expression of BACE1 (β-site amyloid precursor protein cleaving enzyme) implying that metformin and insulin may have counter-effects on AβPP-Aβ aggregation, the administration of both insulin and metformin provided significant neuroprotection. Above all, polypharmacy reduced.

AβPP-Aβ levels, the intensity of AD pathogenesis including AβPP-AB neurotoxic plaques, and oligomeric AβPP-Aβ-mediated down regulation of the insulin receptor. These findings suggest that metformin therapy alone is dangerous due to aggravation of AD-type neurodegeneration [26], while the combination of insulin and hypoglycemic medications may benefit geriatric patients in the incipient stages of the AD by substantially improving cognitive performance and decreasing the rate of neurodegeneration.

2.1.3 Alpha lipoic acid (ALA)

ALA is a natural compound that augments mitochondrial function, serving as a cofactor for pyruvate dehydrogenase and alpha ketoglutarate dehydrogenase. Importantly, ALA enhances production of acetylcholine neurotransmitter by activating choline acetyltransferase and increasing glucose uptake so can be used to treat diabetes [27]. Therefore, the potential benefits of ALA are mediated by the supportive actions of ALA on insulin and GLP-1. However, beyond those effects, ALA has anti-oxidant effects, since it serves as an inhibitor of hydroxyl radical formation and can scavenge reactive oxygen species and lipid peroxidation products such as 4-hydroxy-2-nonenal [28], which are increased in AD brains [27,29]. In addition, ALA inhibits expression of pro-inflammatory cytokines and inflammation-associated nitric oxide synthase, which have important roles in mediating neuro-inflammation in the early stages of AD [30,31,32,33].

2.1.4 Familial/genetic predisposition and the role of nanotechnology in AD treatment

Two genetic / hereditary factors found to predispose a person to Alzheimer's (particularly early onset Alzheimer's disease) and these are either suffering from Down's Syndrome (a genetic defect) or a family history of dementia (a genetic / hereditary condition) as it seems there is a slightly higher risk of developing the condition if a first degree blood relative (parent / brother / sister) has developed it previously. Researchers have linked at least ten percent of late onset Alzheimer's to the inheritance of a gene mutation (on chromosome 14) that directs production of apolipoprotein (ApoE) – a cholesterol carrying protein. There have also been other genetic mutations identified that may account for a predisposition to Alzheimer's and these occur on chromosomes 1, 12, 19 and 21.

One of the treatment strategies of AD remission caused by genetic predisposition is the use of nanotechnology in which encapsulated nanoparticles in the form of small interfering RNAs (si RNAs) could silence genes encoding APP and tau in cell culture models [34]. The siRNAs could also have the potential to inhibit β and γ secretases that generate Aβ proteins. The siRNAs are very delicate and can get easily degraded in the physiological environment, so to maintain efficacy in vivo, the siRNAs must be delivered into the appropriate neurons. The delivery of siRNAs to neurons in the brain can be optimally achieved by encapsulating them in nanoparticles that can cross the blood brain barrier (BBB) or by expressing them in viral vectors, have demonstrated that silencing β-secretase activity using siRNAs delivered through lentiviral vectors reduced amyloid production in transgenic mice that express APP. Transitional blocking of APP using antisense oligodoxynucleotides reduced cerebral amyloid and acetylcholinestrase activity in Tg2576 transgenic mice.

2.1.5 Mitigation via inhibition of tau hyperphosporylation and prevention of tau aggregation

As the intensity of AD pathogenesis including AβPP-AB neurotoxic plaques, and oligomeric AβPP-Aβ-mediated down regulation of the insulin receptor. These findings suggest that metformin therapy alone is dangerous due to aggravation of AD-type neurodegeneration [26], while the combination of insulin and hypoglycemic medications may benefit geriatric patients in the incipient stages of the AD by substantially improving cognitive performance and decreasing the rate of neurodegeneration.

Tauopathies is associated with ailments that emanate from abnormal tau. Tau is a microtubule associated protein that usually binds to microtubule and plays a critical role in stabilization of microtubules. In tauopathies and AD, hyperphosphorylation of tau causes disorientation of tau from the microtubules, causes conformational changes which further form NFT. It is believed that the aggregating process of tau correlates with neuronal dysfunction, and in fact, the severity of AD is positively correlated to the number of NFT. Based on these findings many therapeutic strategies for treating neurodegenerative tauopathies have been elucidated, such as kinase inhibitors, microtubule stabilizing agents, immunotherapy and tau aggregation inhibitor [35]. Synergistic blockade of GSK3β and CDK5 have yielded positive results and have stimulated interest in the treatment of tauopathies and AD. Treatment with the GSK3 inhibitor LiCl have resulted in substantial decrease in phosphorylation of tau and has been shown to dramatically decrease tau aggregation and decrease in degeneration of axons in neurons of mice that have been genetically modified to express tauopathies [36].

Lithium chloride is nonselective inhibitor of GSK3β and GSK3α and can have a good number of other several adverse effects as a result of modulation of other targets effects making assessment of its capacity to block tau phosphorylation via GSK3β a herculean task. However, a well known selective GSK3 inhibitor AR-A014418 was also discovered to possess the capacity to decrease tau phosphorylation, filamentous tau, and degeneration of axons of neurons after oral administration for one month in tau transgenic mice [35]. An analog of AR-A014418 entered into clinical trials for AD in 2007, but its development has been hampered and has since been discontinued. Another selective GSK3 inhibitor, Nypta, is noncompetitive for ATP [37] and appears to be well tolerated and to improve cognitive function in a 4–6-week clinical trial. Although the study was not sufficient enough to be statistically significant and target engagement was not clear.

The intrinsic capacity of cells to remove abnormal tau proteins has been another tactic for

targeting aberrant tau proteins. One of the exact methods of removing aberrant tau proteins is by facilitating or augmenting the breaking down of tau proteins via the ubiquitination and proteasomal mechanism. Misfolded toxic proteins are broken down or degraded through tagging process catalyzed by an enzyme known as ubiquitin ligases. This mechanism can ostensibly be provoked with inhibitors of the calcium or magnesium ATPase activity of heat shock protein (HSP) 90, an intracellular chaperone involved in synthesis, folding, establishment of proper protein conformation and prevention of unwanted protein aggregation. Blockade of this HSP90 activity results in appreciable expression of HSP70, which work synergistically with CHIP (the carboxyterminus of HSP70-interacting protein) induces ubiquitylation of the improperly folded proteins [39]. HSP70 / CHIP is implicated in the degradation of a specific type of tau as elevated phosphorylated tau is seen in genetically modified CHIP in mice [40]. Having said that, disruption of Hsp90 heterocomplexes by the Hsp90 inhibitor can result in degradation of phosphorylated tau through HSP70 / CHIP in cell culture [39,41] and this decreases the expression of hyperphosphorylated tau in tau genetically modified mice [42].

In an effort to identify small-molecule that can provoke the degrading enzymes, ubiquitin-proteasome pathway is available to speed up the clearance of improperly folded nocuous proteins, the discovery that a proteasome-associated deubiquitinating enzyme, USP14, blocks proteasomal degradation of proteins by cutting or knocking off ubiquitin chains inspired a technological advanced high-tech screen to find inhibitors of USP14 activity [43]. The hit compound that emerged from this screen, known as IU1, reversibly blocked USP14 and did so eclectically over other deubiquitinating enzymes. IU1 could also provoke the breakdown of tau in a concentration-dependent manner in cell culture, and this tau degradation required USP14 and active proteasome complexes. The degradation of another protein suspected in neurodegeneration, TDP-43, was likewise enhanced by IU1, while ubiquitin-independent substrate of the proteasome was not affected.

Assemblage of monomers of improperly or abnormally folded tau can be broken down by the proteasome, but it is always an arduous task and practically impossible for accumulated forms of tau to be degraded as such accumulated tau substrate can hardly be threaded through the narrow gated ptoteasomal channel . However, protein aggregates as well as whole intracellular organelles can be getting rid off through an autophagic pathway [44]. In one form of such self consuming or autophagocytosis clustered proteins organelles are endocytosed into vesicles that then fuse with lysosomes for degradation. Some report are of the opinion that reduction of this process can lead to neurodegeneration [45]. Expanded polyglutamine proteins accumulate abnormally in intracellular aggregates and studies have shown that mammalian target of rapamycin (mTOR) is sequestered in polyglutamine aggregates in cell models, transgenic mice and human brains. Sequestration of mTOR impairs its kinase activity and induces autophagy, a key clearance pathway for mutant huntingtin fragments [46]. The immunosuppressant agent rapamycin can improve autophagocytosis and inhibit the hard insoluble plaques, the insoluble twisted fibers called NFTs, and cognitive dysfunction in an AD mouse model [47]. However, the safety of this agent for long-term treatment of AD in humans is a serious concern. Recent results suggest that trehalose also activates autophagocytosis, reduces insoluble tau, and has neuroprotective potentials in a tau transgenic mouse model [48], although trehalose has a plethora biological effects and the safety of this agent at chronic pharmacological doses is likewise vague. Other means of pharmacologically increasing autophagy that are more specific may be required, but even then, the resultant effects of chronic stimulation of autophagy are vague.

One possibility process in which antibodies prevent tau pathology is that they get into the neurons via endocytosis even though there are no reports to support it even if it happened, antibodies would have to somehow evade endocytic vesicles to have access to tau in the cytoplasm. Another probability is that tau is secreted from neurons in the brain cell to some degree and that allows the spread of tau pathological lesions from neuron to another neuron possible. In this case, anti-tau antibodies would interact with tau at synapses and interpret improperly folded or abnormal tau before it is taken up the adjacent neurons. Consistent with this idea is the fact that tau is found in the CSF and is considered a promising molecular biomarker of AD [49].

2.2 Pharmacological Regimens in Clinical Trials

2.2.1 BACE1 inhibitors

2.2.1.1 Miniature molecule BACE1 inhibitor: LY281136

Eli Lilly pharmaceutical was one of the companies to first manufacture and test orally bioavailable non-peptidic BACE1 inhibitors in humans. The small molecule BACE1 inhibitor with clinical trial number (NCT)-LY2811376 showed profound pharmacokinetic and pharmacodynamic characteristics in preclinical animal models that culminated into Phase 1 clinical trial in humans [50]. The failure of LY2821136 to reached phase 2 clinical research paved way for the emergency of LY2886721 to be the first BACE inhibitor to proceed to phase 2 clinical trials to determine its safety and tolerability, and pharmacology. The characteristic retina and brain toxicity observed in LY2811376 treatment was completely absent in LY2886721 paving way for Forty-seven healthy volunteers to be recruited into phase 1 clinical trial and were administered daily oral doses of either LY2886721 or pharmacologically inactive substance (placebo)for 14 days in Phase 2 [51]. Lilly satisfactorily completed six Phase 1 studies of LY2886721's safety, tolerability, and pharmacology in a total of 150 healthy volunteers and people with AD were given doses of 1–70 mg. Single and multiple ascending oral dosing also followed by repeat CSF sampling in the hours and days thereafter. This was done to assess CSF penetration and target engagement by way of measuring levels of the drug, BACE1 substrate, and BACE1 cleavage enzymes products. The compound was found to lowered CSF toxic levels of Aβ40, Aβ42, and sAPPβ concentrations respectively while increasing sAPPα, which is in tandem with expectations for BACE1 inhibition [52]. The success of phase 1 trial culminated in the commencement of the phase 2 clinical trial by Lilly to ascertain and compare the tolerability, efficacy, pharmacokinetics and pharmacodynamics parameters of patients suffering from MCI caused by AD [53] and substantial molecular biomarker evidence of brain amyloid deposition, but results from this phase 2 trial was disappointing with manifestation of obvious and severe liver biochemistries and this eventually bring the trial to a halt. Halting the phase 2 clinical trial of LY2886721 does not rub it off as a genuine therapeutic agent as clinical trial ethics demands that trial should be terminated when an unintended effect are observed as seen in abnormal liver biochemistries in this study.

Because of toxicity outcomes in long term preclinical studies, this compound is no longer progressing in clinical development even though its progression was terminated, LY2811376 etched its name as the first orally bioavailable non-peptidic BACE1 inhibitors that produces a robust A beta lowering effects in animals.

2.2.1.2 Miniature cocktail BACE1 inhibitor: Mk-8931

MK-8931 is a small-molecular cocktail inhibitor of BACE1 and BACE2 manufactured by Merck Company. The BACE1 inhibitor was tested in phase 1 clinical trial in healthy 88 adults as a two-part or two ways traffic randomized, double-blind, placebo-controlled Phase 1 clinical trial [54]. These results showed good tolerability without withdrawals side effects, dose-proportional increases in plasma and CSF exposure, and dose-dependent reduction in Aβ40 across the 2.5 to 550 mg/day administered to the study volunteers. These studies also involved repeated CSF sampling, which found that CSF Aβ was reduced by up to 90 percent .The success and positive results of the cocktail (MK-8931) Phase 1 and 1b studies or 1st and 2nd phase 1 study culminated in the commencement of EPOCH in November 2012. EPOCH was an 18-month Phase 2/3 trial comparing 12, 40, or 60 mg/day of the cocktail given as once-daily tablets to placebo in people with mild to moderate Alzheimer's disease. 200 people AD patients were treated in Phase 2 clinical trial this was expanded to Phase 3 with a total of 1,960 participants after an interim safety evaluation. This clinical trial included conventional cognitive and functional primary outcomes, as well as substudies for biological biomarker outcomes indicating changes in brain amyloid and CSF tau levels, and changes in brain volume. In November 2013, Merck began the APECS trial in 1,500 participants with the initial or early symptoms (prodromal) Alzheimer's disease, also known as mild cognitive impairment due to Alzheimer's disease (MCI). These patients have measureable cognitive deficits and a positive PET scan with the newly FDA-approved amyloid tracer flutemetamol, but are not functionally impaired [55]. APECS will compare the 12- and 40-mg once-daily dose to placebo, and treatment will last for two years. Set to run until 2018, this trial uses alteration from baseline on the Clinical Dementia Rating Sum of

Boxes (CDR-SB), a continuous measure, as its primary assessment and outcome. Secondary outcomes will evaluate a range of newer measures, including a cognitive composite, CSF tau, brain imaging of hippocampal volume and amyloid load, among others.

2.2.1.3 Miniature cocktail BACE1 inhibitor: AZD3293

AstraZeneca is a worldwide, innovation-driven biopharmaceutical company that prides and focuses on the discovery, development and commercialization of prescription medicines, primarily for the treatment of several ailments including AD. AZD3293 which is a 6-substituted isocytosine, is an inhibitor of BACE1, the β-secretase that cleaves the APP protein to release APP's C99 fragment. This fragment then becomes a substrate for subsequent γ-secretase cleavage and Aβ peptide generation. The rationale for using this cocktail is the fact that inhibiting BACE1 will reduce amyloid-related toxicity in Alzheimer's disease. AZD3293 has shown in Phase I studies to substantially reduce levels of dense and insoluble amyloid beta in the cerebro-spinal fluid of people with Alzheimer's disease and healthy volunteers. It is well tolerated with excellent safety profile in addition to possess exquisite pharmacokinetics and pharmacodynamics parameters with no serious adverse effects even with the highest dose administered. AZD3293 cocktail also possess additional advantage in that it displayed significant dose- and time-dependent reductions in plasma, cerebrospinal fluid, and brain concentrations of sAPPβ and sAPPα as well as Aβ40 and Aβ42 [56]. Concentrations in the CSF had similar timelines as the reductions in CSF Aβ40 and Aβ42 was also observed. The Phase 1 studies of AZD3293 in health subjects (NCT01739647) and AD patients (NCT01795339) have been completed, and AstraZeneca and Eli Lilly and Company have agreed to commence Phase II / III study of AZD3293, known as Amaranth trial and the planned initiation of a new Phase III trial for AZD3293, named Daybreak, which will study the safety and efficacy of AZD3293 in people with mild Alzheimer's dementia after positive interim safety data. Daybreak will begin enrolling participants in the third quarter of 2016.

2.2.1.4 Miniature cocktail BACE1 inhibitor: E2609

E2609 is another exquisite miniature cocktail orally bioavailable BACE1 inhibitor manufactured by a drug company called Eisai whose headquarters is in Tokyo, Japan. It was identified through FDBB screening and developed its BACE1 inhibitor through several series of bicyclic aminodihydrothiazines fused with unsaturated five- and six-membered rings. E2609 has shown robust cerebral Aβ reduction in preclinical studies and has advanced to a randomised, double-blind, placebo-controlled phase 1 clinical trial in healthy volunteers [57,58]. The trial comprises of two standard and separate but related phase 1 clinical trials in which 73 healthy volunteers who received single doses of E2609 between 5 and 800 mg (divided into nine cohorts), while another 50 individuals were administered E2609 doses between 25 and 400 mg on daily basis for 14 days. The drug E2609 showed tolerability at all doses tested for single use, with the most common adverse events included headache and dizziness. Individuals receiving repeated doses up to 200 mg had no clinically significant safety concerns. The result of phase 2 clinical trial of this cocktail presented at the end of phase 2 meeting suggested non-adverse safety indices at all doses according to an analysis of safety an pharmacokinetic and pharmacodynamic data from preclinical studies and also from study from phase 1 and the sanguine and encouraging results have culminated in the process of commencing phase 3 clinical trial in which the intended study protocol will be a placebo-controlled design in patients with early Alzheimer's disease where the treatment group will be administered a dosage of 50 mg / day of E2609 with the primary outcome endpoint assessed at 24 months. The primary endpoint will be the Clinical Dementia Rating Sum of Boxes (CDR-SB), with routine safety assessment.

It is a well known fact that most researchers in the field of neurodegenerative diseases therapy especially AD therapeutics are in a consensus believe that miniature cocktail that inhibit BACE 1enzyme activities are blazing the trail, in the forefront and are leading therapeutic approaches, other sanguine and potential techniques to reduce BACE1 processing of APP that produces the neurotoxic, densely and insoluble β-amyloid proteins are vigorously being pursued. Several studies have shown and attested to the fact that BACE1 levels are substantially increased in AD brain and might speed up the production of Aβ, a neurotoxic and densely insoluble proteins implicated in the pathogenesis of AD. Therefore, innocuous therapeutic strategies to exquisitely lower and

normalize BACE1 levels in the brain and slow down AD progression and avoid possible untoward side effects caused by direct BACE1 enzyme inhibition. In light of this, efforts are in the pipeline to elucidate or shed more light on the mechanisms of BACE1 elevation in AD in order to detect drug targets that could block the BACE1 increase when it is potentiated. Increasingly, studies have shown that BACE1 expression is tightly regulated at both the transcriptional and translational level and insight into the regulation of BACE1 gene expression may aid identification of mechanisms that lead to disease, illuminate the role of BACE1 in normal biology, and may suggest approaches to inhibit BACE1 therapeutically in AD patients [59,60]. Much evidence suggests that BACE1 is a stress induce protease that is increased by oxidative stress especially when mitochondrial respiratory mechanism are inhibited, hypoxia, which is shortage of oxygen in the body is a direct consequence of hypoperfusion and can facilitate AD pathogenesis, ischemia, inflammation are among other insults that occur in AD [61,62,63]. Several studies have also led credence to the fact that Aβ on its own potentiates BACE1 levels in neurons [64,65], suggesting a pathogenic chain reaction whereby Aβ could speed up its own amplification through BACE1 elevation. Which, if any, of these complex multi-layered regulatory mechanisms might yield therapeutic strategies for lowering BACE1 levels in AD is farfetched and vague, but unrelenting, unwavering and continuing research in this important area may reveal promising new AD drug targets in the nearest future.

Immunotherapy is one of the techniques deploy to reduce BACE1 processing of APP and therefore decreasing the concentration of Aβ in the AD brain .One of these mechanisms deploys antibodies by direct dismembering of plaques by conformation-selection of the β-secretase cleavage site of APP that sterically block access of the BACE1 active site to APP coupled with induced activation of antibody of microglial cells and phagocytosis of pathological protein deposits [66]. These anti-β-site APP antibodies then decreases the amount of Aβ production cultures cells and when injected intravenously and reduces amyloid plaque pathology in the brains of APP knockout mice mice [67].

Other immunotherapy approaches include anti-BACE1 antibodies that are directed to the non-active site that is completely different from the active site on the surface of the BACE1 catalytic domain that can allosterically regulate enzyme activity [68]. The non-active site is situated on the nearby structure of the C, D, and F loops of the enzyme and by noncomplement mediated phagocytosis [69]. The non-active site antibody binding to BACE1 changes the structural properties and dynamic features near the substrate binding site of the enzyme. Additionally, transport of BACE 1 antibodies across the tight barriers between the brain and the blood vessels (BBB) has been made feasible by engineering one arm of the antibody to recognize transferrin receptor (TfR), which shuttles transferrin across the BBB for the delivery of iron into the brain [70,71]. These bispecific BACE1-TfR antibodies accumulate in the brain and reduce endogenous Aβ levels in mice to a much greater extent than monospecific BACE1 antibodies. Moreover, TfR bispecific antibodies could be useful for treating other neurologic ailments amenable to immunotherapy. These antibody techniques both active and passive immunization are currently in preclinical phases.

2.2.2 Tau aggregation or assembly inhibitors (TAAI)

The assembly of tau into neurotoxic monomeric units or fibrils that makes blocking tau-tau interactions a reasonable strategy for therapeutic intervention. A number of screens in search of compounds that inhibit tau self-assembly have been carried out, and a good variety of compound types have been identified, including PE859 (3-[(1E)-2-(1H-indol-6-yl)ethenyl]-5-[(1E)-2-[2-methoxy-4-(2-pyridylmethoxy)phenyl]ethenyl]-1H-pyrazole), phenothiazines, porphyrins, polyphenols, cyanine dyes, aminothienopyrazines, and anthraquinones [72].

The most recently tau assembly inhibitor is the phenothiazine dye methylene blue (Rember). In 2008, this compound was reported to slow cognitive decline in a small Phase II clinical trial over almost one year, although this result was difficult to analyze and also the fact that the highest dose led to lower than expected drug exposures, and no evidence for target engagement was made known or reported [73].

Transgenic mouse model experimentation showed that high doses that reduced soluble tau levels also resulted in cognitive improvement [74]. Meanwhile phase III clinical trial would help clarify the efficacy of methylene blue in humans,

although such trial has not commenced yet. Although a second-generation methylene blue analog, LMTX, is believe to be in line for a Phase III trial.

2.3 Future Pharmacological Therapeutic Target

2.3.1 Genetic deletion of GPR3: A new concept to halt the progression of Alzheimer's disease

Study by Huang et al. [75] revealed a protein that appears to be a key to the development of Alzheimer's disease and this according to the researchers might provide a new drug target for dementia. Huang et al. [75] found that the deletion of the G protein–coupled receptor 3 (GPR3) gene, a protein expressed in the brain, alleviated the cognitive deficits and reduced amyloid pathology is a potential AD therapeutic target and provides the validation needed for future development of GPR3 modulators.

2.3.2 Modulation of β- and γ-secretases: A potentials therapeutic target for AD intervention

Alzheimer's disease (AD) is characterized by is characterized by an accumulation of abnormal plagues, and tangles in the brain in the form of filaments. Amyloid β (Aβ) peptide is a major components of senile plaques formed as a as a consequence of the beta and gamma proteolytic secretases cleavage of the neurotoxic Aβ proteins. It is over two decades that the proponents of β-amyloid theory came up with the proposal that Aβ peptide deposits, the sticky peptide and even the partially accumulated insoluble peptides are primarily the influential driving agent responsible for the pathophysiology and other cascades of events like neurotoxicity and NFTs which eventually culminated in neurodegeneration [76]. The pathological hallmark of Alzheimer's disease (AD) needed for confirmation of AD diagnosis are the extracellular plaque deposits of the β-amyloid (Aβ) peptide and neurofibrillary tangles of the microtubule binding protein tau. Results have shown that amyloid deposition begins at about the ages of ten to twenty years before the onset of cognitive decline, suggesting that cerebral accumulation of Aβ plays a role early role in the pathophysiology of AD [77].

This is in tandem with the notion that inhibition of Aβ accumulation in the brain is crucial and may led to the remission of AD symptoms, if given early enough during the course of the disease. Aβ are generated in the brain mainly by neurons, transmembranous amyloid precursor protein after proteolytic cleavage by beta and gamma secretase although glia, especially astrocytes, may also contribute to Aβ generation, particularly during normal stress that causes glial activation as happens in AD. The formation of Aβ is a sequential and well orchestrated proteolytic mechanism that started with the cleavage or cutting of amyloid precursor protein (APP) by the β-secretase enzyme, which generates the amino (N) terminus of Aβ and yields the membrane bound C-terminal fragment C99 [78]. Gamma-secretase cuts C99 to release Aβ, which is secreted from the cell [79,80]. Unfortunately, the γ-secretase cut is imprecise and generates Aβ isoforms of different sizes and lengths at the carboxy (C) terminus, of which the longer isoforms are highly associated with AD. Generation of APP, the forerunner of the dreaded and neurotoxic plaque by both β- and γ-secretases is necessary for the generation of Aβ, suggesting that inhibition, proper clearance and modulation of either or both of these proteases in the brain will attenuate AD progression.

3. CONCLUSION

In the meantime, however, new researches should be initiated towards finding a cure for the disease and one o*r* more of the current pharmacological strategies should be invigorated with the hope that the cure that has been elusive for the past ten decades is found. More researches should focus on the attenuation of the two pathological hallmarks, hyperphosphorylation of tau proteins and the elevation and accumulation of abeta especially the very latest discovery involving genetic deletion of GPR3 protein. The protein thought to be largely responsible for the buildup of beta amyloid plaques in the brain so these efforts should be vigorously pursue and sustained couple with Unwavering and philanthropist financial support by well meaning individuals who want to see and ensure that a cure for this insidious, intractable but surmountable disease called AD is found.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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