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A HOLISTIC PERSPECTIVE ON PSYCHOGENIC MALADY: ALZHEIMER

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ABSTRACT: Alzheimer's disease (AD) is an irrevocable most run-of-the-mill neurodeteriorating disease which comprises of lapses in the memory due to the disfigurement of synapse & neurons that leads to numerous types of dementia. As per the outline *via* (WHO) ICD-10 Mental & Behavioural Classification of Dementia, AD is persuaded by distinctive peculiarities of encephalon by either accretion of Amyloid-β, Neurofibrillary tangles, Insulin Resistance or Free radical generation. On top of that, genetic alteration in TREM-2 modified macrophages in encephalon depicts vast clinical manifestations according to different scalings with scorings. These scores are given by dint of the symptoms evinced with the help of newly retrieve diagnosis markers to prevent the wild mood disorder complications alongside rare organ failures. The numerous methodologies are great headways that makes a grateful resulting impact in the field of AD. Ahead of the times information & a wholistic perspective towards holistic malady can make a great avenue to recuperate in bucket of psychogenic malady.

INTRODUCTION: It is an irreversible, anatomical neurodegenerative disorder wherein there is gradual dwindle in memory and cognitive functions due to the synapse deficit and Neuronal demise (i.e., neuronal atrophy) portrayed by Amyloid plaque, Neurofibrillary Tau tangles accumulation throughout the hippocampus and the cerebral cortex. Alzheimer's disease (AD) is polygenic lingering disease manifesting an amnestic and non-amnestic cognitive impairment (i.e., Working, semantic, episodic, protracted period memory, especially explicit memory remains unscathed), language, intellect and capacity to resolve problems, metamorphoses in behaviour moreover conclusively deaths but the earliest symptomatic stage of cognitive impairment in AD is the mildly impaired cognitive function or Mild Cognitive Impairment (MCI) whereby functional skills are mostly retained while potentially having an influence on one or more cognitive domains that are impacted, however mildly [1].

In contrast, The Classification of Mental and Behavioural Disorders (WHO) ICD-10 outlines Dementia as a syndrome spring up because of disease brought on by many illnesses which affects cranial frameworks and processes that lead to a steady decline in memory, additional mental processes plus behaviour with impairment in the daily functional activities that are performed every day [2]. Originally, the AD is rift within two circumstances relying on onset of age, based on initial symptoms affecting individual fewer than 65 years of age is categorised as a presenile dementia. However, following the groundbreaking research of

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Tomlinson, Roth, and Blessed *et al*., a comparable dementia in the elderly, that is, in those over 65 was named Senile dementia of the Alzheimer type. Despite the fact that age-based categories are still widely applied, it is still unable to show a dual-modal age distribution of onset and is widely acknowledged as the entity whose prevalence increases noticeably after the age of 65 [3]. As such, AD has to be set apart from other different sorts of dementia, such as Vascular dementia, dementia triggered by Lewy bodies, dementia along with Parkinson's disease, Frontotemporal dementia, as well as reversible dementias [4] **Fig. 1.** In which, the *Vascular dementia* (10-15% among all dementia) is the second most more assorted dementia than AD and it is transpired when the blood supply to the encephalon gets interrupted by the vascular disease (that may be either due to Diabetes or Smoking) which eventually results in curtailed nerve cell dysfunction and ultimately leads to demise encephalon [5]. While, Dementia tied to Lewy bodies (10% of instances) exist thirdly most prominent and closely links with AD and Parkinson Disease which imparts a cognitive dysfunction in last dementia & evidence of affliction are visual hallucination, increase in awareness regarding consciousness & incubus during sleep [6-8]. The *Frontotemporal dementia* is a super ordinate grouping word affecting various areas of the front of encephalon, which is responsible for emotion, language (called as semantic dementia), motivation & planning while evidence of affliction is defective empathy, change in eating habits with difficulty in speech translation [9].

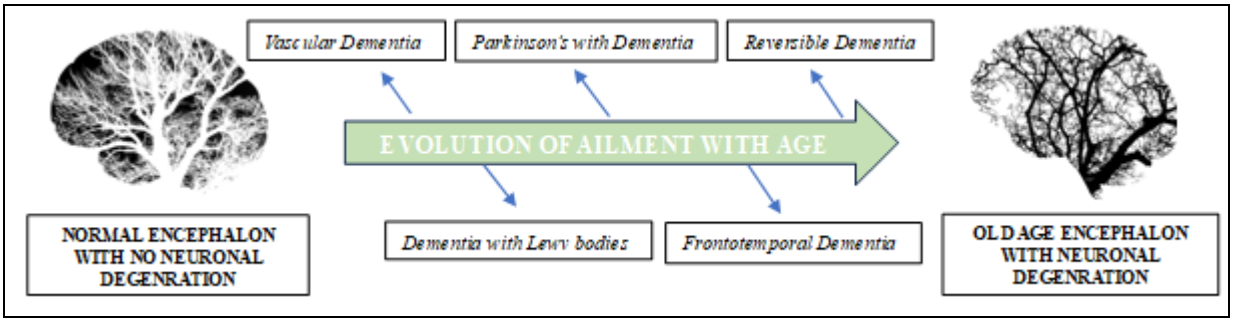

FIG. 1: SCHEMATIC CLASSIFICATION OF AD

Epidemiology: Dementia is the seventh prime most pervasive and the most predictable sort of Alzheimer disorder which encompasses about 60 to 70% all memory loss either in adults 3-4% amidst their former working or seclusion. Multiculturally, studies intimate 50 million citizenry are woe from memory loss apart from which 5% are from USA which reach roughly threefold since 2050 as well as 68% in miserable & third estate persons as demonstrated by meta-analysis that discovered disease impact 7.13% of women & 3.31% of men i.e., mostly women are hit hardest than men by virtue of biological evolutionary distinctions while they are mostly the cradlers, and by systemic review in which all five studies that examined prevalence in men & women revealed a greater prevalence in women [10]. Plenty of surveys in the USA also proves the racial differences related with disorder (worse order in Black beyond white on analysis *via* cerebral activity) [11]. Although, such usualness is nearly twice in women across European continents & Some studies of India with US also shows no reciprocity between the education qualification or gender specificity relating with Alzheimer disorder while the prevalence of AD in India associated with innumerable ailments like all diseases but studies shows dental unhygiene (like inflammatory gums disease etc) is 95 % firmly believe to be collateral with Alzheimer disease in India [12, 13]. On a global scale, AD is the third principal cause of higher fatality rate with 4.4% in 2016 while in 2017, there is 46.4 % dementia allied were owing to AD. And "The World Health Assembly (WHA)" also recently ratified the plan world-wide for the health crisis management in 2017-25 for dementia calling though further effort to implement the measures for pressing health crisis i.e., Alzheimer's Disease [14].

Risk Factors: AD is linked with a scattering of risk factors as it is deemed as a polygenic disease **Fig. 2.** Ageing & gender, inborn factors are the static risk factors associated with AD whereas head cranial trauma, locular afflictions, infections, style of life and ecological factors are dynamic risk factors associated with AD. Although, precise

mechanism in the cause of AD *i.e.* (β-Amyloid, & NF knots provokes synaptic demises) is still obscure. Manifold conjectures underlying the cause of AD looked proposed but the most two important conjectures comprise of the β-Amyloid hypothesis and the cholinergic hypothesis. However, in present there is no proper approved thesis for the pathogenesis of AD [15].

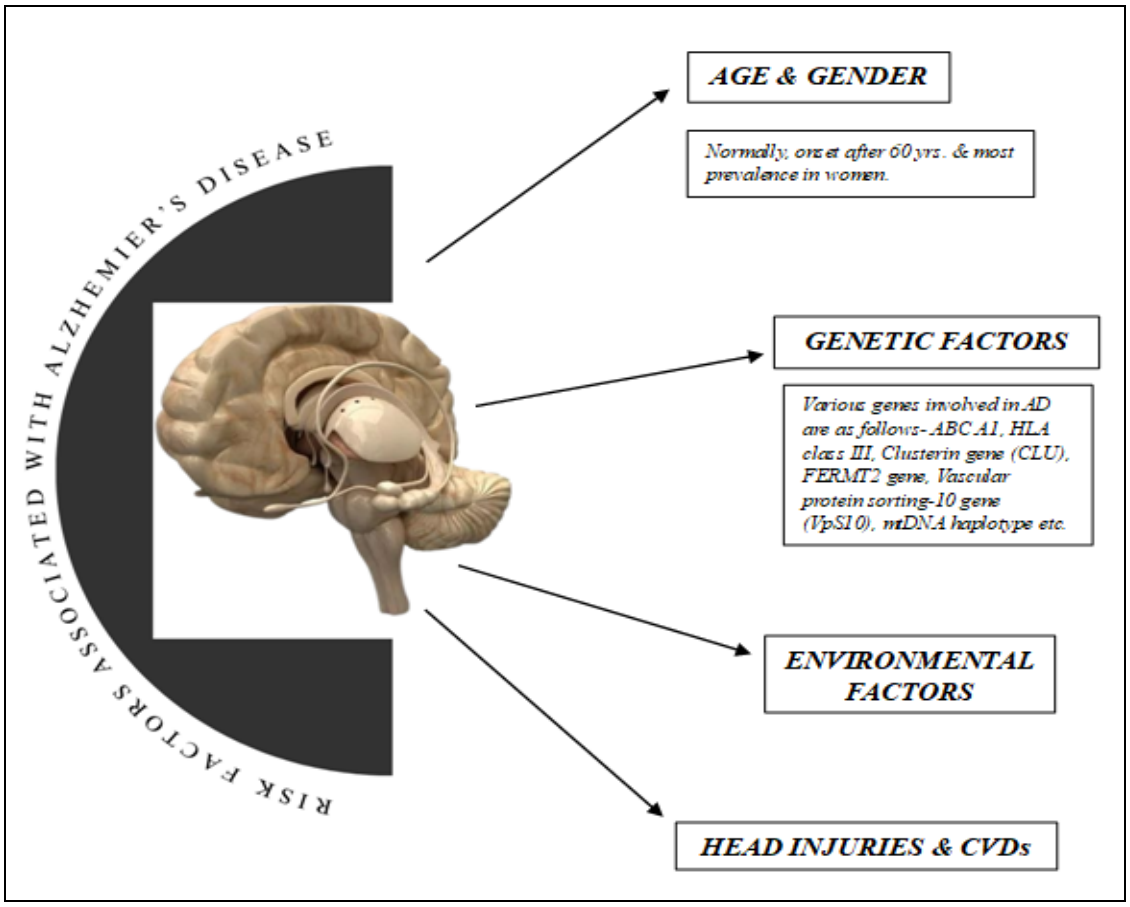

FIG. 2: RISK FACTORS OF ALZHEIMER DISEASE

1. Ageing and Gender: Ageing is the one of the core challenge which is involved in every complex and irreversible diseases as a risk factor mainly in those diseases which involves the cognitive impairment in old age persons due to the decrease in the various factors having impact on Anatomy & Physiology of encephalon with imbalance condition arises during ageing like glucose metabolism, homeostasis of cholesterol & depression *etc* [16]. According to various studies which suggests the women have 2/3rd of prevalence than men due to Anatomical & Physiological differences between them [17].

2. Genetic Factors: In the intervening years, assorted genes for AD emerge as [18]:

(A) Amyloid Precursor Protein (APP): The permutation in APP glycoprotein (i.e., intracellular & extracellular domains) which is present on chromosome no. 21 & cleaved by various proteolytic enzymes (i.e., α-, β-, γ- secretase) from respected sites as thence to formation of β-amyloid peptides and hastens AD [19]*(specifically, $A\beta_{40}$ & $A\beta_{42}$ residues).*

(B) Presenilin 1 (PSEN-1) as well Presenilin 2 (PSEN-2) PSEN-1 (more commonly) & PSEN-2 (rare) i.e., core proteins present on Chromosomes 1 and 14 respectively are somehow correlated with APP cleavage & leads to Aβ formation & the transmutation in these genes lead to abnormal $A\beta_{40}$ / $A\beta_{42}$ & rise $A\beta_{42}$ which prompts AD [20].

(C) Apolipoprotein E(ApoE): The ApoE (i.e., glycoprotein) perched upon chromosome 19 contains a gene which pairs for contrasting traits *i.e.*, Alleles of ApoE that are ApoE 2, ApoE 3, ApoE 4 & ApoEε4 etc. As notably, correlated with lipid metabolism & hematoencephalic barrier

likewise, hastens neuritic atrophy yet literal mechanism is unknown [21].

(D) Other units of inheritance i.e., Genes like ATP-binding cassette transporter A1 (ABCA1), Oestrogen Receptor Gene (ESR), Vitamin D receptor gene (VDR), Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), Transferrin gene (Tf), and Epigenetic factors etc are also allied with an odd of burgeoning AD [22-24].

3. Environmental Factors: Environmental factors like Infections either by viruses, bacteria or any other ecological factors like pollution consisting of heavy metals, diet, chemicals etc affecting CNS leads to AD due to either by of viruses (i.e., herpes virus etc) in encephalon, further leading to abnormal protein synthesis by forming NFTs & Aβ deposition or by oxidative stress generation consisting of inflammation. The invasion in BBB cells can also affects cognitive functions as found in recent studies with loyal viruses, such as Human β-herpes virus 5 (i.e., cytomegalovirus, CMV), Human γ-herpes virus 4 (i.e., Epstein-Barrvirus, EBV) & Herpes sapiensvirus-6 (HHV-6) with secondary prevalence by dental infections & fungus [25, 26].

4. Head Injuries: The bursting injuries to the encephalon damage leads to wrecking of the cognitive abilities with motor functioning and leads to abnormal β-amyloid stacks with NFTs formation which causes axonal damage notably seen as primary clinical utterance in the traumatic cases of which mechanism is not yet cleared [27].

5. Cardiovascular Diseases: Several vascular diseases (*i.e.,* Atrial fibrillation, Stroke, Heart Failure *etc*) which are having major mechanisms as the depletion of regular blood supply & hypoperfusion to the encephalon causing a neuronal demise with arrhythmia. Moreover, it would arouse to the failure of soul organ of circulation (*i.e.,* heart) thus, hypoxia of encephalon can lead to AD [28].

Etiopathogenesis: The conceptual physiology behind the AD is the accumulation of the β-Amyloid protein & Neurofibrillary tangles as a consequence of breach of the progenitor protein viz amyloid precursor protein (APP) *via* mutual action of β-secretase (BACE-1) & γ-Secretase enzyme which lead to the destruction of 36-43 residue i.e., Aβ-chain into the corpora amylacea which is protected from cleavage but as a result consolidate with debris on the neurons and in neuronal area which includes activated cells forming the BBB (i.e., Astrocytes & Microglial) & first unveiled in neocortex region of the encephalon that is the Largest lobe (frontal lobe), the lateral lobe (temporal lobe) & the posterior lobe (occipital lobe) which is involved in higher mental function & throughout the various neocortical regions. They spread to entorhinal (i.e., involved in attention & emotion etc) and hippocampal areas (i.e., involved in the learning and memory). Furthermore, the fact that NFTs were only discovered in areas where amyloid was already present which suggests that the disease caused by amyloid appears to develop beforehand that was caused by tau & numerous investigations have demonstrated that the aged individuals above 65 with normal cognitive function can also have substantial amyloid β deposition [29-31].

Neurofibrillary tangles are the occasionally solitary straight filaments produced intracellularly and consist of Paired Helical Filaments (PHF) which are mostly constituted of an aberrant hyperphosphorylated version of microtubule-associated protein Tau. Numerous kinases, such as microtubule affinity regulation kinase, cyclin-dependent kinase-5, and glycogen synthase kinase-3B may contribute up to until phosphorylation of microtubule associated protein (i.e., Tau) within disease Alzheimer in the encephalon [32].

The function of tau protein is to stabilize the microtubules and lead to the formation of cell organelle i.e., cytoskeleton of the cell & if that phosphorylated tau doesn't gets dephosphorylated then it will be unable to bind to microtubules, hence it will not get abbre*via*ted into a straight chain and due to which the cross linking as PHF-tau i.e., Neurofibrillary Fibrillary tangles formation takes place which further reduces the ability of stabilization of microtubules and leads to disruption of transport in the neuronal cells which cause the death of nerve cells due to the key alterations of metabolic and oxidative stress generation. It will further damage the mitochondrial energy production due to the presence of sufficient reactive oxygen species which leads to the

activation of programmed cell death pathways (either by the mitochondrial permeability pore transition or the Bcl-2 members insertion through mitochondrial membrane) mediated by mitochondria. It plays a critical role among the initial stage towards progression of Alzheimer's disorder [33]. A dysfunctioning in mitochondria and their destruction due to Apoptosis can also leads to loss of cholinergic neurons in the basal part of prosencephalon with synaptic demises & these Neuro Fibrillary Tangles numbers formation in the encephalon regions can positively relates with dementia criticality while the tangles presence in the CSF can also used as the diagnosing marker of AD [34].

Additionally, there are some theories & facts that proves that the diabetes also doubles the cases of dementia and Alzheimer's disease by including the Insulin Resistance (I.R) (in the late stages) and various Insulin Receptors in different ways either by alteration accordingly to glucose level which is correlated with energy production which somehow links with deficiency of energy which can lead to *Oxidative Stress* (O.S) with Free Radicals Generation [35].

The Insulin hormone which acts as important part in cascade of glucose maintenance ought to also yield a Neuroprotective effect (like, proved as certain hormones that can help to encephalon to work optimally) during low blood supply to an organ (i.e., Ischemia) over and above that it has been asserted that glucose controlling 51 amino acid peptide chemical messenger with metabolic inhibitors (as held in gene-spliced mouse Tg2576 along with wild type) reveals the impact of increased levels of both β-secretase & β-Amyloid levels. Likewise, Tau protein which plays crucial role in AD can also be exalted due to hypoglycaemia in which the glucose transporters that gets altered having impact on blood brain barrier of AD patient owing to long term medication uses, due to which low blood glucose level arises having interrelation between many diseases includes vascular diseases affecting encephalon & soul organ of circulation in body (*i.e.*, heart). In the vascular diseases, inflammation or people having inflammation (either due to high markers denoting inflammation or reported role of expression alteration of gene TREM-2 modifying macrophages collateral plaque & levels of β-amyloid) culminating in toxicity due to highly spur of BBB cells (i.e., microglial cell) due to which increase of β-amyloid boost the cell eating property (i.e., phagocytosis) but due to hyperactivated response, the Inflammatory markers get augmented (like, ROS). Thus, the inflammation also gets influence by Tau pathogenesis [36-39].

Clinical Presentation: The most classic features in patient affected with Alzheimer disease, some individual with insidious, developing dilemmas cored on sporadic memory shows cognitive difficulties which in turn become more intense and prevailing to intrude with activities of day-to-day life for that the patient is interpretated with the AD memory loss & next in the disease behavioural changes, impaired agility, illusions, and spasms may arise and end in death from the symptoms after 8.5 yrs [40]. While several unusual symptoms also recognised notably during new onset age due to atrophy of cortical region of posterior side of a unit of encephalon i.e., Neurons, progressive affective language abilities & frontal lobe dementia etc **Fig. 3**. In such cases, it might be recognised by proper interpretation of indications with help of decorous scalings & variety of studies uses distinct scalings for various psycho-neurological conditions few are listed below [41].

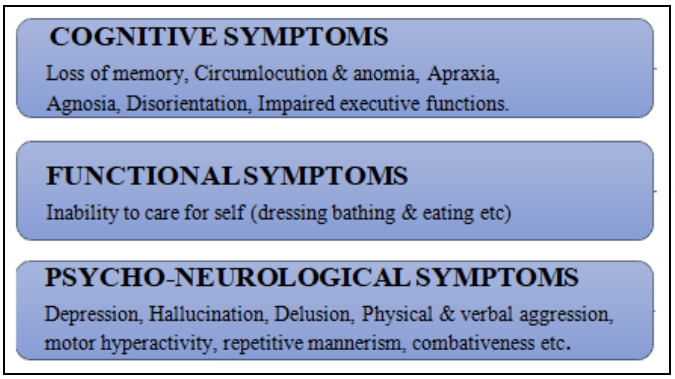

FIG. 3: SYMPTOMS OF ALZHEIMER DISEASE

Montreal Cognitive Assessment (MoCA): In order to resolve the shortcomings of the MMSE (Mini-Mental State Examination), the MoCA was created as a quick screening tool for mild cognitive impairment and mild AD. The MoCA is split down into 7 subscores:

- Language (3pts),
- Abstraction (2pts),

- Orientation (6pts),
- Visuospatial (5pts),
- Name (3pts),
- Memory (5pts for late recall),
- Attention (6pts) & Language (3pts),
- If the subject < 12yrs of schooling, 1pt is added.

Mini-Mental State Examination (MMSE) -

a. Severe (MMSE Score 0-9): If the patient becomes unable to move, talk, or feed himself excrement & urine incontinence. Needs care 7 days a week, twenty-four hours a day.

b. Moderate (MMSE 10-20): If the patient needs help with everyday life tasks, often confused about the time (date, year, season). Memory for recent events is seriously compromised, may forget names of family members & acquaintances as well as certain specifics of prior life occurrences, the way by which work could change day to day. Typically, the patient denies any issues & may start to cry or show suspicion, become incapable of driving safely; Delusions, Anxiety and Agitation are typical.

c. Mild (MMSE 21-26): If the patient is having trouble recalling recent events, declines in the capacity to prepare meals, handle money, & perform other home tasks, can become disoriented when operating vehicle, starts to give up interests and retreats from challenging activities, might dismiss memory issues.

Diagnosis Markers: With the help of various imaging techniques like imaging *via* magnetic resonance (viz Magnetic Resonance Imaging, MRI) as well as *Computational tomography (CT-scan),* the verdict of AD somehow makes easy and very informative either by investigating markers involved in AD physiology like in CSF p-Tau 217 which links with advanced stage (i.e., phosphorylated form of tau protein), p-Tau 181 in plasma which links with cognitive dysfunctioning in disease [42] & protein blood marker pLG72 which differ AD patient from normal healthy patient while the accumulation of Amyloid in encephalon can be detected by Positron Emission Tomography (PET) for the identification of precise manifestations clinically [42, 43]. Some other certain markers like *Serum Vit-B_{12} levels, T_3& T_4 levels, HIV testing, several hepatic, renal markers & SLC7A11genetic marker* (accommodates by cysteine/glutamate Antiporter which also regulates the release of glutamate) with pLG72 detection proves the prime & best outcome whether an individual is suffering from disease or not [44-45].

Complications: The intricacies of the AD are multifarious by virtue of disturbances in the behaviour displayed in many of the patients suffering from the Alzheimer's disorder in which the apathy (i.e., loss of motivation, mellow interest, deteriorated sociability & manifests in the behaviour etc) is intensely analogous which is commonly found due to imbricate in symptoms and may lead to confusion with low mood disorders & dysphoria which appears to occur less frequently as found better researched [46]. The amid of loss of motivation, which is the most common trait, major depression collocates with neurocognitive regions of encephalon mainly striatal region with limbic circuit of sub-cortex while the circulatory failure (i.e., hypoperfusion) to multiple regions of encephalon are also recognized in dejection & sluggishness [47]. Even though a bit of research shows the fatalities owing to pneumonia among the populace sorrows from pneumonic illness (either necrotizing or anaerobic type of aspiration pneumonitis), odynophagia, nasogastric feeding & bedbound are intertwined with heinous Alzheimer's affliction or in mild phase of affliction [48]. Apprehension and Belligerence are widely two well-known in people possessing neuropsychiatric disorders [49].

Recent Headways in Alzheimer's disease: Earlier, the four Drugs that were endorsed for the treatment of Alzheimer disorder by FDA are Memantine, Donepezil, Rivastigmine & Galantamine which emerged as first line approach for AD because of their safety credentials and promising adequacy out of which the rivastigmine, galantamine & donepezil are the main brain chemical enzyme inhibitor (i.e., Acetyl cholinesterase) notably chosen to attain the proper therapeutic outcome while memantine is N-Methyl-D-aspartate receptor antagonist [50]. But due to less proficiency and therapeutic failure in the treatment

of Alzheimer syndromes the various new clinical trials with several approaching steps towards new therapeutic targets are addressed below:

Donanemab, humanised antibody (IgG1) which proves promising and budding anti-amyloid immunotherapy having impact on core cerebral amyloid assemblage by acting against the N-Truncated pyroglutamate β-amyloid peptides *(i.e., pGlu3-Aβ, AβpE3)* a like to Remternetug but the main variation between them is that it can be administered directly through cutaneous route & through the veins and in the wake leads to condensing multiple functional cognitive syndromes in mild to moderate conditions of AD [51]. ISRIB (Integrated Stress Response Inhibitors), a reversal & remarkable new compact molecule which takes part in protein synthesis (i.e., translation) by curbing & reversing the impact of elf2α phosphorylation & PERK signalling pathways which plays a crucial role to initiate the process of amyloidogenesis & shows the ability to reverse the effects of Alzheimer disease in mouse models; further which also creates a way to treat the diseased condition by blocking a protein molecule GSK3B & activating Nrf2 protein which is having protective effects on neurons and inhibiting the respective amyloid plaque heaps in encephalon [52].

According to the recent studies, on the basis of binding approaches of the drugs like lecanemab, aducanumab and gantenerumab in the late phase clinical trials with the protofibrils, monomers, insoluble fibrils & oligomers in plaques wherein, the protofibrils, oligomers with insoluble fibrils has proven toxic & removal of these aggregates initiated under the disparate researches, among which the lecanemab shows weak binding to monomers but presents 10 folds binding avidity with protofibrils while gantenerumab & aducanumab presents more affinity with monomers than any to the removal & preventing of aggregation formed during Alzheimer's disorder [53-55]. Alternative monoclonal highly personalized antibody E2814 which is directed at an antigenic determinant site by I.V. route within the microtubules of splice variants of Tau proteins are found to be most impactful in collective approaches with lecanemab and found anti-against Tau (i.e., p-tau 217/ t-tau ratio in CSF & CSF Neurofibrillary tangles) plus amyloid both as sited in the studies of symptomatic and asymptomatic patients [56-57].

The vaccine which is peptidyl in nature *i.e.*, Tertomotide acts by targeting the Telomerase Reverse Transcriptase (TERT) enzyme which is found to be explicit in many cancers but due to failure to cure cancer of sweet bread of the body (i.*e.*, pancreas) & due to its guarding effects against functional unit of encephalon that is *neurons, it is* used to treat beta-amyloid oligomer 20-35 in stem cells of neuron by reducing the propagation of free radical generations and hampers the further deaths of cells. Hence, this study is not so far completed but will get conclude in preliminary 2026 [58-60]. Semaglutide, i.e., GLP-1 analogue which exhibits the facility to evades the Astrocytes & Microglial cells hurdle in brain (i.e., blood brain barrier) and its effectiveness in Alzheimer disorder was first studied in 2021 on patients exhibiting mild syndromes with pervasive microvascular disease (i.e., Diabetes). And its further studies are to be finished after phase III trials in latterly 2026 [61-62].

CONCLUSION: Last of the preceding along with present insights, the framework of AD comes with newer notions with the assorted mild to moderated pristine clinical manifestations in tandem with massive involvement of varied risk factors endowing to an aetiology from either core factors indulges in abundance of ailments like Age, Gender as well as the severe complexity role of untold genetic peculiarities like vitamin D receptor gene (VDR), GAPDH gene & numerous other attorneys also contributing to an ailment. The growth of the modern era and the concurrent progression of disease furthermore causes challenges with diagnosis in some way in light of this diagnostic scaling improvement i.e., MMSE scaling *via* MoCA scaling plus by knowing the appropriate diagnostic markers underlying within the disease consisting of complications in the form of various analogues of the mood disorders comprising of circulatory failure and a bit of studies showing the fatalities with the necrotizing tissues leading to pneumonia and widely well-known neuro-psychiatric disorders as the disease pathway modifications the earlier medications that were comprised in a first line therapy of AD due to proven safety with proper adequacy but owing their therapeutic failure in treatment the following

modern headways in the medications are approaching various clinical trials with respective new therapeutic targets in which few of them discovered and some are under pipeline which are creating a great hope to help in curing and preventing by improving in finding a new therapeutic targets in the coming modern era.

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CONFLICT OF INTEREST: The authors declare that there is no conflict of interest.

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