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AN UPDATE ON TREATMENT OF ALZHEIMER DISEASE- A LITERATURE REVIEW

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ABSTRACT

Alzheimer's disease represents an enormous global burden in terms of human suffering and economic cost. It is the most common cause of dementia all over the world. The pathological hallmarks of Alzheimer's disease are amyloid plaques and neurofibrillary tangles. The goal of this review is to discuss early diagnosis using biomarkers and newer treatment strategies for Alzheimer's disease. Newer strategies focus on employing disease modifying agents targeting amyloid cascade. The aim of such treatment is to reduce amyloid production, prevent tau hyperphosphorylation, aggregation and improve clearance of both tau and amyloid. Cholinesterase inhibitors and Memantine are the only drugs approved for treatment as yet. Although they improve symptoms they do not cure or totally halt the progression of illness. Nutritional supplements, physical activity plays a role in prevention according to few studies, but their role has not yet been approved.

KEYWORDS: Amyloid production, prevent tau hyperphosphorylation

INTRODUCTION

Alzheimer's disease (AD) is multifactorial neurodegenerative disorder which has poor prognosis. It is the most common cause of dementia in the world. It is progressive and irreversible disease and leads to severe impairment of memory. It is one of the primary causes of cognitive dysfunction in elderly (Aprahamian *et al.*, 2013; Phillips *et al.*, 2015; Kuo and Rajesh, 2017).

AD is named after Alois Alzheimer, a German psychiatrist in 1906. He had a patient named Auguste D in her fifties, who suffered from what seemed like a mental illness. Following her death, the autopsy of her brain revealed dense deposits, now named as amyloid plaques and twisted strands of fiber called neurofibrillary tangles (NFTs) (Mufson *et al.*, 2015; Kuo and Rajesh, 2017).

AD is a highly prevalent neurodegenerative disorder of old age. Alzheimer's association report's 13% prevalence in people older than 65 years in the developed countries. It is the fifth largest cause of death in this age group. According to world health organization the prevalence is expected to quadruple in the next decade reaching 114 million patients by 2050 (Folch *et al.*, 2016). In Europe the estimated number of patients needing treatment is 7-8 million, 4-5 million in USA and 24 million worldwide. It is expected that 42 million would suffer by 2020 due to aging (Leon *et al.*, 2013). In Saudi Arabia the estimated number of people suffering from AD is 50,000 (Alfakhri *et al.*, 2018).

The cholinesterase inhibitors (ChEI) and Memantine (MEM) are the approved drugs for AD which temporarily improve symptoms. Presently there is no effective treatment in terms of cure and prevention of AD. Considering the rise of AD in the population there is urgent need to develop disease modifying agents. These agents by definition are the drugs which reduce the progression of neurodegeneration by inhibiting critical events that happen in the pathophysiology of the disease (Aprahamian *et al.*, 2013).

The present review discusses early diagnosis using biomarkers and the disease modifying agents targeting amyloid cascade, as well as nutritional supplements and physical activity (PA) in prevention and treatment of this devastating illness.

Types of Alzheimer's disease

AD is classified according to the age of onset. Familial AD is early onset, it can start as early as 40 years. The cause is genetic mutations and it accounts for 2% of cases. The genetic mutations are found in amyloid precursor protein (APP) gene on chromosome 21, presenilin 1 on chromosome 14 and presenilin 2 on chromosome 1. Sporadic AD is classified as early onset which starts before 65 years of age and account for 3 to7% of cases and late onset AD which starts after the age of 65 years and accounts for 95% of AD cases.

Significant numbers of patients with sporadic form are carriers of epsilon 4 (e4) allele of Apolipoprotein E (ApoE) gene, which is a lipid transport protein. This allele is less efficient in removal of amyloid beta (Aβ) peptide when compared to other alleles like e2 allele (Braskie *et al.*, 2011; Kuo and Rajesh, 2017). Risk factors for sporadic AD are age, hypertension, hypercholesterolemia, diabetes and metabolic syndrome (Folch *et al.*, 2016).

1. Pathophysiology

The cardinal neuropathological signs of AD are amyloid plaques and NFTs. Plaques are made up of Aβ peptide and NFTs are formed by hyperphosphorylated tau. Tau is the component of microtubule which is the internal support structure of a neuron. Hyperphosphorylation of tau thus, destroys the cytoskeleton of the neurons leading to their death (Hardy, 2009; Aprahamian *et al.*, 2013; Kumar *et al.*, 2015; Mufson *et al.*, 2015; Kuo and Rajesh, 2017).

Etiopathogenesis of AD is not completely understood. Amyloid hypothesis is the most common pathophysiology of AD since the last two decades. Other factors like oxidative stress, inflammation and neurotransmitter imbalance also play a role (Hardy, 2009; Anand *et al.*, 2014; Geldenhuys and Darvesh, 2014; Dal Pra *et al.*, 2015; Kuo and Rajesh, 2017).

1.1. Amyloid hypothesis

According to amyloid cascade hypothesis, cleavage of APP occurs by nonamyloidogenic and amyloidogenic pathway **(Fig 1.1)**. Nonamyloidogenic pathway, the APP cleavage is done by alpha (α)- secretase and subsequently by gamma (γ) secretase which produce soluble nontoxic peptides. Amyloidogenic pathway, the cleavage occurs by beta (β) secretase and subsequently by γ-secretase. The product of this include two forms Aβ 40 amino acid peptides and the other Aβ 42 amino acid peptide which are toxic and prone to form fibrils (Kumar *et al.*, 2015; Sadigh-Eteghad *et al.*, 2015).

In AD there is genetic abnormality in APP hence it is mostly cleaved by β-secretase of amyloidogenic pathway as a result of this, excessive Aβ peptides are produced which accumulate into soluble oligomers that clump together to form insoluble fibrils called plaques which are deposited extracellularly (Hardy, 2009; Mufson *et al.*, 2015; Kuo and Rajesh, 2017).

These plaques create inflammatory response that activate microglia and astrocytes which produce chemicals such as cytokines and free radicals.

Aβ42 oligomers and the chemical events stimulate kinases which causes hyperphosphorylation of tau converting microtubules into tangles within neuron called NFTs. The buildup of NFTs in the neuron ultimately leads to neuronal death. The synaptic dysfunction and oxidative stress due to amyloid oligomers and neuronal death due to hyperphosphorylation of tau relentlessly progress leading to shrinkage of brain (Dal Pra *et al.*, 2015; Kumar *et al.*, 2015).

Clearance of Aβ42 oligomers occurs by several pathways. Firstly, by the degradation caused by enzymes such as proteases and insulin degrading enzyme (IDE). Secondly, they are removed through the uptake by astrocyte and microglia. Thirdly, by passive flow into cerebrospinal fluid (CSF) (Braak and Del Tredici, 2011).

In AD there is excessive production and inefficient removal of Aβ peptide due to less activity of the degradation enzymes. This imbalance between production and clearance leads to accumulation of amyloid plaques (Folch *et al.*, 2016).

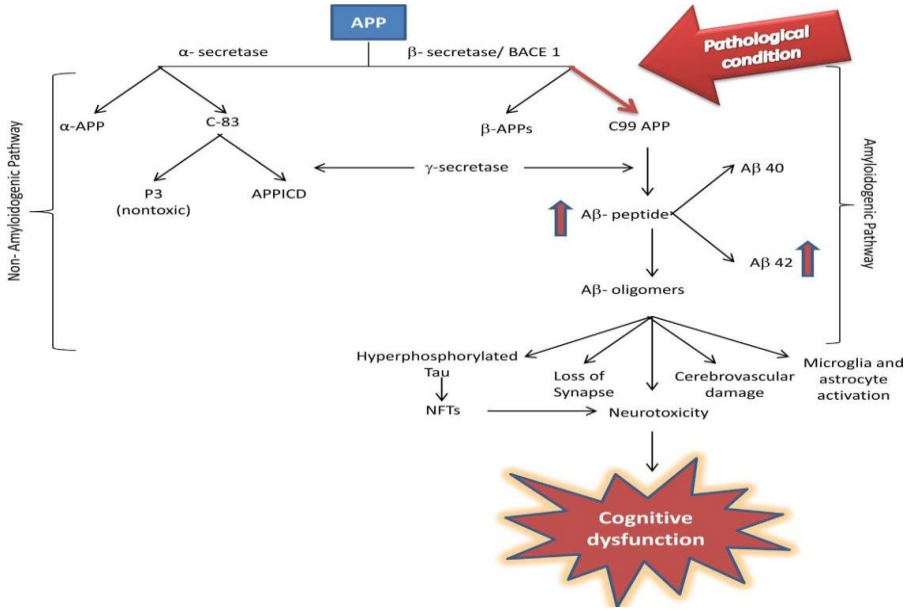

Figure 1.1: Amyloid Hypothesis.

Non-amyloidogenic pathway- the APP is cut via α-secretase into two forms α-APP which is soluble and C-83 (83 amino acid peptide of carboxy terminal). γ secretase further cuts C-83 into smaller peptides p3 and amyloid precursor protein intracellular domain (APPICD). Amyloidogenic pathway- the APP is cut by β-secretase into β- APPs (soluble) and C99APP which is further broken down by γ-secretase into Aβ peptides which form Aβ oligomers. The oligomers cause hyperphosphorylation of tau, loss of synapse, cerebrovascular damage and microglia activation leading to cognitive dysfunction (Kumar *et al.*, 2015).

2. Staging of Alzheimer using Biomarkers

2.1. Biomarkers

Biomarkers play an important role in the identification of preclinical stages of AD and aid in early diagnosis. Biomarker is a measurable parameter which reflects the presence and severity of the disease. The biomarkers for AD are found by CSF analysis and imaging of brain by magnetic resonance imaging (MRI) and positron emission tomography (PET). CSF biomarkers are high phosphorylated tau (p,tau), high total tau (t tau), decreased concentration of the Aβ42 peptide and increased tau amyloid ratio (McConathy and Sheline, 2015).

MRI shows reduced volume of medial temporal lobe and medial parietal cortex. Flurodeoxyglucose Positron Emission Tomography (FDG –PET) is used to see brain glucose metabolism. Flurodeoxyglucose (FDG) is most commonly used PET tracer which gives quantitative measure of glucose metabolism by neurons. In AD there is progressive decline in the glucose metabolism reflecting neuronal injury. Pittsburg compound B (PiB) PET is used to image amyloid in living brain (Frisoni *et al.*, 2010; McKhann *et al.*, 2011; Edmonds *et al.*, 2015; McConathy and Sheline, 2015).

2.2. Stages of Alzheimer's disease

2.2.1. Stage 1 preclinical stage or asymptomatic stage

The importance of early diagnosis holds good as the pathological process starts at least 10-20 years before clinical manifestation (Sperling *et al.*, 2011; Rygiel, 2016). Asymptomatic patients are those who are biomarker positive without clinical symptoms. The National Institute of Aging and Alzheimer's Association (NIA-AA) classifies AD into 3 stages, Preclinical stage, Mild cognitive impairment (MCI) and Dementia **(Fig 2.1)** (Sperling *et al.*, 2011).

Preclinical stage is further subdivided into 3 stages which are: Stage 1, it is asymptomatic with PiB PET showing cerebral amyloidosis and low CSF amyloid Aβ 42 which are the markers of amyloidosis. Stage 2, show features of stage 1 with an evidence of neurodegeneration as shown by increase in CSF tau, abnormal volumetric loss on MRI and reduced glucose metabolism with FDG-PET and finally stage 3, which includes all features of stage 2 and subtle cognitive decline as evidenced clinically. Stage 3 is more likely to progress to MCI when compared to stage 1 and 2 **(Fig 2.2)** (Edmonds *et al.*, 2015; McConathy and Sheline, 2015).

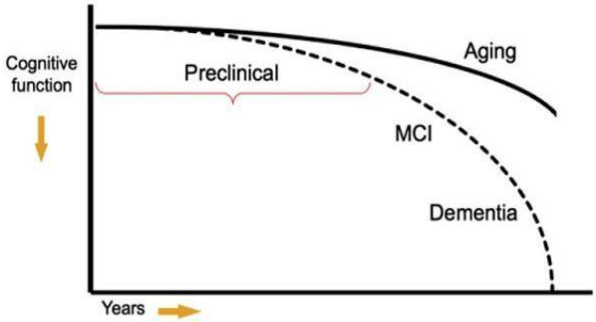

Figure 2.1: Continuum of Alzheimer's disease. The above figure is depicting the cognitive function decline with increase in age as compared with cognitive function decline in preclinical stage, MCI and Dementia over a period of time (Sperling *et al.*, 2011).

Figure 2.2: Preclinical Stages of Alzheimer's disease according to biomarkers. Depiction of the preclinical stages. Some individuals may not progress beyond stage 1 and 2. Individuals with stage 3 are more likely to progress to MCI (Sperling *et al.*, 2011). Abbreviation: fMRI: functional magnetic resonance imaging, sMRI: Structural Magnetic resonance imaging.

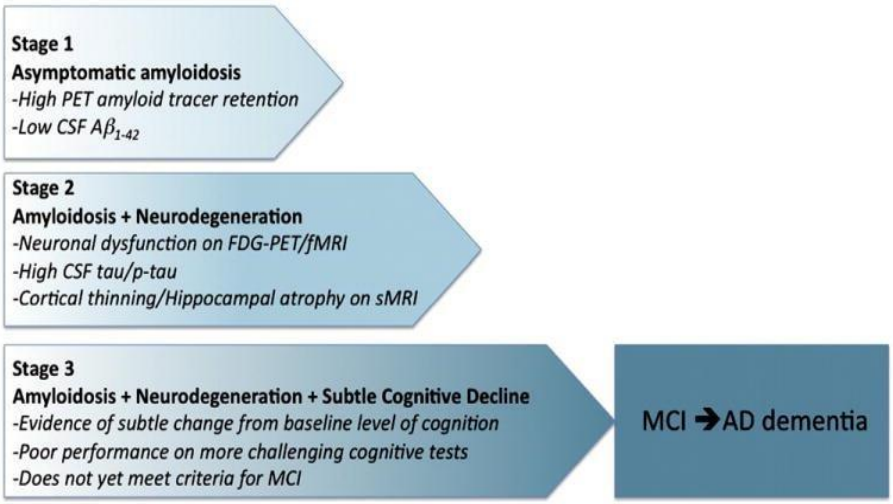

Figure 2.2 : Preclinical stages of Alzheimer's disease according to Biomarkers

2.2.2. Stage 2 Mild cognitive impairment due to Alzheimer's disease

According to NIA-AA, MCI is defined as subjective and objective evidence for cognitive decline without functional decline (Albert *et al.*, 2011). The NIA-AA criteria for MCI due to AD is, having cognitive impairment in one domain, with positive biomarkers for amyloid accumulation and neurodegeneration **(Table 4.1)**. MCI clinically presents as difficulty remembering names, word finding difficulty and difficulty in concentrating. Over 10 to 20% patients with MCI convert to AD dementia per year (Albert *et al.*, 2011; Edmonds *et al.*, 2015; McConathy and Sheline, 2015).

Table 4.1: Biomarker of amyloid accumulation and neurodegeneration for Alzheimer's disease (Stahl, 2013).

Biomarkers of amyloid accumulation	Biomarkers of neurodegeneration
Abnormal radioactive tracer retention on amyloid PET scans	Elevated CSF tau (total and phosphorylated tau)
Low CSF amyloid levels of Aβ42	Decreased FDG uptake on PET
	Atrophy on structural magnetic resonance imaging • hippocampal atrophy • ventricular enlargement • cortical thinning

2.2.3. Stage 3 Dementia due to Alzheimer's disease

Dementia sets in with the development of cognitive decline in at least two cognitive domains and behavioral symptoms which effect their daily functioning. Dementia of AD is diagnosed when there is a proof of pathophysiologic process of AD as evidenced by clearly positive biomarkers for brain amyloidosis and neurodegeneration (McKhann *et al.*, 2011).

3. Clinical features and diagnosis of Alzheimer's disease Dementia

Dementia is loss of mental function in two or more areas such as memory language, or executive functions severe enough to interfere with daily activities and abilities to function at work. Probable AD dementia is diagnosed when the onset is insidious with progressive worsening of cognition with time. The initial and most prominent cognitive deficit of AD dementia as evident on history and examination are categorized into two types of presentations amnestic and non-amnestic. Amnestic presentation is inability remembering new things. Non-amnestic presentation includes language impairment, visuospatial impairment and executive dysfunction. Changes in personality and behavioral symptoms include fluctuations in mood, agitation and socially unacceptable behavior. The diagnosis of probable AD dementia should not be applied when there is evidence of cerebrovascular disease (McKhann *et al.*, 2011).

The diagnosis of AD dementia relies on good clinical workup and neuropsychological testing. Dementia is categorized into mild, moderate a severe using a scale called Mini Mental Status Examination (MMSE). Score of 21-26 is mild, 10-20 moderate, 10-14 moderate severe and less than 10 is severe Dementia (Robinson *et al.*, 2015).

Although positive biomarkers of AD such as CSF amyloid, tau and amyloid imaging by PiB PET may guide towards the diagnosis of AD it is not used in clinical setup. Guidelines by NIA-AA suggest the use of biomarkers and imaging only for research application. Moreover, the diagnosis of AD is only confirmed by brain autopsy with 80% accuracy (Edmonds *et al.*, 2015; McConathy and Sheline, 2015).

4. Symptomatic treatment approved by Food and Drug Administration

4.1. Acetylcholinesterase inhibitors

According to cholinergic hypothesis the cognitive dysfunction is due to loss of cholinergic neurons. Therefore, blocking cholinesterase enzyme which metabolizes acetylcholine (Ach) may help increase Ach levels which improves the cognition. The Food and Drug Administration (FDA) has approved Donepezil, Rivastigmine and Galantamine for treatment of mild to moderate Dementia due to AD (Geldenhuys and Darvesh, 2014). ChEI have significant efficacy in improving cognitive symptoms but not neuropsychiatric symptoms in mild to moderate Dementia due to AD (Kobayashi *et al.*, 2016).

4.2. N-methyl-D-aspartate receptor antagonists

The Aβ42 oligomers stimulate N-methyl-D-aspartate (NMDA) receptors which lead to excitotoxicity and free radical damage of neuron. MEM is a NMDA receptor antagonist which prevents this damage. It is approved by FDA for moderate to severe AD. MEM monotherapy improves cognitive and behavioral symptoms (Geldenhuys and Darvesh, 2014; Matsunaga *et al.*, 2015).

Moreover, combination of ChEI and MEM is superior in moderate to severe Dementia than only MEM or only ChEI (Gareri *et al.*, 2014; Matsunaga *et al.*, 2015; Schmidt *et al.*, 2015). Although these drugs have been able to relief the symptoms they are unable to cure Dementia due to AD (Anand *et al.*, 2014; Geldenhuys and Darvesh, 2014; Kumar *et al.*, 2015).

5. Disease modifying treatment under research not approved by Food and Drug Administration

5.1. Treatment focused on amyloid

The goal of the treatment is reducing production of Aβ peptides via inhibition of β and γ-secretase and increasing the clearance via monoclonal antibodies (Kumar *et al.*, 2015; Folch *et al.*, 2016).

5.1.1. Drugs targeting amyloid production

5.1.1.1. Gamma secretase inhibitors

Semagacestat is the most studied γ-secretase inhibitor which reduced Aβ peptide in the CSF of healthy humans and in patients with mild and moderate AD but did not show improvement in cognitive dysfunction. The clinical trials were stopped due to its detrimental effects on cognition and reports of skin cancers (Imbimbo and Giardina, 2011; Folch *et al.*, 2016).

5.1.1.2. Gamma secretase modulators

Nonsteroidal anti-inflammatory drugs (NSAIDS) act as selective γ- secretase modulators. They have the ability to reduce amyloid by increasing microglial activity. However, studies have shown lack of efficacy of NSAIDS like ibuprofen in treating AD (Folch *et al.*, 2016; Rabins *et al.*, 2017). CHF5074 is an NSAID in phase II clinical trial which has the ability to reduce amyloid production and increase its clearance by increasing microglial activity (Folch *et al.*, 2016).

5.1.1.3. Beta secretase inhibitors

β-site amyloid cleaving enzyme 1(BACE1) inhibition is the major target of newer disease modifying agent as it is the key enzyme involved in production of Aβ peptides. The greatest limitation faced by these BACE1 inhibitors is the dose adjustment, as any excessive decrease may lead to synaptotoxicity. Aβ peptides is synaptotrophic and neuroprotective in physiological dose and synaptotoxic and neurotoxic in excess, hence less than physiological level may be synaptotoxic. Therefore, careful dosing is the key issue in this regard (Yan and Vassar, 2014).

Lanabecestat is latest BACE 1 inhibitor. It had good brain permeability and can be given orally. It has shown promising results in reduction of amyloid load via reducing its production. It is in phase III clinical trial mainly done on patient of MCI due to AD and mild AD dementia (Sakamoto *et al.*, 2017; Sims *et al.*, 2017).

AZ3293 is another BACE 1 inhibitor which is orally active and show good permeability to blood brain barrier (BBB) and exhibits slow off rate. The drug is currently in phase III clinical trial and has shown robust decrease in CSF and plasma Aβ peptides to the range of more than 51% with 15mg dose in CSF and more than 64% reduction in plasma with similar dose (Eketjall *et al.*, 2016; Cebers *et al.*, 2017).

5.1.2 Drugs targeting Amyloid aggregation

Glycosaminoglycans (GAGs) promotes Aβ aggregation and deposition. Tramiprosate antagonize interaction of Aβ with endogenous GAGs thus, preventing aggregation. However, the research on this drug was stopped due to lack of efficacy in phase III clinical trial (Aisen *et al.*, 2011; Kumar *et al.*, 2015).

Colostrinin (CLN) inhibits aggregation of Aβ and dissolve already formed fibrils. CLN is a proline rich polypeptide complex which was isolated first from ovine and bovine colostrum. This drug has shown improvement in mild AD, but the effect was not maintained (Janusz and Zablocka, 2013; Folch *et al.*, 2016).

Methylene blue has shown to inhibit both tau and amyloid aggregation. The clinical trials for the derivatives of methylene blue are underway to demonstrate its utility in treating AD (Folch *et al.*, 2016;

Kuo and Rajesh, 2017).

5.1.3 Drug targeting amyloid clearance

5.1.3.1 Vaccinations

Immunotherapy aims at clearance of amyloid load. Antibodies inhibit amyloid fibril formation by antigen antibody interaction. Both antigen administration via active immunization and antibody administration by passive immunization show reduction in Aβ accumulation. Active immunization using Aβ (1-6) peptide produces active Aβ specific antibody response in 75% patients without causing adverse inflammatory reaction. CAD106 is A (1-6) peptide designed in the form of drug which is presently in phase II clinical trial. Passive immunization includes administration of monoclonal antibodies against Aβ peptide (1-6). Monoclonal antibodies like bapineuzumab has shown disappointing results and was stopped in phase III clinical trials due to reports of meningoencephalitis. Although this drug increase Aβ peptide clearance it has not shown to improve cognition in patients with mild to moderate AD (Folch *et al.*, 2016). Solanezumab and gantenerumab are other monoclonal antibodies which are researched on patients in preclinical stage. These drugs are currently in phase III clinical trial (Barrera- Ocampo and Lopera, 2016; Folch *et al.*, 2016).

Treatment focused on tau protein

Tau protein has critical role in microtubule stabilization. Hyperphosphorylation of tau leads to formation of NFTs. This leads to cytoskeleton destabilization of neuron and neurodegeneration. The goal of tau centered treatment is inhibition of phosphorylation, aggregation of tau and effective clearance of tau aggregates (Folch *et al.*, 2016).

5.2.1 Drugs inhibiting tau phosphorylation

Lithium and valproate have inhibitory actions on Glycogen synthase kinase-3 (GSK-3) which is one of the primary enzymes involved in phosphorylation of tau. Although these drugs have shown to slow the progression of cognitive deficit further large scale clinical trials are required to assess its benefit in treatment of AD (Kumar *et al.*, 2015). Tideglusib is an irreversible inhibitor of GSK-3. The research was stopped in phase II clinical trials due to lack of efficacy (Anand *et al.*, 2014; Folch *et al.*, 2016).

5.2.2 Tau based vaccination

Both active and passive immunization against tau has demonstrated increased clearance of tau aggregates. Administering tau antibody to rodents with mild to moderate AD reduced the total and phosphorylated tau in hippocampus. Although it has shown clinical improvement of memory in rodents, its effect has not yet been replicated in humans (Folch *et al.*, 2016; Dai *et al.*, 2017).

6. Nutritional supplements

6.1. Phytochemicals

Neurotrophins are substances in brain which are required for survival of neurons. They are reduced in neurodegenerative disorders such as AD.

Neurotrophins administration may be an effective treatment option (Venkatesan *et al.*, 2015).

Phytochemical is a plant extract from fruits such as grapes and nuts. They have the capacity to increase the Ach by inhibiting ChEI, increase neurotrophins which promote growth of neurons and their survival. They also act as antioxidants, prevent neuronal damage by scavenging reactive oxygen species (ROS) and neutralize the free radicals. They are not cytotoxic (D'Onofrio *et al.*, 2017). Regular intake of phytochemicals improves general states like physical and cognitive performance by decreasing the oxidative stress and increasing neuronal cell survival. They are less toxic than synthetic drugs (Winner *et al.*, 2011).

Studies showed that polyphenols which are present in grape seed extract plays an important role not only by reducing oxidative stress but also by inhibiting Aβ aggregation, reducing Aβ oligomerization (Mattson, 2015). They also reduce tau hyperphosphorylation and aggregation. The metabolites are capable of passing the BBB. Resveratrol is another naturally occurring polyphenol which has shown efficacy in animal models of AD (Pasinetti *et al.*, 2015). The phytochemicals formulated as nanoparticles have more efficacy, as such particles can easily pass through the BBB. Among phytochemicals curcumin and quercetin are formulated into nanoparticles and thus, have good bioavailability (Jadhav *et al.*, 2017).

6.2. Antioxidants

6.2.1. Omega-3 fatty acids

Although some studies have shown the improvement in cognitive function in early stage of disease there is no convincing evidence for its supplementation to treat AD (Sydenham *et al.*, 2012; Burckhardt *et al.*, 2016; Canhada *et al.*, 2017; Rabins *et al.*, 2017).

6.2.2. Vitamin E

The idea that free radical injury contribute to pathological process in AD holds good for the use of vitamin E, which is an antioxidant. Antioxidants scavenge free radicals and reduce oxidative stress. However evidence for its efficacy in treatment and prevention of AD and MCI is not yet found (Farina *et al.*, 2017).

6.2.3. Vitamin D

Vitamin D stimulates Aβ phagocytosis, promotes neuronal survival and has antioxidant effect. Vitamin D deficiency is associated with cognitive dysfunction in elderly and AD dementia. However, no large randomized controlled trials have yet demonstrated efficacy of vitamin D in treatment and prevention of AD. Further studies are needed to establish its effectiveness in treatment and prevention of AD dementia (Dickens *et*

al., 2011; Grimm *et al.*, 2017).

7. Physical activity

Physical activity (PA) can reduce the risk of AD by promoting the hippocampal neurogenesis, reducing inflammation, increasing synaptic plasticity and reducing oxidative stress. A meta-analysis of six prospective studies published from 1990 to 2007 had found 45% decreased risk of AD with PA (Santos-Lozano *et al.*, 2016).

Non-demented older individuals walking more than 4000 steps each day has shown better cognitive function and thicker hippocampus than those older people who walked less than 4000 steps per day (Siddarth *et al.*, 2018). Regularly performed PA may be protective against AD (Santos- Lozano *et al.*, 2016).

In a meta-analysis of 8 studies, one study found increase in hippocampal volume with exercise whereas another found detrimental effect on hippocampus and rest of the studies found no correlation (Frederiksen *et al.*, 2018). The current evidence is not enough to formulate the exact frequency, type and duration of PA that may be protective against AD (Stephen *et al.*, 2017).

8. Treatment guidelines for Alzheimer's disease Dementia

According to British Association of Psychopharmacology Guidelines 2017 the recommendations for anti-dementia drugs in clinical practice are as follow. ChEI such as Donepezil, Rivastigmine, Galantamine are useful in mild to moderate AD dementia. MEM is effective in moderate to severe AD dementia. Combination therapy of MEM and ChEI is better over monotherapy with either of them alone in moderate to severe cases. Neither ChEI nor MEM is recommended for use in MCI. Drugs should not be stopped even if dementia severity is increasing. Nutritional supplements and anti-inflammatory is not recommended for treatment or prevention unless further evidence suggests its use. No disease modifying agents which reduce amyloid or tau deposits are licensed in clinical practice as yet (O'Brien *et al.*, 2017).

9. CONCLUSION

The approved treatment for AD is symptomatic. It mainly consists of ChEI and NMDA antagonist which reduce the symptoms but do not modify the progression of illness. Disease modifying agents like β and γ blockers and monoclonal antibodies solanezumab and gantenerumab has shown good efficacy in reducing the amyloid load.

Drugs preventing tau hyperphosphorylation and tau-based vaccines has also shown to reduce tau tangles. Such multimodal therapy targeting amyloid accumulation and tau protein can modify the disease course. Although the translation of the research into effective medication is very challenging there is still a hope. Till date no disease modifying agents have been licensed either because of their toxic effects or lack of efficacy. The lack of efficacy can be explained by the fact that these drugs were used in a population which already presented with clinical symptoms. This means that the neurodegeneration had already started and progressed, which is hard to be reversed. This suggests the need to start treatment in the early stage of illness. To achieve this, the most accurate way of diagnosing illness in the early stage using biomarkers should be considered. These diagnostic techniques should be employed in patients with MCI who has high risk of conversion to AD dementia and such cases should be recruited for further research with these agents. Even though these agents are not FDA approved they still remain a glimpse of hope in the journey towards treatment of this devastating illness.

10. Recommendations

1) Tremendous success of disease modifying agents targeting amyloid hypothesis in preclinical studies but subsequent failure in humans, suggests a need for development of better animal models for future research.

2) The failure also reflects the need to target other factors involved in the illness as it is multifactorial. Therefore, multiple drug modalities should be tried in near future.

3) As the pathological changes occur far before the clinical onset of illness, initiation of treatment in preclinical stage or MCI may yield beneficial results. Hence, future studies should be done employing disease modifying agents in early stage of the illness.

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