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Towards understanding Alzheimer's Disease: An Overview

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ABSTRACT

Alzheimer's disease is the most frequent neurodegenerative disorder and the most common cause of dementia in the elderly. Diverse lines of evidence suggest that amyloid-β (Aβ) peptides have a causal role in its pathogenesis, but the underlying mechanisms remain uncertain. Recent evidence shows that Aβ may be part of a mechanism controlling synaptic activity, acting as a positive regulator presynaptically and a negative regulator postsynaptically. The pathological accumulation of oligomeric Aβ assemblies depresses excitatory transmission at the synaptic level, but also triggers aberrant patterns of neuronal circuit activity and epileptiform discharges at the network level. Aβ-induced dysfunction of inhibitory interneurons likely increases synchrony among excitatory principal cells and contributes to the destabilization of neuronal networks. Strategies that block these Aβ effects may prevent cognitive decline in Alzheimer's disease. Potential obstacles and next steps toward this goal are discussed. This review will discuss the case study, types and prevelance of Alzheimer's disease pathogenesis.

Keywords: Amyloid-β (Aβ) peptides, Alzheimer's disease (AD).

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INTRODUCTION

Alzheimer's is the most common form of dementia, a general term for memory loss and other intellectual abilities serious enough to interfere with daily life. Alzheimer's disease accounts for 50 to 80 percent of dementia cases. It is estimated that by the year 2020, approximately 70% of the world's population aged 60 and above will be living in developing countries, with 14.2% in India [1]. One in eight people age 65 and older (13 percent) has Alzheimer's disease, nearly half of people age 85 and older (45 percent) have Alzheimer's disease, an estimated 4 percent are under age 65, 6 percent are 65 to 74, 44 percent are 75 to 84, and 46 percent are 85 or older [2]. The figure includes 5.2 million people age 65 and older and 200,000 individuals under age 65 who have younger-onset Alzheimer's [3,4]. Alzheimer's disease is without doubt one of the most terrible afflictions of late middle age to old age. It has often (on the analogy of heart failure) been termed 'brain failure'. Alzheimer's disease is a neurodegenerative disorder characterized by cognitive deficit and loss of memory [5].

Clinical manifestations of AD are severe impairments in thought, learning, memory and language abilities. The neuropathological hallmarks of AD are characterized by extracellular deposition of the amyloid beta (Aβ) peptide in senile plaques, presence of intracellular neurofibrillary tangles (NFTs) tau proteins, and neuronal loss [6]. The abnormal processing of the amyloid precursor protein (APP) is the initiating event in AD pathogenesis, subsequently causing aggregation of Aβ, specifically Aβ42 [7]. Amyloid beta-peptide [Aβ(1–42)], elevated in AD brain, is associated with oxidative stress and neurotoxicity [6,7].

This review will provide a description of Alzheimer's disease and its types, its measurement and present the prevalence and incidence of Alzheimer's disease in India and the world. The burden of Alzheimer's disease in India will be explored. Risk factors for Alzheimer's disease, co-morbid conditions, best management practice and treatment of Alzheimer's disease will be also included.

First case study with Alzheimer's disease:

The first description of AD was given by Alois Alzheimer in 1907. His words are worth quoting:

A woman of 51 years old, showed jealousy towards her husband as the first noticeable sign of the disease. Soon a rapidly increasing loss of memory could be noticed. She could not find her way around in her own apartment. She carried objects back and forth and hid them. At times she would think that someone wanted to kill her and would begin shrieking loudly. In the Institution her entire behavior bore the stamp of utter perplexity. She was totally disorientated to time and place. Occasionally she stated she could not understand and did not know her way around. At times she greeted the doctor like a visitor, and excused herself for not having finished her work; at other times she shrieked loudly that he wanted to cut her, or she repulsed him with indignation, saying that she feared something against her chastity. Periodically she was totally delirious, dragged her bedding around, called her husband and her daughter, and

seemed to have auditory hallucinations. Frequently, she shrieked with a dreadful voice for many hours. Her ability to remember was severely disturbed. If one pointed to objects, she named most of them correctly, but immediately afterwards she would forget everything. When reading she went from one line to another, reading the letters or reading with a senseless emphasis. When talking she used perplexing phrases and some periphrastic expressions (milk-pourer instead of cup). Sometimes one noticed her getting stuck. Some questions she obviously did not understand. She seemed no longer to understand the use of some objects [8,9].

TYPES OF ALZHEIMER'S DISEASE

Early-onset Alzheimer's:

This is a rare form of Alzheimer's disease in which people are diagnosed with the disease before age 65. Less than 10% of all Alzheimer's disease patients have this type. Because they experience premature aging, people with Down syndrome are particularly at risk for a form of early onset Alzheimer's disease. Adults with Down syndrome are often in their mid to late 40s or early 50s when symptoms first appear. Early- onset Alzheimer's appears to be linked with a genetic defect on chromosome 14, to which late-onset Alzheimer's is not linked. A condition called myocloms- a form of muscle twitching and spasm which is more commonly seen in early-onset Alzheimer's than in late-onset Alzheimer's [10].

Inherited Alzheimer's is also referred to as familial Alzheimer's disease (FAD). Mutations on three genes have been linked to familial, early-onset Alzheimer's disease. These genes have been labeled PS1, PS2 and APP by researchers. Research from the 1990s indicates that mutations on a gene labeled PS1 may be responsible for 30% to 60% of early-onset Alzheimer's cases. Newer research is inconclusive regarding the exact prevalence of specific mutations, but confirms that a PS1 gene is the mutation most commonly linked to FAD. The early indicators of early-onset Alzheimer's disease are similar to those of late-onset Alzheimer's. These symptoms include regularly losing items, difficulty executing common tasks, forgetfulness, personality changes, confusion, poor judgment, challenges with basic communication and language, social withdrawal and problems following simple directions [10,11].

Late-onset Alzheimer's:

This is the most common form of Alzheimer's disease, accounting for about 90% of cases and usually occurring after age 65. Late-onset Alzheimer's disease strikes almost half of all people over the age of 85 and may or may not be hereditary. Late-onset dementia is also called sporadic Alzheimer's disease [12]. The cause of late-onset Alzheimer's are not yet completely understood, but they likely include a combination of genetic, environmental, and lifestyle factors that influence a person's risk for developing the disease [13].

PREVALENCE –INDIAN SCENARIO:

According to the Delphi census, 93.1 million older people over 60 years of age, globally

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were estimated to be living with dementia; an overall prevalence of 1.6 % [14]. The Delphi census estimated that in India, 3.7 million people aged over 60 have dementia [14]. Evidence based on more than 42,000 older people studied in eight centres (5 urban and 4 rural areas) across India, suggests that Ballabgarh and Vellore have the lowest estimated prevalence rates whilst Tiruvandrum and Thiropour have the highest rates (Table 1) [15].

Setting	Location	Preference	References
Urban	Chennai	0.9% for age > 65	19
	Kochi	3.3% for age > 65	20
	Kolkata	1% for age > 60	21
	Mumbai	2.3 % for age > 65	22
	Trivandrum	4.8% for age > 65	23
Rural	Ballabgarh (Delhi)	3.1% for age > 60	24
	Thiropour-semi rural (Tamil Nadu)	3.5% for age > 60	25
	Ernakulum (Kerala)	3.1% for age > 60	26
	Vellore (Tamil Nadu)	0.8% for age > 65	19

Table-1: Prevalence rates for dementia in India.

3.7 million Indian people aged over 60, 2.1 million are women 1.5 million men [16]. It is argued that this cannot be explained by the fact that women live longer in India, because, studies of age-specific incidence of dementia among older people show no significant differences between women and men [17]. The prevalence of dementia increases steadily with age and higher prevalence is seen among older women compared with men (figure 1).

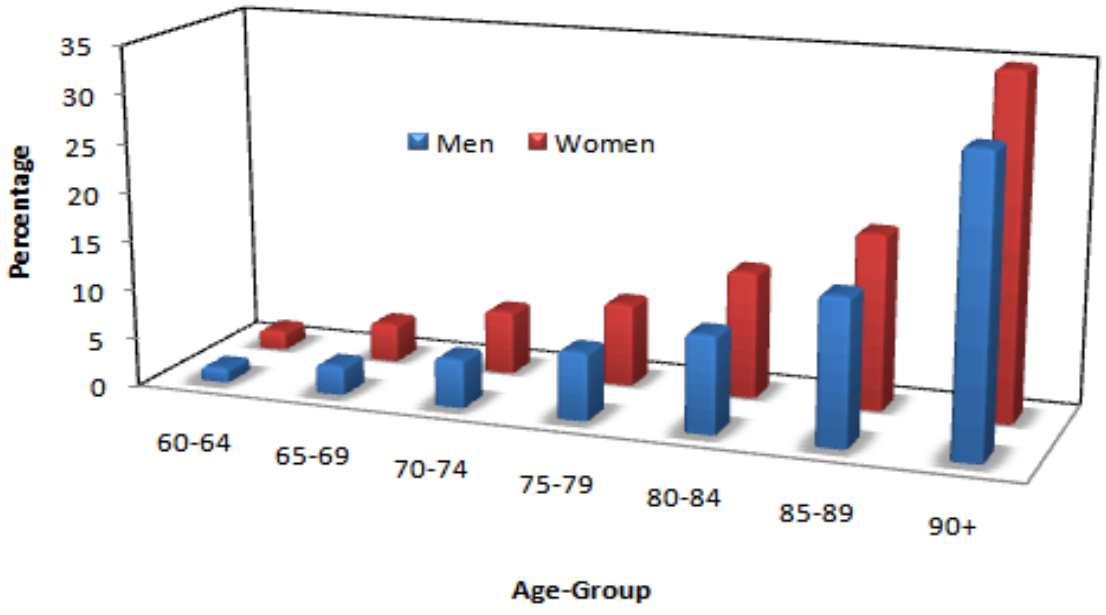

Figure 1: Prevalence of Dementia for India by Age and Gender, 2012 [10,18].

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SYMPTOMS OF DISEASE

It may be hard to know the difference between a typical age-related change and the first sign of Alzheimer's disease. Major 10 warning signs for Alzheimer's disease [27] are listed:

Memory loss that disrupts daily life: Forgetting recently learned information important dates or events. (*Typical age-related change*- Sometimes forgetting names or appointments, but remembering them later.)

Challenges in planning or solving problems - Some people may experience changes in their ability to develop and follow a plan or work with numbers. (*Typical age-related change*-making occasional errors when balancing a checkbook.)

Difficulty completing familiar tasks at home, at work or at leisure - Hard to complete daily tasks. (*Typical age-related change*-occasionally needing help to use the settings on a microwave or to record a television show.)

Confusion with time or place - People with AD can lose track of dates, seasons and the passage of time. (*Typical age-related change*- Getting confused about the day of the week but figuring it out later.)

Trouble understanding visual images and spatial relationships - vision problems, difficulty reading, judging distance and determining color or contrast are signs of Alzheimer's. (*Typical age-related change*- Vision changes related to cataracts.)

New problems with words in speaking or writing - May have trouble for joining a conversation. They may struggle with vocabulary, have problems finding the right word or call things by the wrong name (e.g., calling a watch a "hand clock"). (*Typical age-related change*- sometimes having trouble finding the right word.)

Misplacing things and losing the ability to retrace steps - A person with AD may put things in unusual places. (*Typical age-related change*- misplacing things from time to time, such as a pair of glasses or the remote control.)

Decreased or poor judgment - They may experience changes in judgment or decision making. (*Typical age-related change*- making a bad decision once in a while.)

Withdrawal from work or social activities - They may start to remove themselves from hobbies, social activities, work projects or sports. (*Typical age-related change*- sometimes feeling weary of work, family and social obligations.)

Changes in mood and personality - The mood and personality of people with AD can change. They can become confused, suspicious, depressed, fearful or anxious. They may be easily upset at home, at work, with friends or in places where they are out of their comfort zone. (*Typical*

age-related change-developing very specific ways of doing things and becoming irritable when a routine is disrupted.)

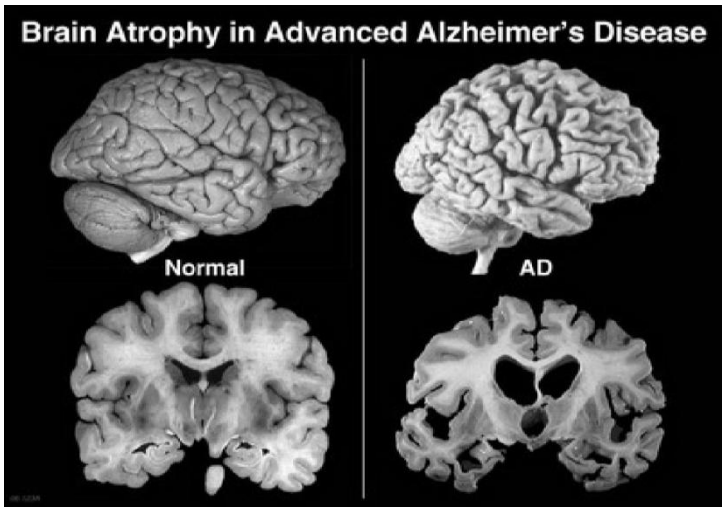

Fig 2: Brain Atrophy in Advanced Alzheimer's Disease [41]

CAUSES OF DISEASE

Basics and Environmental risk factors:

The greatest known risk factor for Alzheimer's is increasing age. Most individuals with the illness are 65 and older. After age 85, the risk reaches nearly 50 percent. Another risk factor is family history. Research has shown that those who have a parent, brother or sister with Alzheimer's are two to three times more likely to develop the disease. The risk increases if more than one family member has the illness. The genes that directly cause the disease have been found in only a few hundred extended families worldwide and account for less than 5 percent of cases. Experts believe the vast majority of cases are caused by a complex combination of genetic and nongenetic influences [28]. During the 1960s and 1970s, aluminum emerged as a possible suspect in causing Alzheimer's disease. This suspicion led to concerns about everyday exposure to aluminum through sources such as cooking pots, foil, beverage cans, antacids and antiperspirants. Since then, studies have failed to confirm any role for aluminum in causing Alzheimer's. Almost all scientists today focus on other areas of research, and few experts believe that everyday sources of aluminum pose any threat [28, 29]. Environmental exposure to some heavy metals such as cadmium appears to be a risk factor for Alzheimer's disease (AD), though, definite mechanism of their toxicity in AD remains to be elucidated. The impacts of Cd(II) on the conformation and self-aggregation of Alzheimer's tau peptide R3, corresponding to the third repeat of microtubule-binding domain has revealed [29]. The initial state of R3 was proven to be dimeric linked by intermolecular disulfide bond, in the non-reducing buffer (Tris–HCl buffer pH7.5, containing no reducing reagent). The Cd(II) can accelerate heparin-induced aggregation of R3 or independently induce the aggregation of R3, as monitored by ThS fluorescence. In the presence of Cd(II), the resulting R3 filaments became

much smaller, as revealed by electron microscopy. Binding to the Cd(II) ion, the dimeric R3 partially lost its random coil, and converted to α-helix structure, as revealed by CD and Raman spectrum [29]. On the other hand, gain in α-helix structure on the peptide chain, by coordinating with Cd(II), could be a critical role to promote self-aggregation, as revealed by Raman spectrum. These results provide a further insight into the mechanism of tau filament formation and emphasize the possible involvement of Cd(II) in the pathogenesis of AD [28, 29].

Amyloid hypothesis:

Alzheimer's disease and cerebral amyloid angiopathy are characterized by the deposition of β-amyloid fibrils consisting of 40- and 42-mer peptides (Aβ 40 and Aβ 42). The aggregation (fibrilization) of these peptides is closely related to the pathogenesis of these diseases [30]. Aβ 42 plays a more important role in the pathogenesis of these diseases since its aggregative ability and neurotoxicity are considerably greater than those of Aβ-40. Aβ peptides result from the proteolytic cleavage of β -amyloid precursor protein (APP) [31] by two proteases, β – and γ-secretase [32-34]. Under physiological conditions, the ratio of Aβ 42 to Aβ 40 is about 1:10. Aβ 42 plays a critical role in the pathogenesis of AD since its aggregative ability and neurotoxicity are much greater than those of Aβ 40 [33, 36]. Aβ 42 oligomers initially formed as a seed accelerate the aggregation of Aβ 40 to form the amyloid plaques that eventually lead to the neurodegeneration (amyloid cascade hypothesis) [37]. Although the direct involvement of Aβ peptides in AD is well documented and their aggregative ability is closely related to their neurotoxicity, the precise mechanism of the neurotoxic effects of Aβ peptides remains unclear. Moreover, it has recently been reported that the neurotoxicity of Aβ peptides might be ascribable to the oligomeric species, not the fibrils [38, 39]. The structural analysis of Aβ fibrils is one of the most promising ways of revealing the mechanism of AD. Recent biophysical investigations using electron microscopy, Fourier transform infrared spectroscopy (FT-IR), and circular dichroism (CD) spectroscopy showed that Aβ fibrils adopt a β -sheet structure [39]. However, a high-resolution structural analysis of Aβ fibrils has yet to be conducted since single crystal X-ray crystallography and solution NMR cannot be applied to insoluble Aβ fibrils.

Tau hypothesis:

Alzheimer's disease (AD) (Alzheimer, 1907) is a neurodegenerative disease which is characterized by the presence of two types of neuropathological hallmarks: neurofibrillary tangles (NFTs) and senile plaques [40]. It is collectively designated as ''tauopathies'', because they are characterized by the aggregation of abnormally phosphorylated tau protein. NFTs are intraneuronal aggregates of abnormally phosphorylated tau (phosphorylated at non physiological sites). Senile plaques are extracellular and mainly composed of amyloid β -peptide (Aβ) deposits. The mechanisms responsible for tau aggregation and its contribution to neurodegeneration are still unknown. The regulation of tau takes place predominantly through post-translational modifications. To aggregate into PHFs (paired helical filaments), tau affinity for microtubules must be decreased to release tau in a soluble form. Dissociation of tau from microtubules, probably by phosphorylation, results in microtubule destabilization. Then, newly

soluble tau proteins are targeted by post-translational modifications that directly or indirectly alter tau conformation, promoting tau dimerization in an anti-parallel manner. Stable tau dimers form tau oligomers, which continue in the aggregation process and constitute subunits of filaments, called protomers. Two protomers around each other formed PHFs and PHFs assembly makes NFTs [40]. As a result of neuronal death, tau oligomeric species are released into the extracellular environment, thus contributing to microglial activation and providing positive feedback on the deleterious cycle that lead to progressive degeneration of neurons in AD brains [41]. Therefore, information obtained in the process of testing this new hypothesis experimentally will likely be helpful to formulate an innovative AD therapy and to design reliable biomarker strategies for its diagnosis.

Tau gene, mRNA and protein structures:

Tau protein (tubulin-associated unit) was identified in 1975 [39,42]. Tau is a microtubule-associated protein highly conserved and exclusively found in higher eukaryotes [39]. Tau is mainly expressed in neuron and its primary role is to stabilize neuronal cytoskeleton by interacting with microtubules. Tau is encoded by a single gene located in locus 17q21.3 in human [43]. Among the 16 exons of tau gene, exons 2, 3 and 10 undergo alternative splicing, whereas exon 4A is only transcribed in the peripheral nervous system [39, 44, 45]. To date, exons 6 and 8 have not been described to be transcribed [44]. In the central nervous system, alternative splicing of tau primary transcript generates six isoforms of 352–441 amino acids with an apparent molecular weight between 60 and 74 kDa [39]. Exon 14 is transcribed but generates a premature stop codon preventing translation [44].

Depending on the presence or absence of exon 10, tau isoforms are called 4R (with exon 10) or 3R (without exon 10) [39]. Tau isoforms are called 0N (without N-terminal insert), 1N (with one N-terminal insert encoded by exon 2) or 2N (with two N-terminal inserts encoded by exons 2 and 3). This gives six combinations corresponding to the six tau isoforms: 4R/2N, 4R/1N, 3R/2N, 4R/0N, 3R/1N and 3R/0N. Each repeat domain contains a conserved consensus motif KXGS, which can be phosphorylated at serine [46]. Serine phosphorylation at KXGS motifs, belonging to MBD region, decreases tau affinity for microtubules and consequently prevents its binding to microtubules which results in the destabilization of the neuronal cytoskeleton [47]. Cytoskeleton destabilization is well known to cause disruption of tau-dependent cellular functions including axonal growth, vesicle and organelle transport as well as nervous signal propagation along the nerve network formed by microtubules [48].

TREATMENT

Approved drugs in markets:

Alzheimer's disease is a devastating neurodegenerative disorder manifested by deterioration in memory and cognition, impairment in performing activities of daily living, and many behavioral and neuropsychiatric illnesses. The pathological hallmark of Alzheimer's disease is widespread neuritic plaques which are accumulations of amyloid beta protein and

neurofibrillary tangles. Studies report that deficit in cholinergic system is responsible for cognitive decline and memory loss in patients with Alzheimer's disease. The leading edge therapies of Alzheimer's disease are approved drugs listed in table 2 [49].

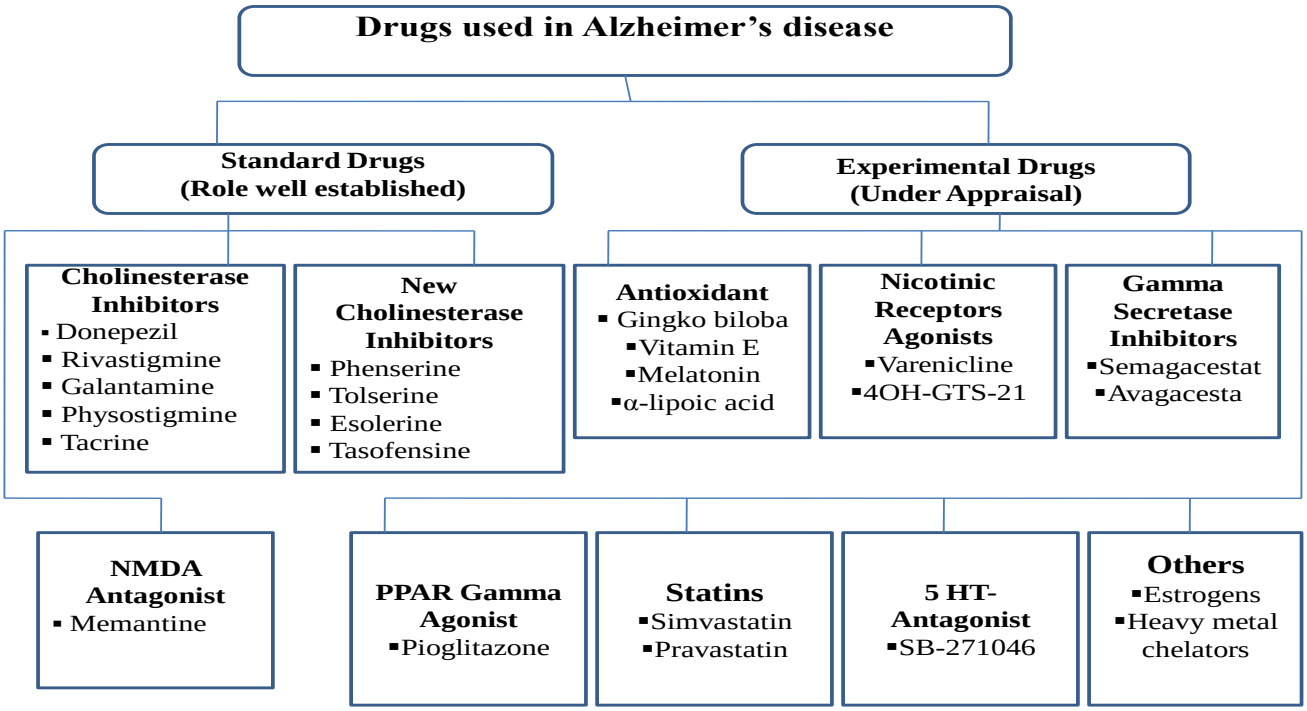

Fig. 2: Drugs used in Alzheimer's disease.

The pharmacological agents used for treatment of Neuropsychiatric illnesses include antipsychotics, antidepressants and mood stabilizers. Treatment of Alzheimer's disease also includes health maintenance activities and proper nursing care of the patients.

Treatment -Alternative forms of medicine:

There are several non pharmacological strategies, which manage the functional and behavioral deterioration (www.gmhfonline.org). A recent review has suggested that there is evidence to support the efficacy of activity programs, music, behavior therapy, light therapy and changes to the physical environment [50].

Independence promoting strategies: Usage of incentives, verbal and physical prompting and physical guidance. Helps the patient in maintaining hygiene, dressing, grooming etc.

Exercise: Simple exercises like walking and cycling can improve sleep and decrease agitation.

Incontinence management: By monitoring incontinence and scheduling bathroom time or by putting reminders.

Sleep management: Enhance night time sleep by dark environment at night and limiting day time napping.

White noise: Continuous background monotonous noise reduces agitation and is soothing. Music therapy also helps to stir memories.

Visual cueing- Pasting pictures of bed on bedroom door can help the patient find his way around home.

Counseling, reminiscence therapy, validation, simulated presence, pet therapy, recreational therapy and art therapy are other ways of reducing behavioral swings in a patient suffering from Alzheimer disease.

APPLICATION OF MODERN TECHNOLOGY FOR DIAGNOSIS AND TREATMENT – UNDER DEVELOPMENT-HYPOTHESIS

Cell based therapy:

Skin cells from patients with Alzheimer's disease have been reprogrammed to form brain cells, offering clues to their dementia and the prospect of early diagnosis and new ways of finding treatments. Goldstein and his team created Induced pluripotent stem (IPS) cells from four patients with AD and two people without dementia. IPS cells are made by treating fibroblasts, a type of skin cell, with reprogramming factors to revert them to an embryonic-like state. Like the stem cells in early embryos, IPS cells can form any tissue in the body — including neurons [51]. The researchers generated neurons from patients with two types of Alzheimer's: familial, which is caused by inherited, rare mutations in specific genes, and sporadic, which results from an interplay of genetic and environmental factors. The reprogrammed neurons from the patients with familial AD have showed defects that had been seen before in the brains of Alzheimer's patients. Compared to unaffected cells, their neurons produced higher levels of amyloid-β, a protein that builds up and forms plaques in patients with Alzheimer's. This is not surprising, as their mutation is in a gene that encodes amyloid-β. But their neurons also produced high amounts of another protein, tau, which forms tangles in the brains of patients [51].

Many researchers are concerned that these *"disease-in-a-dish"* models based on IPS cells may not be true reflections of the disease, but may be artifacts from the reprogramming process.

Antibodies could be key defenders against Alzheimer's, recent evidence [42]

The newly found antibodies selectively target aggregates of beta amyloid proteins that

are toxic to brain cells, while ignoring the benign single-molecule forms of the same proteins. The existence of such antibodies was predicted by animal studies, but they were never previously demonstrated to be present in substantial quantities in blood from normal humans. Relkin's team [52] has been testing an antibody-based immunotherapy called intravenous immunoglobulin (IVIg), which is made from the blood of healthy donors, as a potential new treatment for Alzheimer's.[52] Since IVIg was known to contain small amounts of antibodies against β-amyloid, the researchers hoped for a correspondingly modest reduction in the harmful plaques in Alzheimer's patients. Studies demonstrated that IVIg initially bound very little single-molecule (monomer) β-amyloid in a test tube [52]. However, it gathered up much more of the protein when the amyloid was aged in a way that allowed clumps of many molecules -- called oligomers -- to form. These oligomers can grow into the insoluble fibers that cluster around brain cells; a hallmark of Alzheimer's. While monomers are produced from birth and appear to be relatively benign, the oligomers have been implicated as potent toxins responsible for Alzheimer's-linked memory loss and brain cell death [52].

CONCLUSION

Over the last two decades, tremendous knowledge has been gained on AD, and its diagnosis, pattern of care, epidemiology, and economic impact. Alzheimer disease is one of the most debilitating diseases affecting the old age. A clear understanding of the natural history of Alzheimer disease has enabled us to develop appropriate trial designs and outcomes for the various stages of this condition. Clear benefit for the treatment of symptoms in mild to severe AD using AChEIs and Memantine is seen. Also, there is cautious optimism for successful disease modification using a number of agents currently under study. Guidelines for the treatment of Alzheimer disease have to be constantly updated to take into account new evidence for the ultimate benefit of patients and care-givers. As the population ages, the venue of new treatments for the management of AD, as well as the reforms occuring in the health care system, will force the integration of the current knowledge base with the aim of better addressing the needs of patients with AD, and their families.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

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