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REVIEW ARTICLE

Alzheimer's Dementia: An Overview

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Abstract | Alzheimer's disease (AD), the most common cause of dementia, is a chronic illness characterized by cognitive symptoms, behavioural and psychological symptoms and difficulty in performing activities of daily living. Mild cognitive impairment (MCI) is regarded as a transitional state between healthy cognitive ageing and dementia and around 12–15% of individuals with MCI progress to dementia annually. This provides unique opportunity to initiate treatments targeted to delay or prevent the onset of AD. Based on the age at onset, AD is divided into two broad categories: early onset and late onset. Early onset AD follows the classical mendelian pattern of inheritance, whereas the late onset AD has a complex interplay of gene–environment interaction, with several lifestyle-related risk factors strongly implicated in the pathogenesis of this degenerative condition. The onset of AD pathology predates the clinical symptoms by several years. The neurodegenerative processes in AD is related to the accumulation of abnormally folded Aβ and tau proteins in amyloid plaques and neuronal tangles. Diagnosis of AD is by presence of cluster of clinical features and aided by biomarkers such as CSF Aβ42 and PET amyloid imaging, CSF tau and tau imaging, 18fluorodeoxyglucose uptake on PET and atrophy on structural magnetic resonance imaging increase the diagnostic certainty. In the absence of curative treatments, the management of AD involves pharmacological treatment to delay the onset or progression of AD and supportive care by family members. Targeting these lifestyle-related factors in young adulthood and middle age may be protective against AD. High educational achievement in early life, involvement in cognitively stimulating activity, physical activity and social engagement including rich social network have been associated with reduced risk of late-life dementia and AD.

1 Introduction

Dementia, a chronic, progressive condition, is characterised by global deterioration in cognitive functions like memory, learning, orientation, language, comprehension, visuospatial abilities, problem-solving and judgement.[1] Alzheimer's disease (AD) is the most common type accounting for more than 80% of the dementia cases worldwide, in the elderly population.[2] In addition to deteriorating cognition it is also characterised by behavioural and psychological symptoms.[1]

The global prevalence of Alzheimer's dementia worldwide in 2015 was estimated at 46.8 million and estimated to reach 74.7 million in 2030 with East Asia having the most people living with dementia in the world, 9.8 million in 2015. The

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global cost of dementia was around US$818 billion in 2015 and estimated to increase to US$ 1 trillion in 2018.[3] In India, around 3.7 million people above the age of 60 years had dementia in the year 2010, which is expected to increase to 7.61 million in 2030. The estimated total societal cost of dementia for India was US$ 3.4 billion with informal care being more than half of the total cost (56%).[4]

2 Clinical Features and Diagnosis

AD is characterised by three primary groups of symptoms: cognitive symptoms, behavioural and psychological symptoms and also by difficulty in performing activities of daily living. Cognitive dysfunction includes impairment in memory, visuospatial abilities, language and executive functioning. The behavioural and psychological symptoms of dementia (BPSD) include agitation, aggression, delusions, hallucinations, depression, disinhibition and apathy. Difficulty in performing activities of daily activities includes both basic and instrumental activities.[1,5] The onset and progression of the illness is gradual. It usually begins with mild memory disturbances and word finding difficulties and is only recognised by care givers when the symptoms impair functioning.[1] In the initial stages, the differences between typical age-related cognitive and behavioural changes and signs of AD can be subtle making the diagnosis difficult. With progression of AD, impairments in other cognitive domains such as difficulties in finding one's home or where they are with a risk of wandering and becoming lost, difficulty in handling money or counting, trouble understanding complex two-step commands, making grammatical mistakes while speaking, unable to name common objects or failing to understand the meanings of common words, unable to recognize the emotions of people around and empathize with them, disturbance in the ability to exercise self-restraint and maintain appropriate inhibitions, losing regard for customs or morals, tendency to repeat the same behaviour or utter the same words or phrases over and over. In later stages, behavioural and psychological symptoms like depressed mood, lack of interest, worrying about the future, being tearful and easily upset, exhibiting verbal and physical aggression, excessive walking, beliefs of being persecuted, infidelity, perceptual disturbances in the visual or auditory modality, changes in sleep pattern and sleep cycle are seen.[1]

The clinical diagnosis of dementia involves history from an informant, physical examination and cognitive status assessment. In addition, it must be differentiated from other conditions that mimic dementia. Various clinical diagnostic criteria have been in use to diagnose AD such as the Diagnostic and Statistical Manual of mental disorders (DSM) IV[6] and DSM 5 criteria.[7] The National Institute on Aging-Alzheimer's Association (NIA-AA) criteria (2011) is widely accepted. It has proposed criteria for all-cause dementia followed by criteria for probable AD (Table 1) and possible AD for use in clinical settings and probable or possible AD with evidence of the AD pathophysiological process intended for use in research settings.[8]

Mild Cognitive Impairment (MCI): Evidence from several lines of research suggests that the onset of AD pathology predates the clinical symptoms by several years. MCI is regarded as a transitional state between healthy cognitive ageing and dementia[9]. The most widely used revised diagnostic criteria consider impairments in other cognitive domains as well, in addition to memory.[10,11] (Table 2) Patients diagnosed with MCI can be categorized either as amnestic MCI (a-MCI), if the patient had impairments in performance on episodic memory and non-amnestic MCI (na-MCI) if cognitive domains other than memory, namely executive functions, language or visuospatial abilities were involved. Impairments can involve one (MCI single domain) or multiple domains (MCI multiple domains).[11] Multiple longitudinal studies have shown that amnestic MCI and multi-domain MCI subtypes progress more frequently to AD, whereas non-amnestic MCI progresses more frequently to non-AD forms of dementia, including vascular dementia. It is important to note that among patients with MCI a substantial number remain cognitively stable or even improve, reverting to normal cognitive status.[12,13] Only 12–15% of individuals with MCI progress to dementia annually[14] (Table 2).

3 Neurocognitive Changes in Normal Ageing, MCI and AD

Cognitive decline is a natural process with aging. However, the decline is not global but scattered. While crystallized abilities like vocabulary and general knowledge remain preserved, fluid abilities like processing and learning new information, solving problems and manipulating the environment are known to decline in the process of natural aging.[15–17] Cognitive domains of executive function, processing speed, memory and psychomotor ability are considered fluid abilities. Speed of processing information, selective and

Table 1: Core clinical criteria for probable Alzheimer's Disease.

Probable AD dementia is diagnosed when the patient
1. meets criteria for dementia and in addition and has the following characteristics:
A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
B. Clear-cut history of worsening of cognition by report or observation; and
C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:
i. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
ii. Nonamnestic presentations:
Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia and alexia. Deficits in other cognitive domains should be present.
Executive dysfunction: The most prominent deficits are impaired reasoning, judgment and problem solving. Deficits in other cognitive domains should be present.
D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioural variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or non- fluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup.[8]

divided attention, that is, the ability to focus on specific information and on multiple streams of information are known to decline with ageing. Decline in memory is a common occurrence in ageing. While procedural memory, the memory for motor and cognitive skills is preserved, declarative memory is impaired with age. In declarative memory, learning[18,19] as well as the retrieval stages of memory[19–21] is impaired with age but the retention of information, that is, information that is successfully learned[22] as well as recognition of that information[23] is preserved.

There is a considerable overlap in cognitive performance between normal ageing, and preclinical dementia, which is also known as MCI.[24] Cross-sectional studies on ageing and cognition suggest that MCI is characterised by cognitive declines that are greater than expected for a given age and educational level.[25] Cross-sectional investigations comparing controls, MCI and patients with AD demonstrate that following episodic memory deficits, deficits in semantic cognition performance pre-empt the appearance of attention/executive dysfunction and visuospatial impairment.[26] Amongst the different cognitive domains, episodic memory and semantic fluency are the most important and have consistently shown to best predict transition from MCI to AD with 85–89% accuracy.[27]

While there is a continuum between normal ageing and MCI, it is important to note that AD is not normal part of ageing. The memory impairments in AD are qualitatively different; patients with AD usually do not benefit from cueing or inherent structure (logical sequence) and their recognition ability is as impaired as their free recall performance, contrary to normal ageing. In addition, AD patients show impaired consolidation of learned information, perform deficiently on episodic memory tasks, regardless of the perceptual modality of the stimuli used in these tasks.[28] Normal elderly subjects typically perform better on the category fluency task (number of words generated in a minute belonging to a

Table 2: Clinical criteria for MCI.

1.	Subjective cognitive complaint, preferably corroborated by an informant
2.	Objective memory and/or other cognitive impairments that:
a.	Are abnormal for the individual's age and education, as documented using neuropsychological testing
b.	Represent a decline from previous levels of functioning
3.	Normal ability to perform activities of daily living
4.	Absence of dementia

category) than on the letter fluency task (number of words generated in a minute starting with a specific alphabet); however, this is reversed in AD. On the other hand, AD patients show preserved perceptual priming effects in implicit memory, but have impaired priming in word stem completion and category exemplars tasks.[29]

In summary, following episodic memory deficits, impairment on semantic cognition performance heralds the appearance of deficits in attention, executive and visuospatial functions. Appropriately selected neuropsychological tests employed in a longitudinal methodology could substantially contribute to the identification, staging and tracking of AD. The major challenges which limit the test selection in developing country like India are the need for modification of the tests for illiterate population and lack of culturally appropriate test. Considering illiteracy is a major risk factor for dementia it is important to develop culturally appropriate tests which are valid in illiterate population.

4 Risk and Protective Factors of AD

Despite considerable research in the past few decades the pathogenesis of AD is not completely known. Several lines of research point towards a multi-factorial causation with a significant gene–environment interaction in the development of AD. Two types of AD have been identified based on the age at onset: early onset AD (EOAD) and late onset AD (LOAD). While the EOAD is autosomal dominant LOAD is sporadic and hence the pathogenesis of AD involves contributions from both genetic and environment factors.

4.1 Genetic Risk Factors

- *Genes implicated in Autosomal dominant AD* The autosomal dominant AD follows a classical Mendelian pattern of inheritance with age-dependent penetrance. Mutations in β-Amyloid precursor protein (*APP*), Presenilin 1 (*PSEN1*) and Presenilin 2 (*PSEN2*) cause early onset AD.[30]
- *Genes involved in cholesterol metabolism* APO-E gene, associated with cholesterol metabolism is the strongest risk factor for LOAD.[31] This gene encodes three common isoforms (ε2, ε3, ε4) that differ by one or two amino acid substitutions which alters their binding properties and stability, rate of production and clearance.[32] Homozygote for APOE ε4 allele is associated with 12-fold increase in risk of AD.[33–35] APOEε4 isoform is estimated to contribute to approximately up to 50% of the cases of sporadic AD. The lifetime risk of AD is 20–30% in heterozygotes for ε4 and increases to 50% in homozygotes. In addition to APOE, polymorphisms in other cholesterol metabolism genes, namely Clusterin and ABCA7 are also implicated as risk for development of AD. Clusterin *(CLU)* gene, located on chromosome 8p21.1, and ATP-binding cassette transporter A7 *(ABCA7) gene,* located on chromosome 19p13.3, also increase the risk of late-onset AD.
- *Genes involved in immune response* Considering the growing literature of immune dysregulation in AD genes involved in immune response have been examined in AD pathogenesis. Variants in genes *CR1,* CD33*, MS4A, CLU* and *EPHA1*are shown to have a small effect on the risk of LOAD. Common variants in the genes involved in the process of endocytosis, a critical step in the normal processing of APP, namely BIN1, PICALM, CD2AP, EPHA1 and SORL1 also have a small effect on the risk of LOAD.[30]
- *Rare variants* Recent studies on smaller samples using whole genome or exome sequencing have identified rare coding variants in two genes, PLD3 and TREM2, which have moderate to large effects on the risk of AD. TREM2, located in the region on chromosome 6q21.1, encodes a receptor on microglia which stimulates phagocytosis and suppresses inflammation. Rare coding polymorphisms in this gene, for example RH7H variant increase the risk of LOAD by 1.7–3.4 times.[30]

4.2 Other Risk and Protective Factors

- Demographic factors: Increasing age is the most important risk factor for the development of AD, with the risk doubling every 5 years after the age of 65 years.[36] Women have higher risk of developing AD but this could be due to the higher life expectancy of women.[36]
- Prenatal, perinatal and childhood adversity: Intrauterine environment and nutrient intake, during the prenatal period and early postnatal development, are important for development and maturation of nervous system which may in turn influence the risk of cognitive impairment and dementia in old age.[37] Early life events like death of the parent in childhood and adolescence have increased risk of developing late life AD.[38,39] The critical periods for maternal and paternal death for risk of later life AD probably varies.[39]

- Education: Low education has been found to be a consistent risk factor for AD across various studies.[40,41] Higher level of education is considered to delay the onset of clinical symptoms in patients with risk of developing AD by probably compensating for the risk factors.[42] There is robust evidence that higher levels of education and to a lesser extent higher occupational attainment are protective factors against the risk of AD as they enhance cognitive reserve.[43,44]
- Late life depression: Depression has been studied as one of the possible risk factors for development of AD. There is substantial evidence of late life depression being specifically associated with increased risk of dementia.[45,46] However, late life depression can be a part of the prodrome of dementia due to its underlying neurodegenerative processes or a manifestation of very early pre-clinical symptoms of cognitive impairment.
- Cardiovascular risk factors: Various cardiovascular risk factors increase the risk of AD such as smoking,[47] midlife hypertension,[48] late-life diabetes,[49,50] midlife obesity, specifically central obesity,[51,52] increased plasma homocysteine levels[53] and midlife hypercholesterolemia.[54] In addition, cardiovascular diseases such as stroke (asymptomatic or silent stroke), atrial fibrillation, coronary heart disease (CHD) and heart failure increase the risk of AD.[53] These cardiovascular risk factors can play a role in AD pathogenesis through multiple pathways (Fig. 1).
- Smoking: Smoking is an important modifiable risk factor in the pathogenesis of AD through multiple pathways. For example, smoking increases the risk of cardiovascular disease which in turn is associated with the risk of AD. In addition, smoking has a direct effect on the AD pathology as it also decreases amyloid precursor protein processing, increases neuroinflammation, causes synaptic damage and reduces clearance of Aβ amyloid.[55,56] Risk increases in people with heavy consumption; however, the evidence for this association is not consistent.[46]

5 Pathophysiology

Based on the above-mentioned risk factors and based on the neuropathological, biochemical studies, several hypotheses have been proposed to explain the pathogenesis of AD. Amongst them the Aβ hypothesis is most influential. However, it is increasingly recognised that the Aβ hypothesis alone does not account for the complex pathophysiology of AD. Abnormalities in several other pathways, namely cholinergic, tau and inflammatory, independently or by influencing Aβ pathway, play key role in the pathogenesis of AD.

The strongest support for Aβ and tau hypothesis emerges from the neuropathological studies. The neuropathological hallmark of Alzheimer's disease includes synaptic loss and selective neuronal death and the presence of abnormal proteinaceous deposits in neurons (known as neurofibrillary tangles) and in the extracellular space (as cerebrovascular, diffuse and neuritic plaques).[31] Aβ, the main constituent of plaques, is a normal product of APP metabolism and is generated at high levels in neurons throughout an individual's lifetime. As per the amyloid cascade hypothesis, APP is normally cleaved by alpha secretase and pathologically cleaved by beta and gamma secretase.[2]

Mutations in the APP gene and PSEN1 and PSEN2 gene, as in autosomal dominant AD, lead to increased production of Aβ, particularly Aβ42 and increased Aβ42/Aβ40 ratio in the CNS which has more tendency to aggregate.[2,31] However, in patients with sporadic AD, Aβ clearance is decreased in the CNS in the absence of significant abnormality in Aβ production. This Aβ peptide has the tendency to spontaneously aggregate into soluble oligomers and then coalesce to form fibrils which are insoluble. These in turn result in beta-sheet conformation which is deposited in diffuse senile plaques.

Aβ oligomers that dissociate from the plaques and Aβ fibrils cause synaptic and mitochondrial damage through oxidative stress and induce tau aggregation. The amyloid plaques also contribute to the damage by attracting microglia that produce and release pro-inflammatory cytokines which stimulates nearby neuron–astrocyte complex to produce more Aβ oligomers.

Tau which normally binds and stabilizes the microtubules is essential for axonal transport. The tau aggregation results in the formation of neurofibrillary tangles leading to neuronal damage.[2,31] APOE acts as a pathological chaperone for Aβ which affects its clearance and subsequent deposition leading to plaque formation, causes alteration in the phosphorylation of tau leading neurofibrillary tangle formation and causes alterations in lipid metabolism leading to inhibition of neurite extension[31] (Fig. 1).

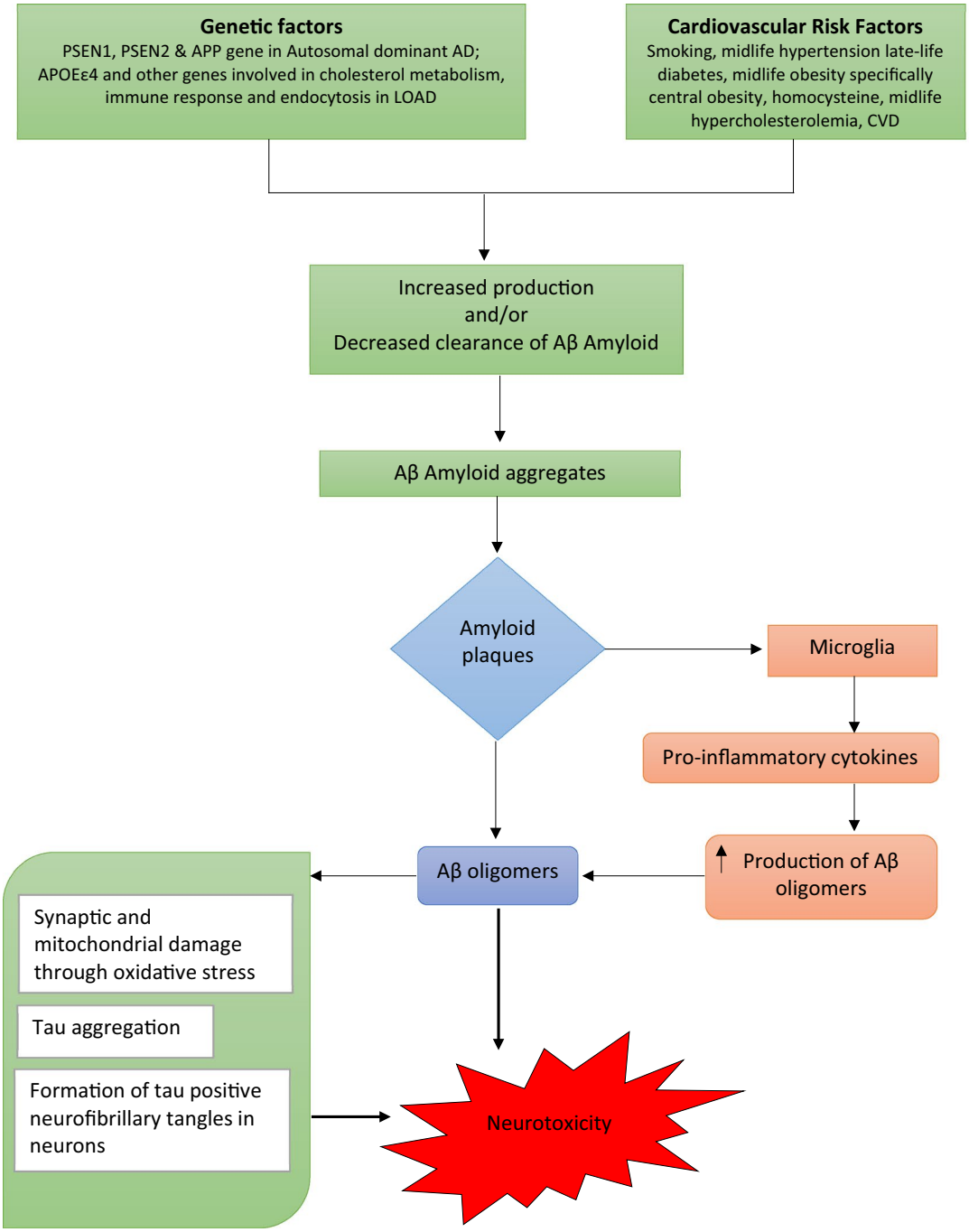

Figure 1: Schematic represenation of pathophysiology of AD.

6 Investigations

Different laboratory tests along with structural brain imaging with CT or MRI are performed during the evaluation of patients presenting with dementia or cognitive symptoms to exclude potentially reversible causes of dementias. Depression, adverse effects of drugs, alcohol abuse, intracranial space-occupying lesions, normal pressure hydrocephalus, endocrine abnormalities like hypothyroidism and nutritional deficiency (like vitamin B_{12}/folate deficiency) are the common, potentially reversible conditions in patients with cognitive impairment or dementia. Thyroid function tests and vitamin B_{12} level are the two initial tests frequently performed during the initial evaluation. Apart from

these complete blood cell count, serum electrolytes, serum calcium and serum glucose, Serum creatinine, BUN aid in excluding potential infections or metabolic causes for cognitive impairment. Few investigations like serology for syphilis, Lyme disease, human immunodeficiency virus (HIV), urinalysis with urine culture and sensitivity, heavy metal assays, erythrocyte sedimentation rate, liver function, serum folic acid level or other vitamin level assays will be performed in case of clinical suspicion.[57,58]

Definitive diagnosis of Alzheimer's dementia based on clinical details and history only is difficult and challenging. However, diagnosis aided by biomarkers improves the level of its certainty. The biomarkers included in the criteria for the evidence of pathophysiological process include (a) brain amyloid-beta (Aβ) protein deposition—low CSF Aβ42 and positive PET amyloid imaging (b) markers of downstream neuronal degeneration, elevated CSF tau (both total tau and phosphorylated tau (p-tau)) (c) decreased 18fluorodeoxyglucose (FDG) uptake on PET in temporo–parietal cortex (d) disproportionate atrophy on structural magnetic resonance imaging in medial, basal, and lateral temporal lobe and medial parietal cortex.[8]

7 Treatment of AD

In the absence of disease modifying or reversing treatments the management of AD involves (a) pharmacological treatment to delay the onset or progression of AD (b) supportive care by family members and (c) attending to the needs of caregiver. In addition to the cognitive symptoms, the treatment also addresses the behavioural and psychological symptoms of dementia which nearly affect all patients during the illness. It is important to actively address BPSD as it leads to increased economic burden and stress among the carers and is associated with early placement in nursing home and poor patient-related health outcomes.[5]

7.1 Pharmacological Management

- *Cognition enhancing agents* Two classes of drugs have been approved for use in patients with AD which enhance cognition, cholinesterase inhibitors (CI) and the *N*–methyl-d–aspartate (NMDA) receptor antagonists. Cholinesterase inhibitors donepezil, rivastigmine and galantamine are approved for treatment of mild to moderate AD.[59] The cholinergic hypothesis of AD states that the basal forebrain is involved early in the disease process leading to the loss of acetylcholine neurons and resulting in the deterioration of memory and other cognitive processes and later leading to the non-cognitive symptoms like BPSD.[59] These drugs act by enhancing the cholinergic transmission by decreasing the extrasynaptic metabolism of acetylcholine and thereby increasing its synaptic residence time. All cholinesterase inhibitors have same efficacy and there is no evidence of superior efficacy for any amongst them. Several randomized double-blind placebo-controlled trials of cholinesterase inhibitors have reported improvement in the cognitive function, measure of daily living and behaviour. However, it is to be noted that none of the treatment effects observed were large.[60] Patients on these medications show initial mild improvement in cognitive functions over the first 3 months as compared with those on placebo treatment. Subsequently, over the next 3–9 months the mean decline in cognitive functions was also less rapid.[59] Common adverse effects and recommended dose of cholinesterase inhibitors are given in Table 3.[61,62]
- *NMDA receptor antagonist* Memantine is a non-competitive NMDA receptor antagonist approved for treatment of moderate to severe AD.[2] In animal models of AD, it improved spatial learning, protected neurons from Aβ induced toxicity, decreased apoptosis, free radical mediated damage and restored synaptic degeneration. It has small beneficial effect to treat cognitive and functional decline at 6 months in moderate to severe dementia.[63] Combination therapy of cholinesterase inhibitor and memantine is well tolerated, provides additive benefits and helps in moderate stabilization of the disease course.[31] Rather than cognitive improvement which is seen in a small number of patients, majority of the patients experience delay in further decline of cognition for 6–9 months following initiation of treatment with cognitive enhancers.[64,65]
- *Drugs used for treatment of BPSD* Drugs used in the treatment of neuropsychiatric disturbances in dementia are used off label, as no drug has been approved specifically for use in this condition. Antipsychotics risperidone and aripiprazole have been found to have maximum evidence for use in aggression, agitation and psychosis associated with dementia. Evidence for quetiapine was found to be insufficient and efficacy for olanzapine was found only for aggression and agitation with less effect in patients with psychosis. However, it is to be noted that use of antipsychotics is associ-

Table 3: Common adverse effects and recommended dose of medications used in treatment of dementia.

Drug	Recommended Dose	Side Effects	Contraindications
Donepezil	5-10 mg/day	Diarrhoea, nausea, headache, weight loss, insomnia, dizziness, muscle cramps, Increased gastric acid secretion fatigue, depression	Proven allergy to Donepezil To be used with caution in cases with cardiac impairment, asthma, pulmonary disease, gastric ulcers
Rivastigmine	1.5 mg BD to 6 mg BD	Anorexia, dizziness, Nausea, Vomiting, Diarrhoea, appetite loss, weight loss, increased gastric acid secretion, headache, fatigue, sweating	Proven allergy to Rivastigmine To be used with caution inn cases with cardiac impairment, asthma, pulmonary disease, gastric ulcers
Galantamine	4 mg BD to 12 mg BD	Nausea, Vomiting, appetite loss, weight loss. Increased gastric acid secretion, headache, fatigue, sweating	Proven allergy to Galantamine To be used with caution inn cases with cardiac impairment, asthma, pulmonary disease, gastric ulcers
Memantine	5 mg/day to 20 mg/day	Dizziness, headache, lethargy, constipation, hypertension, seizures(rare)	Proven allergy to Memantine, Amantadine analogues Severe renal impairment

ated with metabolic side-effects, somnolence, extrapyramidal side effects and increased risk of cerebrovascular events.[66–69] Additionally, they are associated with increased risk of mortality when used in patients with dementia[5]. Antidepressants have been found to have minimal benefit for treatment of depression in patients with Alzheimer's dementia. However, they may have a role in management of agitation in these patients.

- *Disease modifying therapies* The primary targets of disease modifying therapies in AD are Aβ amyloid and tau. Anti-amyloid therapies include anti-aggregation drugs, β secretase and γ secretase inhibitors, and immunization strategies, both active and passive. These strategies are in the stage of investigational clinical trials, and at this stage none of the disease modifying therapies are approved.[70]

7.2 Behavioural and Environmental Interventions in Management of AD

- *Supportive care* Care by the family members involves ensuring safety and adequate supervision of the patient as they are at risk of wandering and may harm others if comorbid BPSD is present. Structuring the environment may be required to avoid wandering, avoiding unnecessary changes in the environment, avoiding complex tasks and confrontation. Family members need to be educated about the illness, its progression and available treatment options regarding financial and legal issues.[71]
- *Interventions for BPSD* Various strategies have been used in patients, namely light therapy, stimulated presence therapy, validation therapy, music-based interventions and cognitive training and rehabilitation. Environmental approaches include avoiding under stimulation or overstimulation, ensuring safety, structuring routine activities including exercise and those that match interests of individual. These have been found to prevent and reduce behavioural symptoms. Interventions with the care-givers include problem solving approach with a family member to identify precipitating causes and modifying these behaviours. Other approaches include training the care giver to tailor patient's activities based on interest and cognitive as well as physical functioning.[5]
- *Interventions to decrease caregiver burden* Addressing the needs of the patient's family is equally important. Providing support to care givers, addressing burden, helping them with home modification strategies, enabling them with problem solving strategies and referral to community resources are beneficial for the patient for continued support by the family members.[72]

8 Prevention

Individuals with certain compensatory and protective factors might not develop dementia despite risk, for example those carrying APOEε4 allele. Exposure to various cardiovascular risk factors such as hypertension, diabetes, hypercholesterolemia and obesity in middle age (< 65 years) or several years before the onset of dementia is associated with increased risk of dementia and AD.[73] Targeting these lifestyle-related factors in

young adulthood and middle age would be beneficial to delay the onset of dementia. Other protective factors like high educational achievement in early life, involvement in cognitively stimulating activity, bilingualism, high complexity at work, physical activity and social engagement including rich social network have been associated with reduced risk of late-life dementia and AD.[74] Evidence suggests that various psychosocial protective factors like high education and occupational attainment, and establishing and maintaining rich social networks can maintain cognitive activity compensating for the deleterious effects of vascular and AD pathology on cognitive functioning in the brain.[74]

The importance of preventive strategies is highlighted by the fact that interventions to control the prevalence of these modifiable risk factors by 10–20% per decade, especially low education, midlife hypertension, midlife obesity, diabetes, physical inactivity, smoking and depression could reduce the worldwide prevalence of AD in 2050 by 8–15%.[75] Multicomponent interventions through attention to multiple risk factors simultaneously can probably decrease the risk of incidence of dementia.[76]

In addition, various disease modifying (anti-amyloid) drugs are under trial in asymptomatic populations with increased risk of developing AD detected by increased biomarker burden or a specific genetic profile to intervene before the symptoms emerge. However, these studies are still in investigative stage[74] and there is no approved treatment for prevention of AD.

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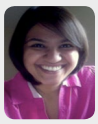

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