

Recent Advances in the Management of Alzheimer's Disease

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Abstract: Alzheimer disease is the most common cause of dementia and contests closely stroke as 4th leading cause of death in developed world. Fortunately, the scale of the problem in India is not as big as of now; but it is likely to grow substantially in the time to come due to the presence of rapidly ageing population in India. The cause of this dementing illness has however remained elusive. Most important hypothesis hovers around the ill effects of beta-amyloid. Myriads of other hypotheses have also been proposed; the latest one is that it may be a disease caused by endothelial dysfunction. Before the development of anticholinesterases, the treatment was non-specific enhancement of cognition with the help of nootropics. Now over half a dozen such drugs are available. They are given with the notion of correcting defective or deficient transmission of acetylcholine. Tacrine is not favored now because of its hepatotoxicity and availability of safer alternatives such as donepezil, matrifonate, and rivastigmine. Some clinical trials have shown that the incidence of gastrointestinal side effects with donepezil are less than rivastigmine. Because of this reason, and the fact that it needs to be taken once daily; it is favored drug now. Some studies are underway to explore the disease modifying or their potential to slow neurodegeneration. Preventive strategies such as NSAIDs, estrogens or statins need to be evaluated further before they can be recommended for mass usage. Vaccine development has suffered a setback due to failure of the maiden clinical trial.

Introduction

Alzheimer's disease (AD) is characterized by progressive loss of memory and cognitive functions¹. The disease affects 10% of the world population. The incidence increases with increasing age steadily from 0.5% after the age of 65 to 8% after 85 years. It is most common cause of dementia and is already a major public health problem in the industrialized countries. Although the incidence and prevalence according to Indian studies has been low; but this can have a devastating influence on the developing countries. This is because according to a World Health Organization projection by the year 2020; approximately 70% of the ageing population will be in developing countries like India, which will account for 14.2% of this number². This simply means that every 7th elderly will be an Indian. This would then impose strains on already thin resources to manage problems related to aging in India.

At present, the disorder afflicts approximately 5 million people in the United States and more than 30 million people worldwide. A larger number of individuals have lesser levels of cognitive impairment, which frequently evolve into a full-blown dementia, thereby increasing the number of affected persons. This disorder is a major public health problem when looked at from the economic perspective. In fact, the cost of caring for patients with AD was over \$ 110 billion per year in the early 1990s in the United States, and the average yearly cost per patient is about \$ 45,000³.

What causes Alzheimer's disease?

Despite the publication of a large number of case control studies about the risk factors of AD over the last decade; our current knowledge of the risk factors is quite limited. Of the some putative 20 risk factors for AD, only advanced age, Down syndrome, and history of dementia in first-degree relatives have

consistently been associated with AD³. Myriads of hypothesis have been proposed; reflecting the uncertainty about its causation. Leading hypothesis are summarized below :

a) *Is Alzheimer a result of exaggerated ageing?* It should be appreciated that many of the changes encountered in Alzheimer's disease are also seen in ageing brain⁴. This had led to the speculation that AD may represent one end of the spectrum of ageing changes. Neuron loss is a feature of normal ageing. It is calculated that after the age of 30 years, all of us lose about 100,000 neurons on daily basis. By the age of 85 years, it translates into loss of 31% neurons in hippocampus (the site where normally neuron loss is marked), and 52% in subiculum. In addition to this, deposition of pigments, formation of plaques, vacuoles, and intracellular inclusion bodies also occurs⁵. These changes are mostly non-specific and indicate degeneration of nervous system, which can also be a manifestation of Alzheimer's disease and other dementias⁶.

b) *Deposition of beta-amyloid causative?* AD is the most common and important degenerative disease of the brain characterized by severe degrees of diffuse cerebral atrophy that evolves over a few years and is invariably associated with dementia⁷. The earliest change is degenerated neuronal processes having degenerated clusters of mitochondria, large number of lysosomal bodies and PHF. Amyloid is a 4 KD beta A4 protein derived by proteolysis of larger amyloid precursor protein (APP). Polyclonal and monoclonal antibodies raised against synthetic peptides of different segments of BA4 are a very sensitive marker for plaque as well as vessel amyloid. There is some evidence that this abnormal amyloid is neurotoxic. Amyloid deposition occurs in meningeal and parenchymal vessels leading to ischaemic damage. They stain with Congo red and give greenish yellow birefringence on polarized microscopy. The anatomic pathology of AD includes cerebrocortical atrophy (predominantly at the expense of association

regions), neurofibrillary tangles (NFTs) and senile plaques (SPs) at the microscopic level; accepted now universally as a hallmark of the disease. Note that while these lesions are characteristic of AD, they are not pathognomonic of the condition⁴. In fact, numerous other neurodegenerative conditions that are distinct from AD are characterized by NFTs (eg, progressive supranuclear palsy, dementia pugilistica, subacute sclerosing panencephalitis, Nieman's Pick disease, Pick's disease, Parkinson-Dementia complex of Guam, post encephalitis Parkinson's myotonic dystrophy) or SPs (eg, normal aging), indicating that the mere presence of these lesions is not sufficient to make a diagnosis of AD. In addition to NFTs and SPs, many other lesions of AD have been recognized since Alzheimer's original papers. These include the granulovacuolar degeneration of Shimkowitz, the neuropil threads of Braak et al, and both neuronal loss and synaptic degeneration that are thought to ultimately mediate the cognitive and behavioral manifestations of the disorder⁵. A recent Indian study by Shanker et al observed NFTs in 14 out of 42 cases, the frequency increasing with advanced age, whereas in his early study on 10 brains above the age of 50 he did not find NFTs⁶. NFTs consist of dense bundles of long branching filaments called paired helical filaments (PHF) which measures 20 micron across with regular constriction of 10 nm occurring at every 80 nm interval. Tau, a microtubule associated protein having abnormal phosphorylation of six isomers is the major component of PHF. Normally, tau protein functions to stabilize the microtubules for rapid axonal transport. Other component of PHF is ubiquitin, a 76 amino acid polypeptide involved in non-lysosomal ATP dependent degradation of intracellular proteins.

c) Defective genes are the key? Substantial progress has been made in last few years in developing the tools to study the molecular genetics of disease. These have shown that there are four genetic loci that contribute to the etiology and pathogenesis of the disease. These include APP, APO E, presenilin 1 and presenilin 2 genes. Whereas APO E gene is a risk factor for late onset (> 60 years), other three genes are responsible for early onset (<60 years) AD⁶. In addition, mutations in alpha-2 macroglobulin have also been identified. These mutant gene products cause dysfunction/death of vulnerable population of neurons important for memory, higher cognitive functions and behavior. Several gene based therapies such as inhibitors of amyloid production, fibrillary plaques, immunization, antioxidants and free radical scavengers, and gene therapy are on horizon.

d) Is AD a neuroinflammatory disease of brain? There is evidence that inflammation may be an important mechanism of neuronal death in AD⁷. World over, this hypothesis has become major focus of attention. In post mortem specimens of cases with AD activated inflammatory cells secreting mediators of inflammation have been found. Use of Non-steroidal drugs has been associated with the decreased incidence of AD⁸.

e) Estrogen deficiency plays a role?? It seems that estrogens play an important role in keeping the neurons healthy. Direct stimulation of cholinergic neuron is a characteristic feature of estrogens¹⁰. Therefore, their deficiency increases the risk of AD and reverse is also true i.e. prophylactic administration reduces the risk¹¹. Other mechanisms by which estrogens might be useful in

keeping the brain neurons functional are; stimulation of development of gliocytes, scavenging of free radicals, down regulation of amyloid beta-proteins and a decrease in excitotoxicity.

f) Latest hypothesis-is AD a vascular disease? It has been proposed that the neuronal damage occurring in AD may at least partly be due to overgrowth of capillary endothelium¹². The endothelium gets damaged by the deposition of beta-amyloid, which then leads to hypoxic damage to neurons.

Diagnosing a case of Alzheimer's disease^{5,13,14,15}

Ever since Dr. Alois Alzheimer diagnosed a case of 51-year-old woman with progressive dementia, he reported a wide range of symptoms. The disease is characterized clinically by prominent impairments in cognition and is often accompanied by neuropsychiatric behavioral disturbances in the face of an otherwise bland elementary neurological examination. Clinical criteria for its diagnosis (DSM-4, ICD-10 & NIH-National Institutes of Health-Alzheimer's Disease and Related Disorders Association-ADRDA) include onset between ages 40 and 90 years, progressive dementia as defined by prominent memory loss plus impairment in at least one other cognitive domain such as language or praxis sufficiently severe to impair social and occupational function; no disturbance of consciousness and absence of other brain and systemic diseases that can cause dementia.

Dementia of AD starts as benign forgetfulness in elderly thus making the early diagnosis difficult. This is because it can easily be mistaken as benign forgetfulness of senescence. It typically begins with gradual onset of amnesia with most prominent early deficit being impairment of explicit memory for recent events, misplacement of objects, and repetitive questions, even though patients themselves may be unaware of the problem (anosognosia). Word finding difficulty (anomia) is the next common manifestation. Over a period of several years, cognitive problems start interfering with daily life of the patient. The problems vary considerably from patient to patient, ranging from complete unawareness of considerable insight resulting in frustration and anxiety in middle stages. Patient gets easily confused and is unable to work except under close supervision. Clinician with appropriate training and expertise can diagnose 85-90% cases with AD.

Though generally considered to be the disease of old age, it has been described at almost all ages of adulthood. Increasing age is in fact the most important risk factor for the development of Alzheimer disease. Majority of the clinically diagnosed cases are in their 60s or are older. Only about 5% patients in whom Alzheimer's disease develops are younger than age 60 at onset (early-onset Alzheimer's disease). In these patients, autosomal dominant inheritance is often involved. Three genetic defects are known to cause early-onset Alzheimer's disease in families. The only well-established genetic risk factor is the 4-allele apolipoprotein E gene (APOE-4) on chromosome 19.

The onset of mental changes is usually insidious and gradual development of forgetfulness is the major symptom. There is difficulty in remembering small day-to-day happenings; seldom or uncommonly used names and appointments. Some degree of memory loss; the hallmark of a case with AD extends to all decades of life-its establishment heralds the onset of other

abnormalities like halting speech, interrupted writing, restricted vocabulary, stereotyped and inflexible expressive language. Difficulty in calculation, defective visuospatial orientation and difficulty in locomotion becomes increasingly apparent. Later, there is echolalia, acalculia, anomia, aphasia, ideational and ideomotor apraxia. Social graces are retained in the initial phases of illness but troublesome alterations gradually appear in this sphere reflecting in imprudent business deals, restless and agitation, inertia and placidity, personal neglect, anxiety and phobias and disturbances in the normal circadian rhythm. Ultimately, the patient is left a mute, rigid, bedridden state requiring complete care.

A number of other severe psychiatric abnormalities manifest like poorly organized paranoid delusional state (with or without hallucinations), suspiciousness, sexual disinhibitions, egocentricity, and indifference with coarsened affect. Later on primitive reflexes also appear like grasping and sucking reflex. Sphincter continence fails and the patient sinks into a state of akinesia and mutism. The symptomatic course of this illness usually extends over a period of 5 or more years and a lengthy preclinical period (7 years or more) of stepwise decline in memory and attention span precedes the clinical diagnosis. Eventually, the patient is in a bedfast state and intercurrent infection such as aspiration pneumonia or some other disease terminates life.

Pharmacological Management of a case with AD^{16,17,18,19,20}

Available pharmacological therapies for AD are symptomatic in nature and are aimed at ameliorating the cognitive and neuropsychiatric impairments without affecting the cause of the disease¹⁶. The mainstay of the treatment; the anticholinesterases are based upon the rationale that cognitive dysfunction in AD are caused at least in part of cholinergic dysfunction¹⁷. Treatment options attempt to relieve behavioral symptoms associated with dementia, including depression, agitation, and psychosis, relieve cognitive dysfunction to improve memory, language praxis, attention, and orientation, slow the rate of illness progression, thereby preserving quality of life and independence, and delay the time of onset of illness. The first two comprise the most important from clinical standpoint. The Treatment can broadly be divided into five types: supportive, specific, preventive, non-specific and educational.

The behavioral complications of the disorder can be responsive to a variety of medications, and increasing evidence has mounted to guide specific therapy. This is important for two reasons because firstly they are present in large number of patients; secondly, they are often the cause of distress in the caregivers.

Supportive treatments : Relieving the behavioral symptoms associated with Alzheimer's disease is an important goal¹⁹, since the lifetime risk of such symptoms in the patient with dementia approaches 90%. Behavioral manifestations of dementia include agitation, psychosis, depressive features, anxious features, apathy, and disturbances in sleep and appetite. In most patients, some or all of these manifestations may be amenable to treatment with safe psychotropic medications, including antipsychotics, antidepressants, and anticonvulsants.

Antidepressants : Depression syndrome of AD exacerbates and produces distress in both patients and caregivers. Amelioration of mood disturbances can bring about rapid symptomatic improvements. Selective serotonin reuptake inhibitors (SSRIs) have fewer side effects than tricyclic antidepressants. Therefore these agents are the treatment of choice for patients who are clinically depressed. Citalopram, sertraline, fluoxetine and fluoxetine can be used. If patient fails to respond to SSRI, the treatment with tricyclic agent with fewer anticholinergic side effects such as prothiphen, nortriptyline or desipramine can be used. Agents with dual mechanism of action such as venlafaxine can also be used.

Antipsychotic agents : Patients with AD who exhibit psychotic features should be treated with antipsychotic medications. The preferred drugs include, clozapine, olanzapine, risperidone, quetiapine. These are preferred due to their fewer propensities to cause extrapyramidal symptoms. Mood stabilizers such as lithium, carbamazepine or valproic acid are increasingly being used to reduce daytime agitation in AD. Carbamazepine has been reported to cause fewer side effects than other agents used for this purpose. Agitation can also be reduced with benzodiazepines such as temazepam or non-benzodiazepine sedative hypnotic named zolpidem.

Anxiolytics : Benzodiazepines are generally avoided in patients with AD because they can cause confusion and can aggravate the cognitive dysfunction. However, when needed, these should be used in low doses¹⁷. Patients with frequent episodes respond to single doses of oxazepam or lorazepam. These are safer in elderly because they have less tendency to accumulate and are not toxic to liver. This is because they are well metabolized in elderly. For patients requiring the long-term administration of anxiolytics; buspirone, an azapirone derivative may be an attractive option. In some cases, treatment with propranolol may be beneficial.

Sedative hypnotics : Sleep abnormalities are common in AD and disturb caregivers and patients alike. Sedative hypnotics may aid in sleep and provide sleep maintenance. Agents include trazodone, zolpidem and temazepam. Longer acting benzodiazepines such as diazepam or barbiturates such as phenobarbitone should be avoided.

Specific Treatment

The most successful therapeutic approach of AD has been based upon aiming improvement in cholinergic transmission²⁰. Mounting evidence indicates that central cholinergic dysfunction is an early and prominent feature of Alzheimer's disease. The primary implication of the "cholinergic hypothesis" is that potentiation of central cholinergic function should improve the cognitive, and perhaps even the behavioral, manifestations of Alzheimer's disease. The search for the specific treatment has been elusive until the synthesis of tacrine (tetraaminohydroquinoline). This was the first drug approved by US FDA in the treatment of dementia. The efficacy of this agent has extensively been studied and documented. Several other cholinesterase inhibitors are either available or nearing the end of clinical trials since the arrival of this agent. It is however only infrequently used and is not available in USA due to its hepatotoxicity and availability of safer agents. Donepezil hydrochloride, a piperidine derivative, the first second

generation cholinesterase inhibitor to be approved by the most widely used agent now a days²⁰. Improvement in cognitive functions often occurs when the drugs is used in single doses of 5-10mg. It needs to be given once daily as opposed to four times daily administration with tacrine. Some clinical trials have suggested that incidence of gastrointestinal side effects like nausea and diarrhoea are greater with galantamine and rivastigmine. Rivastigmine is available in twice-daily doses and has similar efficacy. Galantamine is unique in that it is an allosteric modulator of nicotine receptors. However all of these drugs result in modest improvements in memory and other cognitive functions in the short term. Recent laboratory (and quite unexpectedly) and clinical evidence suggests that they might also have disease-modifying effects. These drugs reduce the neuropsychiatric manifestations such as apathy and visual hallucinations. The major effect of anticholinesterases which remains to be confirmed their ability to slow the progression of disease. So far, only high dose of Vitamin C has been shown to have this effect. Numerous other agents such as acetylcholine precursor (in attempt to boost synthesis of deficient neurotransmitter), direct acting agonists or receptor stimulants (e.g. areocholine), antioxidants, nootropics, hormone replacement therapy, and cerebral vasodilators have been used with little or no success. the existing treatments are summarized in table-1. Before initiating cholinesterase inhibitor therapy, patients should be thoroughly assessed, and the diagnosis confirmed, preferably by a specialist. Compliance with cholinesterase inhibitor therapy should be monitored and the response (in global, cognitive, functional and behavioural domains) reassessed after 2-3 months of treatment.

Acetylcholine precursors such as choline and phosphatidylcholine (lecithin) have been used in an attempt to augment acetylcholine synthesis, analogous to the use of a dopamine precursor in Parkinson's disease. Numerous trials, however, have generally yielded negative results. Small but reliable improvement in memory performance has been found after administration of physostigmine salicylate, although individualized dosing appeared to be necessary to optimize this effect. Short duration of action and a high rate of cholinergic side effects (nausea, vomiting, diarrhea, flushing, sweating, bradycardia) are among the limitations of physostigmine. A sustained-release formulation is being developed. There is evidence that long-term administration of physostigmine retards deterioration in cognitive function over time even in patients who fail to improve with short-term administration. Cholinergic receptor agents: The rationale for the use of direct cholinergic agonists rests on the facts that postsynaptic muscarinic (m1) cholinergic receptors are relatively intact in Alzheimer's disease and that presynaptic m2 receptors, which are decreased in Alzheimer's patients, regulate acetylcholine release. Although past trials of muscarinic cholinergic agents showed them to be minimally efficacious and to cause substantial side effects, newer agents now under development are expected to produce fewer toxic effects and to have greater affinity for the m1 and m2 receptors.

Tacrine

It is a centrally active, reversible, nonspecific cholinesterase inhibitor. An early case series claimed "dramatic" improvements with tacrine

Table 1: Major treatment options for patients with AD

<i>Precursors</i>	<i>Cerebral vasodilator</i>
Phosphatidylcholine (lecithin)	Calcium channel blocker e.g. nimodipine
Choline	
<i>Cholinesterase inhibitors</i>	
Tacrine	<i>Ergot alkaloids</i>
Donepezil	Ergoloid mesylates
Metrifonate	
Eptastigmine	<i>Neuroprotective</i>
Memantine	Nerve growth factor
Long acting physostigmine salicylate	
Galantamine hydrobromide	<i>Neuron regenerators</i>
<i>Cholinergic receptor agents</i>	Estrogens
Arecoline,	
Pilocarpine HCL,	<i>Anti-inflammatory agents</i>
bethanechol chloride	<i>Non-steroidal anti-inflammatory agents (NSAIDS)</i>
oxotremorine, nicotine	<i>Corticosteroids</i>
Milameline	
Xanomeline	<i>Antioxidants</i>
<i>Gangliosides</i>	Vitamin E
Phosphatidylserine	
Nootropics	
<i>Piracetam</i>	

in patients with Alzheimer's disease. Since then, well-designed multicentric trials have shown improvement with tacrine versus placebo in cognitive function and on global clinical scales and indices of daily functioning, leading to marketing approval in the United States and other countries. Fewer than a third of patients originally assigned randomly to receive tacrine showed modest, although meaningful, improvement in comparison with those who received placebo. Up to 20% of patients were unable to tolerate tacrine because of cholinergic side effects, generally gastrointestinal distress. Asymptomatic, reversible elevations of serum transaminase levels caused by direct hepatotoxicity occurred in about 50% of patients.

Tacrine's development and approval process helped set standards for antidementia drug trials and focused attention on proper evaluation for dementia. It afforded hope to patients who had given up on the possibility of an effective therapy. The tacrine experience proved that despite the potential for cholinergic and hepatic toxic effects, nonselective cholinergic therapies can be safe when used properly. Some patients who showed only mild improvement with tacrine therapy nonetheless viewed this as important, as did their caregivers. The tacrine experience also facilitated the development of a host of other cholinesterase inhibitors. Further, recent evidence suggests that prolonged treatment with tacrine, in patients able to tolerate it, results in significant delay until nursing home placement. These data are generally in agreement with early long-term experience with other cholinesterase inhibitors. Finally, preliminary evidence suggests that tacrine, as well as other cholinergic agents, can produce positive behavioral effects.

Donepezil

It is a reversible acetylcholinesterase inhibitor^{20,21} that has dose-dependent activity showing greater selectivity for

acetylcholinesterase and a longer duration ($t_{1/2}$ 70 hours) of inhibitory action than tacrine or physostigmine, as well as greater specificity for brain tissue than peripheral tissue. Encouraging preliminary studies led to the completion of multicenter, placebo-controlled studies examining donepezil at doses of 5 and 10mg/day versus placebo for 15 and 30 weeks, respectively, as well as another 30-week trial conducted in Europe. Results of these studies showed statistically significant benefit in both of the primary outcome measures (cognitive function and global clinical impressions), which was somewhat greater at 10mg/day. Donepezil has been reported to be safer and more tolerable (especially in terms of gastrointestinal distress) than tacrine. Donepezil was approved by the Food and Drug Administration (FDA) in November 1996 for a number of reasons: Its efficacy is generally equivalent to that of tacrine, it is not associated with hepatotoxicity or elevated transaminase levels, and it is thought to have fewer cholinergic side effects than tacrine. The ease of its once-daily dosing may result in improved patient compliance. It also has reduced potential for drug-drug interactions and may be taken with food. Because of donepezil's improved tolerability and because therapeutic doses are achieved quickly, rather than taking months, substantially more patients are expected to experience benefit with donepezil than with tacrine. A study exploring the long-term effects of the drug in slowing the progression is underway. If the results are positive, then the drug may be recommended in patients not yet exhibiting clinically recognizable cognitive decline. It is used in dose of 5mg daily, and it can be increased to 10mg after one week. Further information about donepezil also suggests that, as with some other cholinergic agents, improvement gained with early treatment is sustained with ongoing therapy. Studies are under way to assess donepezil's effectiveness over the long term as well as in patients with more severe dementia or comorbid medical conditions; results should help illuminate its usefulness in a broader patient population.

Metrifonate : This organophosphate was originally developed as an insecticide²². This agent that does not inhibit the enzyme cholinesterase but acts as prodrug^{22,23} for the long-acting cholinesterase inhibitor dichlorvos. The cholinesterase inhibition half-life is nearly 2 months, meaning that its effects are long lasting. Early studies have shown significant improvements on both cognitive function and global clinical scales, accompanied by typical cholinergic side effects. It has a low incidence of extraintestinal side effects and is not associated with hepatotoxicity^{20,23}. Common side effects are cholinergic, as expected, such as abdominal pain, cramps, diarrhoea, flatulence, and bradycardia etc²⁴.

Rivastigmine : It is a reversible inhibitor of acetylcholinesterase and butyrylcholinesterase and was approved in April 2000 for the treatment of mild to moderate AD²¹. It is shown to have significant benefits in the areas of cognition, global functioning and activities of daily living. In controlled studies, the dosages of rivastigmine are found to be 6-12 mg/day, given as twice-daily doses²⁵. It is well absorbed from gastrointestinal tract with half-life of 1.5 hours. Metabolites are excreted mainly through urine. It is widely distributed throughout the body. And is 40% bound to plasma proteins²⁴.

Galantamine : It is also a reversible inhibitor of AchE, and is modulator of nicotinic receptors²⁶. Several double-blind placebo controlled clinical trials have shown its efficacy in the treatment of AD in dosages of 16,24 and 32 mg per day. The adverse effects occur less commonly if the increment in doses is done slowly (e.g. 8mg every 4 weeks). Recommended dose is between 16-24 mg daily.

Memantine : There is evidence that the excitatory activity of L-glutamate plays a role in the pathogenesis of Alzheimer's disease and in the damage from an ischaemic stroke. A low affinity antagonist to N-Methyl-D-aspartate (NMDA) type receptors, such as memantine, may prevent excitatory amino acid neurotoxicity without interfering with the physiological actions of glutamate required for memory and learning. Memantine, an uncompetitive antagonist with moderate affinity for NMDA receptors, demonstrates voltage-dependency and relatively fast on/off receptor kinetics. Black triangle Memantine 20mg/day significantly slowed the rate of deterioration in outpatients with moderate to severe Alzheimer's disease in a 28-week US randomised, double-blind, placebo-controlled, multicentre study. Memantine 10mg/day improved measures of dementia in care-dependent inpatients with Alzheimer's disease or vascular dementia in a 12-week randomised, double-blind study. Significantly more memantine than placebo recipients were responders according to Clinical Global Impression of Change scores and the Behavioural Rating Scale for Geriatric Patients Care Dependence subscale.

Physostigmine : It is a potent inhibitor of ChE with an efficacy similar to others in this group²¹. A sustained release formulation is available now a days. It is better tolerated than the original formulation but is not free from cholinergic side effects.

Eptastigmine : Eptastigmine²⁷ is a ChE inhibitor that has been shown to be an effective enhancer of cognition in patients with AD. As compared to AChE, the cholinergic side effects of this drug are low. Occurrence of dose dependent neutropenia in 6% patients and rarely other hematological side effects (e.g. aplastic anemia) is a concern.

Preventive Treatments

Alzheimer disease ties closely with cerebrovascular disease and is 4th most common cause of death. Therefore, its epidemiological importance needs no emphasis. Prevention of the disease (both primary and secondary) remains to be a dream of most scientists working in this area. A number of preventive strategies have been explored in last few years; however, at the moment none is sufficiently efficacious to be recommended at mass scale. These are summarized below.

Vaccination for Alzheimer's disease: hope or hype? Vaccination against Alzheimer disease has been an area mixed with enthusiasm and frustration. This is because; following the demonstration that A beta (42) competent of amyloid precursor protein is neurotoxic and is responsible for most manifestations of AD: the efficacy of vaccine was demonstrated in transgenic mice. It was believed that the vaccine would be able to destroy this peptide selectively by inducing antibody formation²⁸. This fueled interest among the scientists that vaccine is a reality. However, recent fiasco of the

first ever trial in humans has lessened the enthusiasm of vaccine development. Trial of A beta (42) peptide (AN-1792) vaccine has been abandoned due to development of meningoencephalitis in many patients²⁹.

Non-steroidal anti-inflammatory drugs : Epidemiological evidence has shown that use of NSAIDs for indications like joint diseases is associated with lower incidence of AD compared to the placebo takers³⁰. More than 20 studies conducted in 9 different^{7,8} countries have shown that the risk reduction (50-70%) is clinically significant. However, the side effects of long-term administration force us to take into consideration the risk versus benefit ratio³¹. Even in initial secondary prevention trial with indomethacin, the drug was discontinued due to gastrointestinal side effects^{31,32}.

Hormone replacement therapy : The fact that the risk of developing AD increases steeply after the age of 65; and more so in women led researchers to investigate the effects of sex steroids in prevention or secondary prevention of AD. Two large, prospective, longitudinal studies have shown the risk reduction of 50-70% in elderly women²¹. However, many studies have yielded negative³³ or inconsistent³⁴ results also. However, it continues to be explored³⁵.

Statins : The reputation of statins as remedies of prevention has grown substantially in last decade. Now they are the primary line of treatment in a variety of dyslipidemias (e.g. diabetes, postmenopausal) and prevention of complications in those with high risk for cardiovascular diseases. Pathophysiology of AD appears to be related to AD. Patients carrying an APO E 4 have cardiovascular disease and are also at increased risk of AD^{33,36}. Cholesterol is also involved in deposition of plaques of amyloid. Therefore reduction of cholesterol brings about beneficial effects.

Care giving for the cases with Alzheimer's disease

Increasing attention is being given in developed countries as to how the families of the caregivers should cope up with the stress of caring for a case with Alzheimer's disease. While in west, there are counseling centers and training schools for teaching the relatives and caregivers; in India, the issue is a new one. Caregivers are given training with regard to anatomy of brain, drugs, their side effects, patients disease, and how to cope up with newly arisen stress from care of the patients. Specialists should make sure that they educate the relatives of the patients regarding these issues²⁰. Caregivers suffer a number of adverse health consequences such as anxiety, depression, frustration, poorer immune functions, more respiratory infections, slower wound healing and are at risk for alcoholism, and drug abuse etc. They sleep poorly, less likely to exercise and more likely to have disruption in their lives. Studies in India have shown that the family disruptions are severe enough to cause breakdown of marriages and careers. Possible mechanisms to reduce stress may include counseling to the vulnerable persons who are involved in care giving. In India, there are few institutions or non-governmental organizations that can provide information, support, and appropriate activity for both patients and caregiver easing the burden on the long journey of care. The caregiver should be told to try to develop a new and warm relationship with the impaired person. They should be cordial, kind and helpful without being negative. They should avoid arguing with the patients. Some caregivers benefit

from adopting spiritual means. It seems that if the lost abilities of the person with AD are compensated and remaining abilities are promoted; then rate of decline of disabilities may get decreased.

Conclusion

Due to the advent of numerous anticholinesterase drugs; the most common degenerative disorder of brain is no longer treatable now. Though they cause modest improvement in the symptomatology but still improvement in memory and cognitive decline can help the patients and relatives cope up with the stress. A real test of these drugs would be whether they modify the course of the disease or retard the course of illness; if its confirmed by ongoing studies then they may also be recommended for primary prevention of patients at risk for the development of AD. Many preventive treatments are also on horizon now; these include, NSAIDs, estrogens, antioxidants such as vitamin E etc. To what extent do these agents lead to prevention of the disease remains to be seen in long-term studies; they appear to be attractive options for prevention. Vaccine trial started with great easing the burden on the long journey of care. The caregiver should be told to try to develop a new and warm relationship with the impaired person. They should be cordial, kind and helpful without being negative. They should avoid arguing with the patients. Some caregivers benefit from adopting spiritual means. It seems that if the lost abilities of the person with AD are compensated and remaining abilities are promoted; then rate of decline of disabilities may get decreased.

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BOOK REVIEW

Principles & Practice of Emergency Medicine *Praveen Aggarwal, LR Hurmu, C.S. Yadav, BI Publication Pvt. Ltd., New Delhi 2005*

In the last three decades, medical science has advanced so rapidly that it is difficult to keep pace with the newer knowledge. With the availability of newer diagnostic tool and intervention technique, management of medical disorders has revolutionized and it is extremely difficult for medical practitioners to keep abreast with the advancement.

Medical emergencies constitute an important part of medical practice. Correct diagnosis, prompt and appropriate treatment are essential and life saving. One not only requires the presence of mind but also the speed and confidence to tackle the medical emergencies.

Management of emergencies is the most demanding and stressful aspect of medical training. Very few books on emergencies are available written by Indian authors and they mostly cover only one type of emergency.

This book written by Dr. Praveen Agarwal additional Prof. of Medicine, Dr. L.R. Murmur additional Prof. of Surgery and Dr. C.S. Yadav, associate Prof. of Orthopaedics, includes the general medical, surgical and orthopaedics emergencies. The authors being on the faculty of All India Institute of Medical Sciences, new Delhi have extensive experience in managing the emergencies in their respective fields. They have designed the book in such a way that the doctor can manage the patients in a much more effective manner.

The pathophysiology has been discussed in brief while more emphasis has been laid on clinical features, differential diagnosis and management of the clinical problems. Each chapter starts with an initial approach to a patient presenting with an emergency. The diagnostic and therapeutic aspects are dealt with in a stepwise manner. A large number of tables and flow diagrams are provided for quick reference. In view of the above, this book will help the doctors immensely in rendering effective and safe care to acutely sick or injured patients. This book will be an asset to medical students, residents and practitioners in managing their emergency cases.

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