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A Review on Alzheimer's Disease: Pathogenesis and Management

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ABSTRACT

Alzheimer's disease is the most prevalent form of dementia. Neuropathogenesis is proposed to be a result of the accumulation of amyloid β- peptides in the brain together with oxidative stress mechanisms and neuroinflammation. Drugs effective in Alzheimer's disease (AD) should have several aims: to improve the cognitive impairment, control the behavioral and neurological symptoms, delay the progression of the disease, and prevent the onset. This review discusses the molecular mechanism of Alzheimer's disease with a focus on the different agents those are inhibit the progression of the disease and improved patients condition and status..

Key words: Alzheimer's disease, β-amyloid, Tacrine, Rivastigmine

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by impairment of memory and cognitive function. Initially mild cognitive impairment and deficits in short-term and spatial memory appear [1], but the symptoms become more severe with disease progression, eventually culminating in loss of executive function. Aging is a crucial risk factor for AD; for example, in the population >65 years of age the incidence of AD approximately doubles every five years, so that 50% of the population aged 85 and older are affected with AD. Alzheimer's disease is the most common form of dementia in the Developed World, where it seems to affect some 5 percent of those aged over 65. It is not, however, limited to the elderly, but is found also in a much smaller percentage of the younger population[2-3]. There are now four different genes that confer susceptibility to AD—the amyloid precursor protein (APP), apolipoprotein E (ApoE), and two novel seven trans membrane domain proteins. Although it is likely that multiple molecular pathways can lead to AD, a central issue is whether all causes of the disease lead to a final common mechanism of neuronal death [4].

Two different forms of AD have been described: (i) early onset familial AD (FAD), associated with mutations in the genes encoding amyloid precursor protein (APP), presenilin [5] (PSEN1) and presenilin 2 (PSEN2), all involved with β-amyloid (Aβ) processing and accounting for less than 5% of total AD; and (ii) a more common late onset AD(LOAD), in which a main risk factor is expression of the ε4 allele of the apolipoprotein E gene (APOE). Specifically, the presence of two E4 alleles increase by approximately 12- fold the risk for AD and lowers the age of onset of the disease by about 15 years [6].

Cholinesterase inhibitors (ChEIs) represent the first class of drugs approved for the specific symptomatic treatment of AD. Following the introduction of tacrine, the first ChEI to be approved, donepezil, rivastigmine and galantamine became available[7].

Some studies also suggest that these drugs can stabilize and even reverse the neurotoxic effects of AD thus delaying the disease progression, especially if administered early in the course of the disease benefiting patients with mild to moderate AD. Rivastigmine is also capable of blocking the action of another cholinesterase enzyme, butyrylcholinesterase (BuChE), which increases considerably in the brain of patients with AD changing from a ratio of 99:1 to 2:1[8].

This may have a favourable effect on sustained cholinesterase inhibition and subsequent disease stabilization. On the other hand, galantamine's mechanism of action is sufficiently different from that of other AChEIs as it also acts on the nicotinic acetylcholine receptor (nAChR) sites

increasing the receptor responsiveness to acetylcholine (ACh) facilitating its ionic channel opening[9] .

Pathogenesis of Alzheimer Disease

Alzheimer's disease was originally recognized by Alois Alzheimer in 1907 as a separate form of dementia. Since this original observation the two main histological features of amyloid plaques and neurofibrillary tangles (NFT) have been described in the AD brain [10]. These features are found to be present in the temporal neocortex and hippocampal regions of the AD brain [11]. The hippocampus resides in the cerebral cortex of the forebrain and is thought to be involved in memory storage. Amyloid plaques and NFTs result from an aberration in deposition of the amyloid beta peptide (Aβ peptide) and the hyperphosphorylated tau protein respectively and these depositions lead to neuronal loss and neurotoxicity in the AD affected brain.

The mode of action by which these drugs act is by blocking the breakdown of the neurotransmitter ACh. By inhibiting the enzyme acetylcholinesterase, the levels of the neurotransmitter at cholinergic synapses increase. Acetylcholinesterase has also been found to promote the formation of amyloid plaques, thus inhibiting this enzyme by properly designed AChEIs might not only provide symptomatic relief but also inhibit the progression of the disease itself[12].

Recent research indicates that the excitatory neurotransmitter glutamate may play an important role in the neurochemistry of AD. Glutamatergic neurotransmission has been shown to be important in learning and memory and is severely disrupted in AD. Overstimulation of the NMDA receptor by glutamate leads to an overload of intracellular calcium bringing about neuronal death which is characteristic of AD and other neurodegenerative disorders. Meanwhile, a non-competitive antagonist with moderate affinity for the NMDA receptor appears to block pathologic neural toxicity associated with prolonged glutamate release[13].

Accumulation of Aβ peptides may be the key event in pathogenesis of AD. The exact mechanism by which Aβ peptide deposition induces neurotoxicity is unclear, but it appears the oxidative stress plays an important role. Oxidative stress is extensive in AD[14-15] and Aβ peptides stimulate oxidative stress by both direct and indirect mechanisms. Aβ peptides by themselves may act as enzymes [16], as they are capable of directly producing hydrogen peroxide and generating free radicals through metal ion reduction [17, 18]. As well, Aβ peptide can bind to mitochondrial proteins resulting in the generation of free radicals [19]. Furthermore, Aβ peptides generate oxidative stress via neuro inflammation. Considerable evidence has supported that neuro inflammation is associated with AD pathology [20]. The death of neurons observed in AD is partly attributed to the

activation of two major brain cell types, astrocytes and microglia that participate in the immune inflammatory response to Aβ deposition. However, these cells can have both neuroprotective and neurodegenerative functions. For example, astrocytes cluster at sites of amyloid deposition and are thought to be involved in the clearance of plaques, evident through their ability to degrade amyloid beta deposits in vitro and in situ [21]. Both astrocytes and microglia release proinflammatory molecules upon activation, in particular, astrocytes can be activated by amyloid beta deposits to produce reactive oxygen species, as well as chemokines, cytokines, which lead to neuronal cell death [22]. Aβ peptides also induce the expression of nitric oxide synthase in microglia and the release of reactive nitric oxide which results in the loss of selected neuron populations [23]. Furthermore, Aβ peptides stimulate microglial cells to release a neurotoxin, quinolinic acid [24], which may also play a role in neurotoxicity.

The Amyloid Cascade Hypothesis

The amyloid beta hypothesis predicts that an aberration in the proteolytic processing of the amyloid precursor protein (APP) leads to the increased production of Aβ peptides, this in turn leads to the accumulation of Aβ, a primary event in the pathogenesis of AD [25]. The accumulated Aβ eventually deposits into amyloid plaques present in the AD brain parenchyma. Together with the secondary events of microglial and astrocyte activation and NFT formation there is widespread neuronal dysfunction and selective neuronal loss. Currently, this hypothesis is being referred to as the Aβ cascade hypothesis, where increased production and possibly decreased clearance of Aβ peptides leads to an accumulation of these peptides and the subsequent pathogenesis observed in AD. APP is a ubiquitously expressed type I integral membrane glycoprotein with various major isoforms. APP is expressed abundantly in a variety of tissues and processing of APP is a normal event in nearly all neural and non-neural cells throughout the body. Proteolytic processing of APP that releases the Aβ fragment is a result of cleavage events by secretase proteins. APP processing by the secretase proteins occurs in two distinct pathways, the non-amyloidogenic and amyloidogenic pathways. Soluble APP is cleaved by α- secretase and β-secretase to release the soluble α-APP and β-APP, respectively, into the extracellular matrix [25]. In the non-amyloidogenic pathway, γ-secretase cleavage of the remaining C-terminal fragment (CTF) releases the p3 fragment, while in the amyloidogenic pathway this cleavage releases the Aβ peptide. The cleavage by γ-secretase is a heterogenous event that releases Aβ peptides of different sizes, with Aβ-40 and Aβ-42 being the most common forms. Aβ-40 and Aβ-42 are both toxic peptides, however the Aβ-42 isoform is insoluble and more capable of aggregating into amyloid plaques. Upon accumulation of Aβ-42 there is a resulting neuronal cytotoxicity that

induces neuropathological events leading to neurodegeneration of the brain [26]. More specifically, Aβ-42 can aggregate into two different conformation states. There is the non-β sheet, non-fibrillar state and the β sheet fibrillar state which is cytotoxic and eventually deposits into plaques [27]. Aβ-42 exists initially as a monomer, during oligomerisation the monomers further oligomerise into larger forms such as large oligomers, protofibrils and fibrils. During oligomerisation there are conformational changes occurring in these elements that transform them into a β sheet fibrillar state [27]. The Aβ oligomeric intermediates (oligomers, protofibrils) and the mature fibrils are all neurotoxic, and it has been demonstrated that the oligomers and protofibrils are actually more neurotoxic than the mature fibrils or amyloid plaques [28].

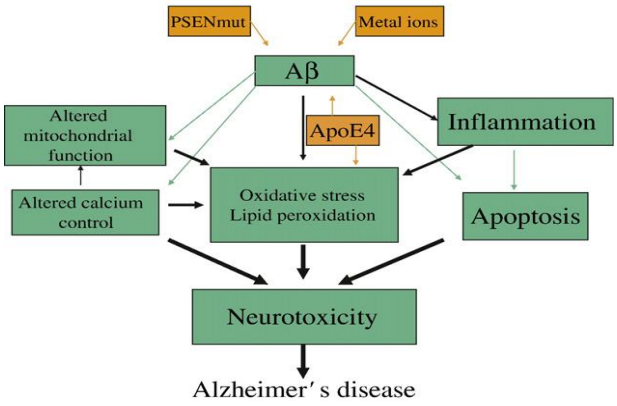

Figure: 1: Amyloid ß-protein (Aß) can accumulate through over production (e.g., presenillin mutation [PSEN mut) or reduced removal (e.g., APOE4). Oligomerization of Aß results in production of oxidative stress by itself (which can be augmented by heavy metals), of via induction of several other interacting mechanisms

Genes Implicated in Alzheimer's Disease

Three genes that have been implicated in AD pathogenesis are APP, presenilin 1 (PS1) or presenilin 2 (PS2), as mutations in these genes have been identified in cases of familial AD [29].

PS1 is central to the γ-secretase complex of proteins that cleave Notch and APP [30]. It is the presenilin-mediated cleavage of APP that results in the release of various lengths of the Aβ peptide. The pathological characteristics of FAD and the sporadic form of AD are proposed to be similar; therefore somatic changes in APP, PS1 or PS2 may potentially have a role in sporadic cases of AD. Along with causative mutations in PS1, PS2 and APP, the apolipoprotein (APOE) gene has been identified as a major genetic risk factor for sporadic AD. E4 is an isoform of APOE and carriers of the E4 allele are at a higher risk of developing AD, with homozygotes usually developing AD earlier than heterozygotes [31]. However the presence of the APOE4 allele has not been found to be necessary or sufficient for the development of the disease.

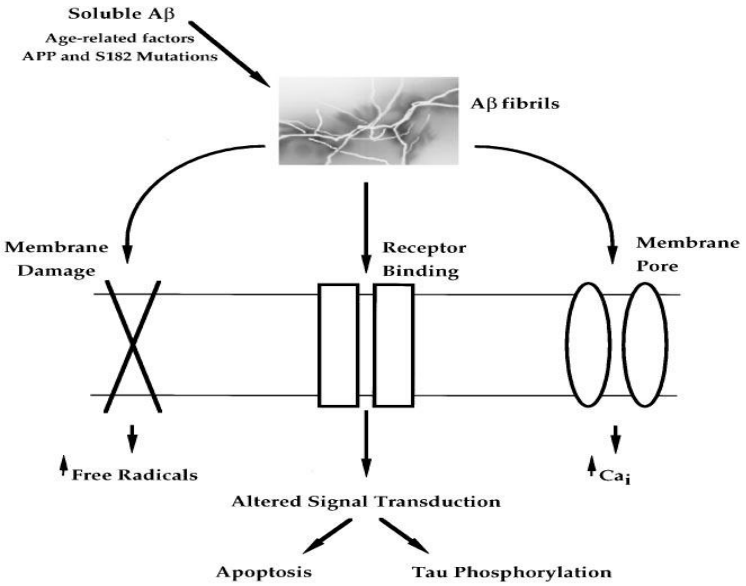

Figure 2: Ab Fibril Formation and Potential Mechanisms of Neurotoxicity Age-related factors or inherited mutations induce the formation of Ab fibrils, which may cause neuronal degeneration through several potential cellular mechanisms.

Linking Oxidative Stress With Alzheimer's Disease

Oxidative stress is associated with a wide range of disease states including cancer, diabetes and neurodegenerative disorders such as AD. Oxidative stress results from a disturbance in the balance of antioxidants and reactive oxygen species (ROS) generated within the body, resulting in an excess of ROS. This leads to the destruction of both neuronal and vascular cells[31].Oxidative stress disturbs the normal functioning of cells through cell membrane lipid destruction and cleavage of DNA. Whether oxidative stress is involved at the onset of AD is still unclear. However it is thought to play a significant role during disease progression, particularly in cellular and tissue damage that occurs throughout AD. As noted above, oxidative stress is extensive in AD. It has also been suggested that there is a close correlation between oxidative stress and Aβ deposition, evident through mouse brain Aβ deposits co-localizing with a variety of oxidative stress markers [32]. Aβ is proposed to be a metalloenzyme that is capable of generating hydrogen peroxide through its superoxide dismutase activity. Hydrogen peroxide is capable of being further transformed to the reactive hydroxyl radical in the presence of transition metals, following this transformation lipid peroxidation reactions bring about oxidative damage, leading to oxidative toxicity in neurons [31].

Alternative Mechanism

Alternative initiating mechanisms for the amyloid cascade hypothesis Apart from the identified FAD point mutations there is evidence that other neurochemical factors may initiate the

deposition of Aβ in FAD or sporadic AD. The following are

The Role of Vascular Dysfunction and Risk Factors for AD

Pathogenesis Cardiovascular disease and type-2 diabetes are risk factors for AD. Vascular risk factors such as hypertension and hypercholesterolemia are proposed to promote the production of Aβ [33, 34,] while being overweight or obese is also now associated with AD [35, 36]. Vascular risk factors appear to be exacerbated by the inheritance of the E4 allele of the APOE gene, thus the presence of this allele increases the risk of developing both vascular dysfunction and AD. A recent studies whether being overweight or obese contributes to AD development by modulating Aβ levels. In their study of 18 adults they found a correlation between the direct measures of obesity and plasma levels of Aβ-42 [37]. Recent findings have also suggested that neurovascular dysfunction is an important feature of chronic neurodegeneration in AD [38]

Redox active metal:

Redox active metals are key mediating factors in the pathophysiology of AD. It is likely that there is a pathological interaction of Aβ with redox active metals such as zinc, copper and iron, due to these metals having a high concentration in the areas of the brain that are affected by AD, namely the cortex, hippocampus and cortical vasculature [39,] Redox active metals may play a role in oxidative stress as they influence the production of hydrogen peroxide. The binding of trace levels of these metals to Aβ, promotes the catalytic production of hydrogen peroxide from oxygen through metal reduction. The effect of these metals on the oxidative mechanisms of Aβ cytotoxicity is complex and not yet fully elucidated, however the effect of zinc on AD pathology may be explained by 'The Zinc Paradox' [40].

PHARMACOTHERAPY OF AD

ChEIs Therapy

This class of drugs is presently regarded as the standard treatment of AD. Four ChEIs have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of mild to moderate AD. They are tacrine, donepezil, rivastigmine, and galantamine. These compounds increase the concentration of acetylcholine and the duration of its action in synapses by inhibiting the degradation of acetylcholine. These compounds provide symptomatic treatments and may also have disease-modifying effects. They have been shown in several large, multicenter, randomized, double-blind, placebo-controlled trials (of 3–6 months' duration) to improve cognitive function, global outcome, and activities of daily living. There is also accumulating evidence that ChEIs may improve behavioral and psychological symptoms of AD, such as psychosis and apathy [41].

Table :Characteristics of pharmacological agents commonly used in the management of AD

Medication	Pharmacological Class	Mode of action	Recommended use	Potential adverse effect
Donepezil hydrochloride	AChEI	Block acetylcholinesterase enzyme	Mild-to-moderate AD	Anorexia, diarrhoea, dreams, fatigue, insomnia, muscle cramps, nausea, vomiting, weight loss
Rivastigmine tartrate	AChEI	Block both acetyl-andbutyryl-cholinesterase , enzymes	Mild-to-moderate AD	Anorexia, diarrhoea, nausea, vomiting, weight loss
Galantamine hydrobromide	AChEI	Block acetylcholinesterase enzyme. Allosterically , stimulates nAChRs ,	Mild-to-moderate AD	Anorexia, nausea, vomiting, weight loss
Memantine hydrochloride	Glutamatergic-system , modifier	Partial NMDA-receptor , antagonist	Moderate-to-severe AD	Agitation, constipation , dizziness, hallucinations, headache, insomnia

AChEI: acetylcholinesterase inhibitor; AD: Alzheimer's disease; nAChRs: nicotinic acetylcholine receptors; NMDA: N-methyl-D- aspartate

Tacrine[42]

Tacrine was the first ChEI to be approved specifically for the symptomatic treatment of patients with mild to moderate AD. The starting dose for tacrine is 10 mg 4 times daily, and this dose is increased by 40 mg/day no more frequently than every 4 weeks (according to tolerance), to a maximum daily dose of 160 mg (40 mg 4 times daily). Tacrine has been associated with hepatotoxicity. Tacrine is extensively metabolized by the liver via the cytochrome P450 1A2 isoenzyme system; therefore, it has the potential to interact with other medications metabolized by this isoenzyme, such as theophylline, fluvoxamine, and cimetidine. Tacrine should be avoided in patients with liver disease.

Donepezil

Donepezil was the second ChEI approved by the FDA for symptomatic treatment of mild to moderate AD in the United States. Two placebo-controlled clinical trials of donepezil have been reported in which efficacy was demonstrated for 1 year in mild-to-moderate AD based on cognitive [43] and functional measures. It is metabolized by the cytochrome P450 isoenzymes 2D6 and 3A4. Clinically relevant drug interactions with other drugs have not been studied. Interaction with paroxetine (patient developing increased confusion and agitation) has been reported [44]. Caution should be exercised in using donepezil in patients with severe hepatic or renal disease.

The recommended starting dose is 5 mg daily, which is increased to 10 mg daily after 4–6 weeks. Morning dosing of donepezil may be preferable in some patients who experience nightmares or insomnia. It may be taken without regard to meals unless gastrointestinal side effects occur, in which case it should be taken with meals.

Rivastigmine

Rivastigmine should be titrated every 4 weeks, as opposed to every 2 weeks, as recommended when the drug was first made available. Slower titration and taking rivastigmine with a full meal significantly improves tolerability, especially with regard to gastrointestinal side effects. One unique feature of rivastigmine that distinguishes it from other ChEIs is the very low risk of drug interactions in AD patients receiving multiple medications for ‘‘real-world’’ comorbidities [45].

This is because the metabolism of rivastigmine occurs primarily via enzymatic cleavage (hydrolysis) by cholinesterases at the site of action and does not require the cytochrome P450 enzyme system. The starting dose is 1.5 mg twice a day with meals (breakfast and supper), and this dose is increased by 3 mg/day, not faster than every 4 weeks (as tolerated), to a therapeutic dose of 6–12 mg/day. The highest tolerated dose is recommended, as there is some evidence that higher doses may provide greater benefits. A more rapid progression of AD while receiving placebo treatment was predictive of a significantly stronger patient response to rivastigmine therapy on various measures [46].

Galantamine

This was the fourth ChEI approved by the FDA for symptomatic treatment of mild to moderate AD in the United States. Metabolism is hepatic via glucuronidation and the cytochrome P450 isoenzymes 2D6 and 3A4; interactions with other drugs that are metabolized through this pathway are therefore possible. Caution should be used in patients with liver disease. The starting dose is 4 mg twice a day, and this dose is increased every 4 weeks. The therapeutic dose is 16–24 mg/day. A 6-month study showed no additional benefit and a higher rate of side effects with a dose of 32 mg/day [47].

OTHER AGENTS FOR TREATMENT OF AD

Metrifonate

Metrifonate is another ChEI that has been investigated for the treatment of mild to moderate AD. Metrifonate was found to be beneficial in areas of cognition, global functioning, and ADLs, compared to placebo in patients with mild to moderate AD, in a meta-analysis of 4 randomized, double-blind, placebo-controlled trials [48].

Memantine[49]

Meantime, a noncompetitive, highly voltage- dependent NMDA antagonist, has been approved for use in the treatment of dementia in Germany for over 10 years and recently was approved for use in the treatment of AD in the European Union. It has been found to be useful in more advanced (moderate to severe) cases of AD.

Ginkgo Biloba Extract

Oken and colleagues reviewed the published literature on efficacy of Ginkgo biloba for AD[54]. They identified well-designed, randomized, placebocontrolled studies that met their inclusion criteria. They concluded that treatment with Ginkgo biloba extract (120 to 240 mg/day for 3–6 months) had a small but significant effect on objective measures of cognitive function in AD. We need further research to determine whether there is improvement in noncognitive behavioral or ADL functions with Ginkgo biloba extract, since this is critical in evaluating the use of treatment in AD[50].

Antioxidants (Vitamin E and Selegiline) [51]

A lower dose (400 iu bid) of vitamin E is recommended by many experts for patients with AD and may be associated with lowered risk of adverse effects without compromising the beneficial effects. In patients with AD, selegiline leads to small short-term improvement in cognition and activities of daily living. Selegiline does not improve emotional state or global response. For patients with AD who can tolerate vitamin E, there is no reason to take selegiline.

Estrogen[52, 53, 54]

Clinical trials indicate that oral conjugated equine estrogen is not an effective treatment for AD in postmenopausal women. Hence, estrogen is not recommended for the treatment of cognitive or functional deficits attributable to AD. There is increasing evidence that estrogen may decrease the risk for or delay the onset of AD in postmenopausal women. However, this has not been universal and a number of methodological shortcomings in these studies have been identified. These potential benefits have to be weighed against the known risks of estrogen, such as increased risk of thromboembolism and gynecological cancers

GOALS OF MANAGEMENT OF ALZHEIMER'S DISEASE

Patients Care Goals

- Educating the patient regarding the disease
- Symptomatic treatment with a cholinesterase inhibitor (ChEI)
- Reducing excess disability
- Addressing safety concerns (driving, firearms, wandering, poisonous substances, etc.)

- Addressing ability to make medical and financial decisions and capacity to live independently
- Screening for abuse and neglect
- Treating medical comorbidity with intensity appropriate to the stage of the disease and patient/family wishes
- Treating psychiatric comorbidity (depression, psychosis, agitation) with nonpharmacological and, if necessary, pharmacological interventions
- Addressing end-of-life-issues
- Counseling regarding research options

Family Care Goals

- Increasing effectiveness of care and coping strategies
- Increasing satisfaction with the family member's preferred level of involvement—often, no matter how much an individual is doing for his or her family member with AD, he or she harbors feelings that it is not enough
- Decreasing negative consequences on the family
- Minimizing family conflicts

NONPHARMACOLOGIC INTERVENTIONS FOR REDUCING BEHAVIORAL DISTURBANCES IN ALZHEIMER'S DISEASE

- Provide the patient with a predictable routine (i.e., exercise, meals, and bedtime should be routine and punctual).
- Allow the patient to dress in his or her own clothing and keep possessions.
- Before performing all procedures and activities, explain them to the patient in simple language.
- Simplify all tasks; break complex tasks into steps and provide instructions for each step.
- Use distraction and redirection of activities to divert the patient from problematic situations.
- Ensure that comorbid conditions are optimally treated.
- Provide a safe environment (i.e., no sharp-edged furniture, no slippery floors or throw rugs, no obtrusive electric cords).
- Equip doors and gates with safety locks.
- Install grab bars by the toilet and in the shower.
- Use calendars, clocks, labels, and newspapers for orientation to time.

- Use color-coded or graphic labels (i.e., on closets, table service, drawers) as cues for orientation in the home environment.
- Use lighting to reduce confusion and restlessness at night.
- Avoid glare from windows and mirrors, noise from a television, and household clutter.
- Reduce excess stimulation and outings to crowded places
- (Overexposure to environmental stimuli can lead to agitation and disorientation).
- Consider using a day care program for patients with Alzheimer's disease.
- Register the patient in the Alzheimer's Association Safe Return Program.

BEHAVIORAL PROBLEMS AND MOOD DISORDERS[55]

Behavioral symptoms such as agitation and wandering become common as Alzheimer's disease progresses. These behavioral symptoms are especially challenging to the primary caregiver. Nonpharmacologic interventions measures should be exhausted before drugs are used to treat behavioral symptoms and mood disorders. When drug therapy is required, concomitant nonpharmacologic interventions may enable a reduction in the dosage, duration, or complexity of treatment. Suggested nonpharmacologic interventions for use in patients with Alzheimer's disease are provided in. Caregivers can be taught strategies to reduce behavioral disturbances in patients with dementing illnesses such as Alzheimer's disease. One approach involves the three R's (***r***epeat, ***r***eassure, and ***r***edirect). With this approach, the caregiver repeats an instruction or answer to a question as needed and redirects the patient to another activity to divert attention from a problematic situation. A predictable routine is also important and may avert certain behavioral problems. For example, scheduled toileting or prompted voiding can reduce urinary incontinence.

DISCUSSION AND CONCLUSION

AD is one of the principal causes of disability and decreased quality of life among the elderly and is a leading obstacle to successful aging. AD is a treatable condition. Today's treatment options are greatly improved over those available a few years ago. ChEIs should be considered in all patients with mild to moderate AD. ChEIs have been shown to temporarily stabilize cognition. Other drugs such as memantine which modify the glutamatergic system, which is a partial NMDA receptor antagonist. It shows promising in their effect in slowing functional decline in patients with moderate to severe AD. Ginkgo biloba extract also improve the condition of Alzheimer disease with less or little side effect more research work it need to establish it as an Standard therapeutic agent for Alzheimer disease . Physician may prescribe

vitamin E instead of prescribing Selegiline for the treatment of Alzheimer disease in patients who can tolerate Vitamin E. As it improve the condition and reduces the adverse effect. As estrogen is associated with increased risk of thromboembolism and gynecological cancers so not need to prescribe this medication. Early diagnosis and regular therapy can improve the status of patients and also increase the life expectancy.

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