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Novel therapeutic approaches for Alzheimer's disease

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Abstract

The currently approved therapies for Alzheimer's disease (AD) in the US are designed to modify the function of specific neurotransmitter systems in the brain. While these palliative treatments can benefit some patients for a period of time, they do not halt the relentless cognitive and behavioral deterioration that characterize this neurodegenerative disorder. Alzheimer's disease (AD) and vascular dementia (VaD) are both associated with deficits in cholinergic neurotransmission that are amenable to therapeutic intervention. The cholinesterase inhibitor, donepezil, is clinically effective in both AD and VaD. There are various additional therapies which might be useful, if the diagnosis and treatment is started at the early stage.

Keywords: *Alzheimer's disease, cholinesterase inhibitors, hormonal therapy, omentum transfer,vitamins*

INTRODUCTION

Alzheimer's disease (AD) was first described by a German Neurologist "Alois Alzheimer" in 1906. It is defined as a group of disorders involving those parts of the brain that control memory, thoughts and language. It is marked by a progressive deterioration which effects both the memory and reasoning capabilities of an individual [1].

AD is a degenerative neurological disorder which is characterized by irreversible progressive loss of memory followed by dementia. AD destroys the nerve cells in the brain (Neurons) and so weakens the brain performance resulting in progressive worsening symptoms varying from memory loss to decline in the cognitive ability [2].

The prevalence for this disease increases each decade. People in their ninety's stand for their fifty percent chance of having developed the disease. The death of neurons has been linked to seven different insights including inflammation, oxidative damage and the deposition of the abnormal clumps of small proteins called as B-amyloid. This complexicity makes the disease, a challenge to investigate [3]. AD is the most common cause of dementia in adults. In 1997, it was estimated to affect fifteen million people globally. AD is seen more frequently as age increases 0.1% to 0.3% of individuals aged between 60-64 years are affected. The proportion increases to 42-68% in individuals 95 years and older. The symptomatology and duration of AD makes it an extremely challenging disease for patients and costs associated with care of dependent patients with AD, makes difficult for caregivers and society as whole [4].

Therapeutic Strategies

Cholinesterase inhibitors (ChEIs)

Studies were conducted to determine the effect of ChEIs on the natural course of AD. In a study involving one hundred and thirty five matched pair of patients, it was found that, people who were treated with ChEIs were 2.5 times more likely to progress slowly and have a lower risk of nursing home admissions after 2 years [5].

(A)The endothelial effect

The ChEIs are believed to exert a protective effect on endothelial damage in patients with AD. These inhibitors influence the platelet amyloid precursor proteins metabolism towards the non-amyloidogenic pathway. After an intramuscular treatment with ChEIs, a significant reduction of thrombomodulin and selectin levels towards the normal range was observed [6].

(B)Cerebral perfusion

ChEIs improve or stabilize the cognitive impairment in patients with AD. Studies have shown that, there was a significant increase in regional cerebral perfusion after a short term therapy with ChEIs. ChEIs were related to clear increase in (regional cerebral blood flow) rCBF in crucial area involved in attentional and limbic networks[7].

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(C)Treatment of vascular dementia (CVD)

Cerebrovascular disease as well as secondary ischaemic brain injury from cardiovascular disease was the common cause of dementia and cognitive decline in elderly. ChEIs shown improvement in cognition, behaviour and activities of daily living [8].

Individual agents used in treatment

Rivastigmine

The *efficacy* and tolerability of ChEI in treatment of AD have been demonstrated in several clinical trials, activities of daily living shown statistically significant benefits with Rivastigmine across all the severity cohorts [9-15] Treatment with Rivastigmine increases regional CBF by 5 to 7 percent in temporal areas during the first twelve months. In the frontal areas the increase was 3 to 5 %. However, cognitive functions detoriate after 24 months [16, 24].

Galantamine Hydrobromide

A dual Cholinesterase inhibitor and allosteric modulator [21] of nicotine receptors were studied in treatment of AD. It has significant benefits on cognitive function and behavioural symptoms of mild to moderate AD. In Korean patients [17]. Galantamine was well tolerated with common adverse effects such as nausea, vomiting and diarrhea [18, 19] Galantamine safety profile is proportional to that of other ChEI with respect to cholinergically mediated gastrointestinal symptoms [20].

Memantine

Until now, the only available drugs for AD were cholinergic treatments which symptomatically enhanced the cognitive state to some degree, but, were not neuroprotective. Recent phase 3 trials have shown that, memantine is effective in treatment of moderate to severe AD and possibly VAD. (Multiinfarct dementia) [21-25]. Memantine is uncompetitive NMDA receptor antagonist. Recently completed clinical studies demonstrate positive effects in AD, both as monotherapy and in patients receiving continuous Donepezil treatment. Safety and tolerability is also excellent [26,27]. Memantine is efficacious in providing cognitive and global benefit for patients at all stages of AD. It is approved in the US for the treatment of moderate to severe AD [28] also useful in Wernicke-korsakoffs syndrome [29, 30].

Donepezil

A ChEI which prevents the hydrolysis of Ach has been approved for the symptomatic treatment of AD for over a decade [9]. A study involving 134 patients was conducted and it was found that, donepezil has significant efficacy in the treatment of neuropsychiatric symptoms in patients with mild to moderate AD [10]. In both AD and VAD (Vascular Dementia) donepezil proved significant benefits on measures of cognition and global function. Patients in co-morbid conditions and with concomitant medications, donepezil is effective and well tolerated in both the types of dementia [11].Donepezil induced inhibition of cortical ChE activity is moderate in patients with mild AD. The degree of cortical enzyme inhibition correlates with changes in attentional functions[12]. Donepezil not only affects the cognitive functions but also the sleep patterns in ATD (Alzheimer's type Dementia) With sleep patterns, the percentage of REM sleep to the total sleep time increased after the administration of donepezil [13]. Donepezil has significant treatment benefit in the early stage AD, supporting the initiation of the therapy in the early course of the disease to improve the daily cognitive functioning [14]. An open label comparative study of Rivastigmine, donepezil and galantamine in a real world setting was also conducted and shown that, no statistically significant differences between the three drugs in the first three months while numerical trends were observed suggesting that the effect of Rivastigmine greater than donepezil greater than galantamine [22, 23].

NSAIDS

There is an epidemiological observation that, the long term treatment of patients with rheumatoid arthritis with Ibuprofen results in reduced risk and delayed onset of AD [31, 32]. Ibuprofen is a cox-1, cox-2 and ppar (peroxixome proliferator activated receptor agonist) decreased production of nitric oxide (NO) protects the neurons against glutamate toxicity and decreased production of pro-inflammatory cytokines [32]. Other NSAIDS such as flurbiprofen, indomethacin, sullindac also posses amyloid B-lowering properties in both AD transgenic mice and cell cultures of peripheral glial and neuronal origin [33].

HORMONAL THERAPY

Epidemiological studies implicate that, oestrogen deprivation is a risk factor for AD and post menopausal oestrogen replacement as a protective factor [34, 35].

Evidence from basic science demonstrates that, oestrogen has multiple protective effects on neurons and neurotransmitter systems [36] Studies were conducted to develop a brain selective oestrogen receptor modulator. Such molecules are termed as NeuroSERMS [37]. Raloxifene, a SERM that binds with high affinity to the oestrogen receptor has no significant effect on cognition. Tamoxifen showed some improvement than the non-users [38]. Oestrogen, though, increases brain activity in women, there was no significant improvement in verbal and non-verbal memory tasks. It has been observed that, low endogenous levels of DHEA (Di-hydro-epi-androsterone) found in advancing age has correlation with health condition. DHEA replacement therapy may be effective in treating patients with variety of conditions in addition to AD [39, 40].

METAL CHELATORS

Oxidative stress and excessive redox metals have been implicated in the pathogenesis of AD, which, leads to tentative employment of radical scavengers and metal chelators in clinical therapy of AD [41]. A new bi-functional molecule XH1 is developed. This lipophilic molecule has both the amyloid binding and metal chelating moieties covalently connected with amide bonds [42]. Clioquinol, a potential drug for AD induced resumption of copper suppressed febrile growth of Beta (1-40). The synergetic effect of clioquinol and Zinc suggest that, Zinc – Clioquinol complex effectively retards the febrile growth. Thus, clioquinol has dual effects although it disaggregates the amyloid B- metal ion induced through metal ion chelation. It further retards the febrile growth along with Zinc [43].

OMENTUM TRANSFER

There is increasing evidence that, cerebral hypo-perfusion plays a key role in the development of AD. As one ages, the cerebral blood flow (CBF) decreases as a direct reflection of a normal aging process. Maintaining a critical blood flow level becomes essential. Omentum transposition to the brain is a surgical procedure by which, a large volume of blood and other biological agents can be delivered to the brain over an indefinite period of time [44]. Omentum incorporates into its tissues a variety of biological factors that exerts favourable effects on CNS. Success in this area raises the probability that, the omentum may prove a treatment for AD patients [45].

VITAMIN E

The brain contains high levels of oxidisable lipids that must be protected by anti-oxidants. Low concentration of Vitamin E quantitatively, major lipophilic anti-oxidant in brain is frequently observed in CSF of AD patients suggesting that, the supplementations with Vitamin E might delay the onset of AD [46]. Vitamin E has anti-oxidant hydrophobic properties that render the molecule as a main anti-oxidant present in the biological membranes preventing lipid peroxidation, carbonyl formation and inducing intracellular modulation of cell signalling pathways [47]. Various forms of tocopherol rather than alpha-tocopherols are protective in AD [48]. One of the clinical trials showed a significant delay in the onset of disease in vitamin E supplemented group; however, underlying molecular mechanisms remain poorly understood [49].

VITAMIN B12

Cobalamine deficiency may cause cognitive defects and even dementia. 19 patients with low levels of Vitamin B12 were neuropsychologically evaluated before treatment and a year later. 12 patients with dementia improved with treatment. The dementia caused may be differentiated from that of AD by neuropsychological evaluation [50].

MISCELLANEOUS AGENTS

Huperazine: It is a potent reversible and selective inhibitive of AchE. Animal and clinical trial findings show that, it exhibits memory boosting activities. It has proven to be a powerful and lasting effect on the brain, while keeping the side-effects to a minimum [51]. It lacks in the prevention of cholchicine induced apoptosis in cerebeller granule neurons, which suggests that, they cannot prevent neuronal loss [52].

Nicotine: A decrease in the number of nicotinic acetylcholine receptors in brain is thought to contribute to the cognitive dysfunction associated diseases as worse as AD and schizophrenia. Certain animal experiments were conducted which suggested that, repeated exposure to nicotine results in positive effects on central cholinergic markers and memory functions, which, may be mediated via effects on high affinity NGF (Nerve Growth Factors) receptors [53,54].

DRUGS USED FOR TREATMENT OF SYMPTOMS ASSOCIATED WITH AD

(1) Risperiodone: Studies conducted to determine the effect of risperidone on specific behavioral and psychological symptoms of dementia. They suggest that, risperidone is more effective in treating a variety of symptoms associated with Dementia [55].

(2)Docosahexaenoic acid: (DHA) administration of DHA, a major fatty acid of brain, ameliorates the impairment of learning ability in an animal model of AD [56].

(3)Quatiapine and Rivastigmine: Clinical studies conducted to determine the efficacy of Quatiapine and rivastigmine for agitation in people with dementia in institutional care and evaluate them with respect to change in cognitive performance, but, it was found that, none of them were effective in treatment of agitation in people with dementia in institutional care [57].

OTHER AGENST USEFUL IN AD

(1) Novel nitrates: (GT1061) is in phase 1c trials for AD. This is one of the families of novel nitrates that have demonstrated neuroprotective properties along with cognition and memory enhancing properties in animal models [58].

(2) Ginko-biloba: (GB) extract 761 can improve cognitive function in patients with AD[59]. It has anti-amnesic effect by minimizing the inhibitory effect of B-amyloid peptides on cholinergic transmission [60].

(3)Alcohol, wine: - The relative risk of coronary heart disease (CHD) and overall mortality are reduced by moderate consumption of alcoholic beverages, particularly, wine. This beneficial effect is extended to some mental disorders[61].

(4) Xanthiones: The methanolic extracts of gentianacampestris leaves exhibited significant inhibition of AChEactivity[62].

AGENTS THAT MAY HAVE BENEFICIAL EFFECTS IN AD

(1)Alpha glutamylcystene ethyl ester (GSEE):- Glutathione (GSH) is an important endogenous anti-oxidant found in milli-molar concentration in brain. GSH levels decreases with aging. Administration of GSEE increases the cellular levels of GSH and may play a protective role in oxidative and neurotoxicity induced by b-amyloid proteins in AD brain [63].

(2)Ginger:- Ginger may be useful in delaying the onset and progression of neurodegenerative disorders[64].

(3) Anthraquinones: They are able to inhibit PHF (paired helical filaments) formation and hence provide a basis for the treatment of tau pathology in AD[65].

(4) Aminothiazoles: They inhibit cyclin-dependent kinase 5 and 2 and thought to have anti-Alzheimer effect [66].

(5)4, 5-di-annilino-pthalimide: - (DAPH) decreases the B-sheet content of AB (1 - 42) peptide. Hence, it is a promising candidate for AD therapy [67].

TABLE 1. Pharmacological strategies under investigation for the treatment of AD [68].

No.	Strategy	Example	Clinical Trial Phase
1	AMPA receptor agonist	S 18986	1
2	G.protein stimulant	R 1485	1
3	5 HT-4 receptor agonist	PRX 03140	1
4	5 HT-6 receptor agonist	GSK 742457	1
5	glucosaminoglycans agonist	HF 0420	1
6	Guanylatecyclase stimulant	GT 1061	1
7	NGE agonist	CERE 110	1
8	Phosphodiesterase-4-inhibitor	MEM 1414	1
9	Ca^{+2} channel agonist	MEM 1003	2
10	Cannabinoid 1 receptor antagonist	AVE 1625	2
11	Choline uptake stimulant	COLURACETAM	2
12	Dopaminergic agonist	SRN 001	2
13	5 HT-1A receptor antagonist	SRA 333	2
14	Immunostimulant	COLOSTRININ	2
15	LHRH agonist	LEUPROUDE	2
16	Protein synthesis stimulant	PYM 50028	3
17	5 HT-1 A receptor agonist	XALIPRODEN HCL	3
18	HMG CoA reductase inhibitor	STATINS	3
19	NMDA agonist	NERAMEXANE	3

CONCLUSION

Alzheimer's disease is the most common form of dementia. The current treatment only helps to manage the symptoms of the disease. There are no treatments

available that stop or reverse the progression. As of 2012, over one thousand clinical trials have been conducted but, there is no foolproof treatment available for cuing AD. No foolproof strategies for curing AD have been developed as the exact cause is unknown. The only therapy that is available for patients is symptomatic treatment [69]. AD is a devastating disease that is increasing in real numbers as population ages. The toll on individuals, family, health care and society will continue to escalate unless a more effective treatment approaches are developed [70].

Mental stimulation, exercise and balanced diet have been recommended to delay the onset of cognitive decline. Early diagnosis of AD and initiation of anti-alzheimer therapy delay the severity of symptoms. There are five prescription drugs approved by US-FDA to treat symptoms of AD. These are Cholinesterase Inhinitors like donepezil, galantamine, rivastigmine and tacrine. The fifth one is Memantine which is a NMDA receptor blocker. Apart from the approved therapies, there are studies conducted that suggest use of NSAIDs, hormonal replacement therapy, metal chelation therapy if initiated at the time of early diagnosis may delay the onset of AD, however, the path to therapeutic strategies will be based on research data from clinical trials.

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