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## Alzheimer'S Disease: A Brief Quintessence Medical Management Study

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### ABSTRACT

Previously, Alzheimer's disease was called rare chronic neurodegenerative disorder that, now these days, gets worse over time and non-curable. And, it has been considered as a major public health issue that is seriously affecting millions of peoples in America, Western Europe and other Asian countries followed by in Sub-Saharan Africa. Alzheimer's disease is caused due to formation of amyloid-beta ( $A\beta$ ) plaques in brain, which lead to accumulation of neurotoxic cerebrovascular lesions that damaging connections of one neuron to another whose main causes are due to stressful life of modern-era or sometimes. It may be also drug induced medicated therapies or drug addiction. One more protein called "Tau protein" is accumulated as stable tangles inside neurons leading to the neural cells death in brain. Dementia associated with Alzheimer's Disease (AD) is directly linked with the formation of amyloid-beta plaques and Tau protein observed in patients' brain by PET/CT scan. Existing therapies for Alzheimer's disease are often provided patients with some symptomatic relief form onset of symptoms including memory loss and decline any intellectual ability for a short interval of time. However, there are no current curable treatments that change the underlying process of this disease and slow down its progression. So now, cholinesterase inhibitors e.g., Donepezil, Rivastigmine, Physostigmine are prescribed to treat symptoms of Alzheimer's disease related to loss in judgment, memory, thinking, language and other thought processes. These used drugs are worked by increasing the level of acetylcholine, which is chemical messenger involved to regulate all type of thought processes. An N-methyl-D-aspartate receptor (NMDA receptor) antagonist such as Memantine is used to control the synaptic plasticity and memory function to work as glutamatergic pathway to block excessive release glutamate via blocking NDMA receptors. Generally, cholinesterase inhibitors and Memantine can be used for safe therapeutic medication with excellent efficacy for the treatment of patients suffering from Alzheimer's disease. So, form this brief preview, we can get the possible frameworks to carry out the more potential and efficient clinical management strategies including effective diagnostics advanced approaches and drug targeted therapies to treat this disease. It might be lead to deceased mortality and morbidity rate of the affected individuals worldwide.

**Key words:** Alzheimer's disease, cholinesterase inhibitors, N-methyl-D-aspartate receptor, NMDA receptor, memantine, cholinesterase

### INTRODUCTION

During an average lifetime, any individual can experienced to have at least occasional memory lapses from time to time with the increasing age. Such lapses are relatively normal but, when they become a common recurrence with worse consequences. It is found to be neuropathological fatal

conditions of dementia and later on, called Alzheimer's disease (Qiu *et al.*, 2009). Acetylcholine is neurotransmitters for normal memory function. Patients of Alzheimer's disease have low levels of acetylcholine in their brain as compared to normal individuals due to normal biochemical activity of enzyme called cholinesterases (Selkoe, 2001; Hendrie, 1998). Dementia is a broad category of neural disorder that causes a long term and often gradual decrease in the intellectual ability and routine thought processes including vascular dementia, Lewy body dementia and frontotemporal dementia with noticeable cognitive and behavioural interventions (Rivas-Vazquez *et al.*, 2000). Cholinesterase inhibitors, such as donepezil are often used to treat dementia in patients of Alzheimer's disease, which may be beneficial to get potentially improve outcome in mild to moderate relief with respect to daily life activities (Cummings, 1995). The primary symptoms of Alzheimer's disease are amnesia, aphasia, agnosia and apraxia, which are going worse with the time as occurrence of secondary symptoms, dementia, psychosis, personality changes, depression, hallucinations and delusions (Gooch and Stennett, 1996). Formation of amyloid-beta plaques and Tau protein tangles was found to be observed in the regions of brain of patients of Alzheimer's disease with early onset of symptoms especially in cortical ganglia, basal ganglia, substantia nigra and cerebral cortical regions of brain (Tapiola *et al.*, 2009; Corbett *et al.*, 2012).

Amyloid Precursor Protein (APP) is an integral membrane glycoprotein expressed in the brain and Central Nervous System (CNS). It can undergo sequential proteolytic processing by two pathways:  $\alpha$  pathway and  $\beta$  pathway. In most cases, APP is sequentially cleaved via  $\alpha$  pathway by  $\alpha$ -secretase and  $\gamma$ -secretase. The  $\alpha$ -secretase cleavage of APP is non-amyloidogenic, whereas the  $\beta$  pathway leads to A $\beta$  formation which is peptides having 99-amino-acids which accumulates as plaques in the regions of patients brains with the time (Cummings *et al.*, 2014). Alzheimer's disease is a complex neurodegenerative disease involving the interactions of various potential biological and environmental factors, which require effective development of biochemically and molecular -modifying drugs along with improved diagnostic methods. These medical management criteria might have been proved strongly implicated in the underlying neuropathology and neuropathogenesis of familial earlier-onset and sporadic later-onset forms of this disease. Hence, this comprehensive clinical review might be helpful to introduce the clinical management strategies, effective treatments, innovative diagnostics approach and ethical quandary of Alzheimer's disease to deceased the lethal effects of this disease in patients.

## **EPIDEMIOLOGICAL PROBE OF ALZHEIMER'S DISEASE**

Alzheimer's disease is a complex non-curable neurodegenerative disease involving the interactions among various potential biological and environmental factors. Among them, abnormal deposition of amyloid-beta plaques (A $\beta$ ) have been strongly implicated in the underlying its neuropathogenesis including; Tau protein tangles, reduced cholinesterase activity and abnormal activity of glutamate receptors in familial early onset and sporadic later-onset forms of Alzheimer's disease (Selkoe, 2001). Accumulation of amyloid-beta plaques and Tau protein were detected by using well established Positron Emission Tomography-Computed Tomography (PET-CT) for the diagnosed of dementia associated with Alzheimer's Disease (AD) (Berti *et al.*, 2011). Others current prognostic, diagnostic approaches, genetic polymorphism and medicated therapies which are gone to be used to treat the patients of Alzheimer's disease may ease symptoms by providing temporary improvement and reducing the rate of cognitive decline (Hendrie, 1998; Gooch and Stennett, 1996). So, pharmacogenetic profile of individual for cholinesterase-inhibitors in the symptomatic treatment of Alzheimer's disease will remain an important clinical investigation along with

therapeutic drugs consideration which might be probably continue to play a role in the management of these devastating disorders in the foreseeable future. Genetic polymorphism within apolipo protein (APOE) and butyrylcholinesterase (BCHE) has been shown to contribute to inter-individual variability in response to cholinesterase-inhibitors (ChEIs) in this neuropathological condition as well as the identification of phylogenetic susceptibility to used drug-related traits especially into accounted allele frequencies (Hendrie, 1998; Gooch and Stennett, 1996; Corbett *et al.*, 2012).

### **CURRENT TREATMENT FOR ALZHEIMER'S DISEASE**

Alzheimer's disease is a progressive, debilitating and non-curable disease but presently, anticholinergic drugs, such as Rivastigmine, Physostigmine and Donepezil has shown good efficacy in improving the cognitive function in Alzheimer type dementia. Tacrine was also reported to be used another effective anticholinergic drug, which inhibits both acetyl cholinesterase and butyryl cholinesterase enzymes, which inhibits the effects promoted by M1 and M2 cholinceptors. Apart this, Donepezil was reported to be safe drug as another acetyl cholinesterase inhibitor which is presently available and used for medication to treat this disease (Ballard *et al.*, 2008). Over stimulation of N-methyl-D-Aspartate (NMDA) receptors in patients was found to be suppressed by doing the treatment using the amantadine derivatives such as Memantine (dimethyl adamantine) as NMDA receptors anatgonists along with antioxidants, such as vitamin-E ( $\alpha$ -tocopherol) monoamino oxidase inhibitor (selegiline), phenolics (curcumin), tannins (gallic acid) and polyphenolics (ferulic acid). Another medication was found to be helpful to reduce the free radical formation and prevent the cognitive syndromes with the vaccines administration of AN-1792 by intramuscular route to reduce amyloid-beta plaques. These plaques were found to be induce the nonfatal inflammation, whose fatal effects can might be reduced with estrogen therapy via administration of raloxifene to improves the cognitive function, medication with advanced transplantation of stem cells having functional cholinoreceptors, medication with patients-palliative home care to reduce the lethal risk of Alzheimer's disease in patients (Seshadri *et al.*, 1997; Gauthier, 2001; Lewis and Bloom, 1987). Patients treated with rivastigmine is well known cholinergic agent used for the treatment of mild to moderate dementia of the Alzheimer's disease which acts as acetylcholinesterase inhibitor. It is inhibited both butyrylcholinesterase and acetylcholinesterase unlike donepezil, which selectively inhibits acetylcholinesterase via cholinesterase-mediated hydrolysis without involving hepatic cytochrome P450 pathway along with its side effects e.g, nausea and vomiting (Blackburn *et al.*, 1981; Perry, 1986). Physostigmine was also reported to be used in the treatment of this disease which is a parasymphomimetic alkaloid, specifically, a reversible cholinesterase inhibitor to improve short term memory (Coelho and Birks, 2001; Lorenzo and Yankner, 1994). In another way, overdose of these drugs can cause cholinergic syndrome as neurotoxic agents with its major symptoms e.g. dyspepsia and seizures in the patients under medication (Arnold *et al.*, 1991; Arriagada *et al.*, 1992; Swerdlow, 2007). Donepezil was reported for its therapeutic use in the palliative treatment of Alzheimer's disease with its side effects especially nausea, vomiting and gastrointestinal disorders (Arnold *et al.*, 1991; Small *et al.*, 2006; Mufson *et al.*, 2008). Donepezil and galantamine have been going to be tested as fairly good parasymphomimetic drugs with expected efficacy having less notable side effects. Hence, these are going to be used for clinical trials recommended by FDA to treat other cognitive disorders, including Lewy-body induced dementia and vascular dementia to improve sleep apnea in patients of Alzheimer's disease (Dooley and Lamb, 2000; Olazaran and Gracia, 2002).

## **CONCLUSION**

There are no drug treatments that can cure Alzheimer's disease or any other common type of dementia. However, medicines/drugs have been developed for Alzheimer's disease that can temporarily alleviate symptoms, or slow down their progression, in some people. Drug based treatment is reported to be very important for the treatment of Alzheimer's disease. But apart this, recommended palliative clinical activities and support are found to be important in helping the patients to live well with Alzheimer's disease. Two types of medications were used in the treatment of Alzheimer's disease: acetylcholinesterase inhibitors (often shortened to just 'cholinesterase inhibitors') and NMDA receptor antagonists. In the brain of a person with Alzheimer's disease, decreased level of acetylcholine was found. It is the chemical, which is played a very important role in sending the neuro-physiological messages. In Alzheimer's disease, there is also a loss of the nerve cells that use acetylcholine that lead to dropping of acetylcholine levels and progressive loss of these nerve cells which linked to worsening symptoms of dementia associated with Alzheimer's disease. In the future, the pharmacogenetics research might have the potential to carry out the simple, fast and inexpensive DNA tests to identify cholinesterase inhibitors (ChEIs) response status and its predisposition to combat the side effects of Alzheimer's disease in the patients. This might would be help the physicians to assist them in making a decision about which drug should be used, at what dose and in whom to initiate treatment to get better positive results in the patients. Furthermore, patients can be sub-grouped for research and clinical trials based on their pharmacogenetic profile on the basis of these clinical consideration in the overall clinical population. Hence, this brief overview on previously studied clinical approach may also aid in elucidating the mechanism of action of cholinesterase inhibitors (ChEIs) and its regulated medication to combat the worse symptoms of dementia associated with this diseases. Additionally, this mini review will might be contribute to a better understanding of the pathogenesis of this complex disease.

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