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Review Article

Safety and effectiveness of Donepezil and Memantine in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) primarily manifests as dementia, cognitive decline, and decline in memory function. The underlying molecular changes include amyloid-beta plaque deposition and intracellular neurofibrillary tangles due to phosphorylated tau proteins in the medial temporal lobe. Many people worldwide are affected by AD. So far, successful treatment for AD has not been found to stop or reverse AD progression. Two drugs, namely donepezil and memantine, have been found useful in alleviating symptoms of AD, and the quality of life improves in AD patients. However, the medications do not prevent or slow down the disease pathology. Donepezil inhibits acetylcholinesterase enzymatic activity, and memantine antagonizes NMDA receptors, which in turn increases levels of acetylcholine and helps to regulate glutamate in the brain, respectively. Both drugs are commonly prescribed in AD, but their effectiveness can vary among patients. Clinical studies on donepezil and memantine, or in combination, in AD patients, have generated conflicting results regarding the overall safety and effectiveness of the drugs. Few studies have found modest improvements in cognitive function, whereas others have found little to no benefit. Thus, this review discusses some key aspects related to the safety and effectiveness of donepezil and memantine prescriptions in AD pathology.

INTRODUCTION

Alzheimer's disease (AD) frequently causes dementia that happens because of neuronal degeneration.^[1] With the advancement of medical science, life expectancy has increased, thereby leading to a rapid growth in the number of AD patients. Approximately 8.8 million Indians above 60 years have dementia.^[2] Alzheimer's disease has no cure and can lead to death.^[3] Donepezil and memantine are used to treat memory loss in people with dementia.^[4,5] donepezil is generally started with a lower dose of 5 mg once daily, which is increased after four weeks to 10 mg once daily.^[6] Memantine is also prescribed at 5 mg once daily and then gradually increased to 20 mg over four weeks.^[7] The present review aims to compare the safety and effectiveness of treatment with donepezil to the treatment with memantine. Thus, the study will discuss whether donepezil is superior in alleviating the symptoms

of cognitive decline in Alzheimer-induced dementia or less safe to use than memantine. When it comes to cognitive outcomes, donepezil and memantine show equivalent efficacy.^[8,9] However, the higher incidence of anxiety in geriatric patients with moderate severity behavior and symptoms of dementia prompted memantine therapy discontinuation.^[10] This review article focuses on the safety and effectiveness of donepezil and memantine therapy in AD patients. Moreover, this review will examine whether the treatment of dementia with donepezil is safer than memantine and whether donepezil has better efficacy compared to memantine in terms of cognitive and global outcomes.

Background and Rationale

The mainstream research on AD with emphasis on medication has grown substantially.^[11] However, the

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present pharmacological treatment options have certain limitations.^[12] Therefore, there is ample room for further exploration of AD treatment strategies. Donepezil, an acetylcholinesterase inhibitor, is used for mild to severe Alzheimer's disease, while memantine is a glutamate receptor antagonist indicated for moderate to severe Alzheimer's disease, either alone or in combination with a cholinesterase inhibitor.^[4] Donepezil administration in mild to severe AD patients might decelerate the rate of cognitive impairment but cannot prevent disease advancement. Moreover, its effect is transient. Similarly, memantine monotherapy causes constipation, coughing and hypertension, headache, dizziness etc.^[12] However, the combination of memantine and donepezil demonstrates significantly fewer cognitive adverse effects than monotherapy.^[13]

This review analyzes the safety and effectiveness of donepezil and memantine, which have shown significant pharmacological activity in AD patients with mild cognitive dysfunction. Donepezil is used as a cholinesterase inhibitor to improve the functions of neurons in AD brain.^[6] Furthermore, oxidative stress in the brain has been decreased by donepezil in a diabetic animal model, so it appears that it may be beneficial in disease-related blood-brain barrier dysfunction.^[14] Other similar medications include galantamine and rivastigmine.^[12]

Alzheimer's Disease: Pathophysiology and Clinical Manifestation

The etiopathology of AD includes amyloid-beta plaque deposition with increased tau phosphorylation in the medial temporal lobe.^[15] Plaques are usually formed extracellularly from the amyloid beta molecule, and tangles are formed intracellularly from phosphorylated tau protein, which causes successive injury in different regions of the brain.^[16] Moreover, a gradual decline in acetylcholine-secreting neurons is observed in AD patients.^[17] Overall, it causes degeneration in brain matter, leading to a decline in memory function and changes in behavior in AD patients.^[1] Pathologies such as oxidative stress, loss of synapses, damage to neurotransmitters, and inflammation can be associated with aging and brain abnormalities.^[18]

The known clinical manifestations parallel the underlying pathophysiology of the brain, characterized by progressive cognitive impairment and memory loss.^[1] At an asymptomatic stage in AD patients, the amyloid beta levels in cerebrospinal fluid decrease before the stage of neuroinflammation when neurofibrillary proteins and tau proteins disappear.^[19] Changes in the neuropathological confirmation time sequence occur in terms of symptomatic and pre-symptomatic appearances.^[20] Furthermore, many researchers have yet to identify clinical changes and variations in different clinical symptoms and their associated occurrences. The hippocampus, one of the

first sites affected by Alzheimer's disease, can be used therapeutically to determine the ability of the brain to decrease the expression of Alzheimer's disease.^[21] In the initial expression of episodic memory and semantic functions, immediate and progressive cognitive decline targets are evident.^[22] Other stages include such additional elements as emotional changes, reduced inhibition, and further deterioration of mood and behavior. Dysphoria, depression, and anxiety can impair stepwise sequence also.^[23] Personality development of Alzheimer's disease is also targeted, apart from cognitive and motor weaknesses. Diagnosis is not classically uniform in Alzheimer's disease. It used to have a wide range of symptoms and estimates.^[24] In certain cases, it is progressive, while in others, it may progress very slowly.^[25] Early detection of AD may be determined through diverse presentations, such as variants of the motor neurodegenerative disease. That implies different patterns of evaluation and management of neurological changes.^[26] Fluid biomarkers along with amyloid beta, tau, p-tau are used for AD classification.^[27] Whether it can serve as an agent for specific pathology remains to be examined in evaluating newly identified clinical manifestations. Early evaluation and management can delay cognitive impairment proportionately and disability in AD patients.

Pharmacological Treatment Options

Currently, there are four approved pathways used as pharmacological interventions for AD, which are classified into three categories: cholinesterase enzyme inhibitors, N-methyl-D-aspartate receptor antagonists, and combined medications.^[28] The acetylcholine theory proposes alterations in the acetylcholine pathway in AD, and all the therapies in this category work to improve cholinergic neurotransmission, which is characterized by the efficiency of cognitive enhancers.^[29] They have been classified into first-line, second-line, and third-line treatment options, which significantly impact the clinical effect, depending on their mechanisms of action and aggressiveness.^[30-32] Among these pharmacological interventions, donepezil and memantine have been approved as effective and safe treatment options in AD.^[33]

Acetylcholinesterase Enzyme Inhibitors

Acetylcholinesterase enzyme Inhibitors prevent acetylcholinesterase and butyrylcholinesterase action, leading to the accumulation of acetylcholine levels in the brain.^[34] Donepezil is well-tolerated and is available in both daily oral and single-daily extended-release capsule formulations.^[6] The strength of donepezil is that it has a low frequency of adverse effects, including minimal drug interactions. Although it has comparable efficacy to rivastigmine and galantamine, which have proven safety and efficacy records, it is associated with dose-dependent adverse effects, necessitating dose titration.^[35] In contrast, galantamine and rivastigmine can be initiated

at therapeutic doses targeting efficacy without the need for titration.^[36] In moderate and severe AD, memantine is widely used as the only NMDA receptor antagonist to manage the symptoms.^[37] Combination therapy of donepezil and memantine has been clinically proven to provide therapeutic benefits in reducing patient suffering associated with AD compared to the monotherapy phase.^[4] In comparison to memantine, which is approved as both monotherapy and adjunctive therapy, the combination avoids conflicting data on use in the adjunctive setting.^[9] The advantage of treatment combined with monotherapy is that lower medical entropy is observed without added benefits provided by the extra therapy.^[38]

Memantine

The mechanism of action of memantine is to block uncontrolled NMDA receptor action.^[39] While donepezil leads to an increase in acetylcholine levels and receptor sensitivity, contributing to stability in Alzheimer's memory function, both drugs work by inhibiting different neurotransmitters in the brain.^[34,39] The combined action of the two drugs helps to better influence separate pathways in the Alzheimer's state than either drug alone. Long-term memantine treatment has improved overall health status and has been shown to be more effective in decreasing dementia-related difficulties such as mood disturbances, agitation, and possibly memory degradation.^[39] However, when donepezil and memantine are combined, some patients have experienced similar side effects like anticholinesterases when beginning monotherapy, including muscle aches, night trembling, burden, or metabolic issues.^[6]

Donepezil and Memantine: Mechanism of action

Donepezil is a cholinesterase inhibitor that increases acetylcholine level in the cortex by inhibiting acetylcholinesterase enzyme activity. It does so through reversible inhibition of the hydrolysis of acetylcholinesterase.^[40,34] AD patients have less acetylcholine in the cortex.^[41] Donepezil does not cure Alzheimer's disease, but it may help Alzheimer's patients think more clearly. It may also help individuals with Alzheimer's to perform daily tasks or participate in more activities.^[6] Memantine, an antagonist, blocks the NMDA receptor activity. The neurotransmitter glutamate activates the NMDA receptor.^[37] In normal nerves, glutamate is released and attaches to the NMDA receptors on the nerves. This action triggers the nerves to become active. In Alzheimer's disease, too much glutamate is released. This excess glutamate stimulates the NMDA receptors continuously. This excessive stimulation by glutamate is believed to be the cause of damaged cortical neurones in AD.^[42] Memantine protects damaged nerves by blocking the receptors from being continuously stimulated. It also reduces the harmful effects of excess glutamate.^[9]

Being a non-competitive antagonist, memantine blocks the NMDA receptor, along with the 5-HT₃ receptor. Memantine replaces magnesium at the NMDA receptor, an open channel, to block the inward flow of excessive calcium ions.^[43] It leads to a slowed progression of symptoms and possibly a decline in symptoms linked to different stages of AD.^[39] Both drugs are thought to have neuroprotective effects.^[44] When considering their use in Alzheimer's disease treatment, clinicians should be aware of these drugs and their mechanisms. This is essential for evaluating the efficacy and safety of each drug.

Efficacy of Donepezil and Memantine

Several studies have demonstrated a significant diversity in metamemory processes in AD.^[45] Donepezil, along with memantine, is indicated for the management of advanced and severe dementia, but they are sometimes used in mild and moderate AD.^[6] Few studies have examined the safety and effectiveness of donepezil compared to memantine, with the results being somewhat controversial.^[40] Henceforth, extensive studies and thorough assessments are the need of the hour to help clinicians make informed clinical decisions that ultimately contribute to improving their patient's well-being. Therefore, this study aims to review the safety and effectiveness of donepezil, in addition to memantine, in treating Alzheimer's disease (AD) and to evaluate cognitive status and functional abilities.

The use of acetylcholinesterase inhibitors, such as donepezil, is a significant therapy to alleviate symptoms in AD. Donepezil affects disease progression by delaying it and is well-tolerated in mild and moderate AD when compared with a placebo.^[46] Donepezil can be used in patients of advanced age, with up to 20 years since the start of the diagnosis of Alzheimer's disease.^[6] Memantine has been shown to exhibit a favorable effect on various outcomes in Alzheimer's disease.^[9] This review seeks to determine which of the aforementioned drugs (donepezil, memantine) is more favorable to use in AD, based on the prevailing evidence. The findings of this systematic review have shown that donepezil and memantine are superior to the placebo in alleviating Alzheimer's disease, thus having a significant positive effect on cognitive and autonomous disorders, increasing progression-free survival compared with the placebo, and improving function.^[32] Overall, the new treatment for Alzheimer's disease should be dual-action medications that, in addition to treating cognitive functions, should ease patients' ability to perform their daily activities independently.^[33,44]

Comparison of Donepezil and Memantine

Memantine, a selective NMDA receptor blocker, and Cholinesterase Inhibitors share similarities at different stages of AD.^[37] Donepezil is a reversible acetylcholinesterase inhibitor.^[47] Two drugs primarily act differently; donepezil increases acetylcholine levels in synaptic neurons, which in turn improves cognitive



behavior by promoting transmission among cholinergic neurons of the system.^[32] Memantine can regulate and control the activity of glutamate in neuronal systems to achieve a balance between antioxidants and pro-oxidants.^[9]

Both donepezil and memantine showed good outcomes.^[4] Therefore, the present study aims to compare the use of donepezil and memantine in different usage strategies and explore which one dominates in AD treatment. In terms of efficacy, it has been confirmed that both donepezil and memantine are effective in moderate AD treatment.^[5] In a large practical study of nursing home facilities, memantine plus cholinesterase inhibitors resulted in a decrease in D741-ADL score, while cholinesterase inhibitors monotherapy resulted in a decline in D-ADL in the same period.^[48] The nursing home residents on memantine, in addition to cholinesterase inhibitor therapy, had a statistically significant higher MMSE score than those on anticholinesterase monotherapy from the 6th month onwards, suggesting that patients can receive more attention and care from family and society.^[48] However, similar to donepezil, memantine also had some side effects, with higher adverse reaction rates in the two treatment groups.^[49]

CONCLUSION

Donepezil and memantine are two important medications for managing Alzheimer's disease symptoms, showing efficacy and safety for Alzheimer's patients, both in donepezil's single use and in the combination of both medications. This study concluded that donepezil and memantine were safe and efficacious for the treatment of AD. A clinician or expert should determine the effective dose of donepezil and memantine upon diagnosis of AD, to initiate treatment promptly.

The objective of this review was to present a comprehensive discussion of the drug, considering meta-analysis, systematic review, preclinical, exploratory, and clinical trial studies that have been conducted.

LIMITATIONS AND FUTURE DIRECTIONS

A number of limitations are noted in this study. It is acknowledged that the studies included in this review varied in their methodologies, with differences in participant demographics, including gender, average age, ethnicity, and duration of illness. Given the variability in methodologies among these studies, it is recommended that future research employ a longitudinal study design to contribute to the findings of those included in this review. It is also recommended that future research into the safety and efficacy of donepezil and memantine examine more diverse participant groups.

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