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Exploring the Combined Efficacy of Rivastigmine and Vitamin E in Dementia Care

¹ Ayush Kumar Dubey, ² Zeeshan Khan, ³ Suchita Wamankar, ⁴ Rajesh Kumar Nema

^{1, 2} Rungta Institute of Pharmaceutical Sciences and Research, Kurud-Kohka, Bhilai, Chhattisgarh, 490024, India

³ Associate Professor, Rungta Institute of Pharmaceutical Sciences, Kohka, Bhilai, 490024, Chhattisgarh, India

⁴ Rungta Institute of Pharmaceutical Sciences, Kurud-Kohka, Bhilai, Chhattisgarh, 490024, India

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Corresponding Author: Suchita Wamankar

Abstract

With the increasing number of individuals affected by dementia, particularly Alzheimer's disease (AD), it is essential to discover new treatments. This review looks at the potential benefits of using rivastigmine and vitamin E together to manage dementia. Rivastigmine, a drug that boosts acetylcholine levels in the brain, helps improve memory and communication between nerve cells. Vitamin E, a powerful antioxidant, shields brain cells from damage induced by oxidative stress. Combined, these treatments may slow down the progression of dementia and enhance patient outcomes.

The review details how rivastigmine and vitamin E work individually and presents clinical evidence supporting their

combined use. It also highlights the potential benefits of this combination therapy in improving cognitive functions and reducing the decline in daily activities. Additionally, the paper outlines areas for future research, such as long-term effectiveness, optimal dosages, and real-world application, to fully understand and utilize this therapeutic combination. In conclusion, while current evidence is promising, Additional research is required to validate the effectiveness and enhance the application of rivastigmine and vitamin E in dementia treatment. This review emphasizes the need for ongoing studies to refine treatment approaches and elevate the quality of life for individuals with dementia.

Keywords: Rivastigmine, Dementia, Alzheimer's disease (AD), World Health Organization (WHO)

Introduction

Dementia refers to a broad category of neurological disorders characterized by an increasing decline in cognitive functions, impacting memory, thinking, behaviour, and the capability to carry out daily tasks. It stands as one of the primary causes of disability and reliance among elderly individuals globally. The World Health Organization estimates that approximately 5 crore people are suffering from dementia across the globe, and this is expected to get tripled by the year 2050 ^[1].

Of the different types of dementia, Alzheimer's disease (AD) is the most prevalent, contributing to a significant burden on individuals and healthcare systems. Present treatments focus on alleviating symptoms and decelerating the progression of the disease ^[2]. Rivastigmine is a cholinesterase inhibitor, that is used to enhance brain function by increasing acetylcholine levels, thereby improving cognitive abilities and daily living activities in those with mild to moderate dementia ^[1, 2].

Oxidative stress significantly contributes to the advancement of dementia, causing nerve damage and cognitive decline. Vitamin E, recognized for its antioxidant qualities, aids in safeguarding neurons from oxidative harm, reducing lipid peroxidation and free radicals ^[2]. Combining rivastigmine and vitamin E offers a promising therapeutic approach, addressing both cholinergic dysfunction and oxidative stress ^[3]. This review explores the synergistic effects of rivastigmine and vitamin E, emphasizing their promising role in improving cognitive function and the overall quality of life for individuals with dementia.

Understanding Dementia

Dementia encompasses various neurodegenerative disorders leading to a continuous deterioration in cognitive abilities, including memory, reasoning, language, and problem-solving skills ^[1]. Alzheimer's disease (AD) is the most prevalent,

accounting for 60-80% of dementia cases. Other types include vascular dementia, Lewy body dementia, and frontotemporal dementia, primarily affecting older adults, with age being the primary risk factor^[1, 2, 3].

The disease's pathophysiology involves complex processes like neuronal loss, amyloid plaques, neurofibrillary tangles, and synaptic dysfunction, all contributing to brain function deterioration and symptom manifestation^[2, 4]. People with dementia often face difficulties in daily activities, personality changes, and behavioural problems, significantly affecting their quality of life and presenting challenges for caregivers.

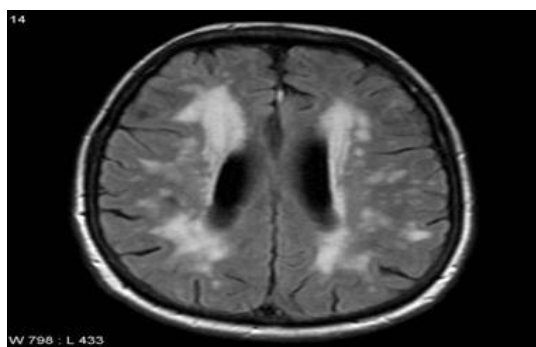


Fig 1.1: Brain scan showing dementia

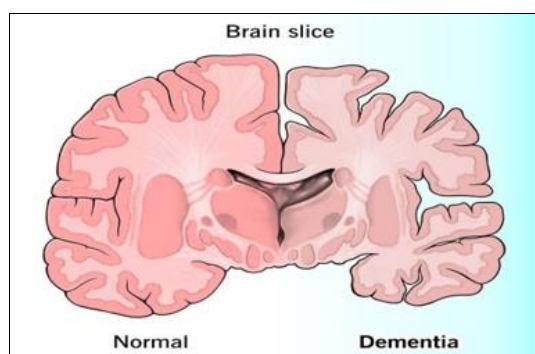


Fig 1.2: Brain slice showing normal brain vs dementia

Given dementia's complex nature, effective management requires a comprehensive approach addressing both cognitive and non-cognitive symptoms. The combination of rivastigmine, targeting cholinergic dysfunction, and vitamin E, reducing oxidative stress, presents a promising treatment approach designed to decelerate the progression of the disease and enhance the quality of life for patients^[3, 4].

Rivastigmine and Its Role in Managing Dementia

Rivastigmine is a medication classified as a cholinesterase inhibitor primarily used to manage mild to moderate Alzheimer's disease and dementia associated with Parkinson's disease. Its mechanism involves the inhibition of acetylcholinesterase, an enzyme that breaks down acetylcholine—a neurotransmitter crucial for memory and cognition^[4]. By preventing acetylcholine breakdown, rivastigmine enhances its levels in the brain, thereby improving communication between neurons and boosting cognitive functions.

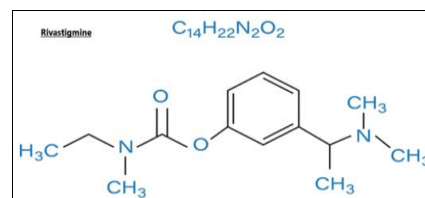


Fig 1.3: Chemical structure of Rivastigmine

Mechanism of action

Rivastigmine is a drug used to manage mild to moderate dementia, especially in Alzheimer's and Parkinson's disease^[2]. It functions by inhibiting cholinesterase, an enzyme that breaks down acetylcholine - a neurotransmitter critical for memory and learning. By blocking cholinesterase, rivastigmine increases acetylcholine levels in the brain, which enhances communication between neurons^[5]. This improved neural transmission helps alleviate symptoms of cognitive decline and memory loss, thus enhancing cognitive function and the overall quality of life for individuals with dementia^[2, 5].

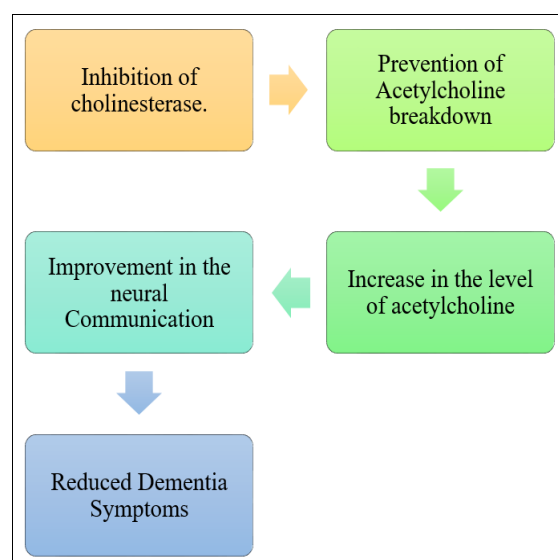


Fig 1.4: MOA of Rivastigmine

Clinical Uses

Rivastigmine is approved for managing mild to moderate Alzheimer's disease and dementia related to Parkinson's disease. Studies have demonstrated its efficacy in enhancing cognitive functions, behaviour, and the capacity to carry out everyday tasks^[6]. It comes in multiple formats, including oral capsules, an oral solution, and transdermal patches, providing flexible administration options.

Clinical Trials and Studies

Multiple clinical trials have assessed the effectiveness and safety of rivastigmine in treating dementia.

➤ North American Trial

A six-month study involving 699 patients with mild to moderate Alzheimer's disease assessed rivastigmine capsules at dosages of 6-12 mg/day, comparing these to a lower dosage (1-4 mg/day) and a placebo. The results

indicated a modest, dose-dependent improvement in cognition, functionality, and daily activities, as assessed by the ADAS-cog, CIBIC-plus, and Progressive Deterioration Scale (PDS) [7].

➤ European Trial

A corresponding six-month trial in Europe, including 725 patients, also compared rivastigmine at dosages of 6-12 mg/day to a lower dose (1-4 mg/day) and a placebo. The findings were similar to the North American trial, showing enhancements in cognitive function and daily living activities [8].

Comparative Analysis of Rivastigmine Patch: Efficacy, Safety, and Tolerability

This research evaluated the effectiveness, safety, and tolerability of 10 cm² and 15 cm² rivastigmine patches in Alzheimer's patients experiencing cognitive deterioration [9]. The trial aimed to compare the patches with other dosages and a placebo.

Impact of Physical Activity and Rivastigmine on Quality of Life

This study investigated the joint impact of exercise and rivastigmine on the quality of life of Alzheimer's disease patients. It aimed to determine whether the combination provided additional benefits over rivastigmine alone [7, 8, 9].

Effectiveness and Safety of Rivastigmine Transdermal Patch

This study aimed to evaluate the effectiveness and safety of the rivastigmine transdermal patch in individuals with mild to moderate Alzheimer's disease, comparing its performance to oral administration [9, 10].

Open-label Extension Research

This study evaluated the long-term effectiveness and safety of the rivastigmine transdermal patch in individuals with probable Alzheimer's disease, aiming to collect data on the patch's performance over an extended period [7, 10].

Dosage and Administration

Rivastigmine is usually begun at a low dosage to reduce side effects, with a gradual increase based on the patient's tolerance and response. The oral form is generally taken twice daily, while the transdermal patch is applied once daily. The preferred dosage form often hinges on the patient's needs and tolerance, with the patch frequently being favoured due to its lower incidence of gastrointestinal side effects compared to oral capsules [5, 7, 10].

Side Effects and Safety Profile

Common side effects of rivastigmine are nausea, vomiting, decreased appetite, and weight loss. These effects are usually dose-dependent and can be managed by initiating treatment with a low dose and gradually increasing it. Other side effects can include dizziness, headache, and fatigue. The transdermal patch often leads to fewer gastrointestinal side effects, making it a preferred choice for some individuals [6, 8].

Comparative Effectiveness

Rivastigmine is one of several cholinesterase inhibitors used to treat dementia, alongside donepezil and galantamine. While all cholinesterase inhibitors provide similar cognitive

benefits, rivastigmine uniquely inhibits both acetylcholinesterase and butyrylcholinesterase, potentially offering broader benefits [9, 10]. The availability of a transdermal patch also provides a valuable option for patients who may have difficulty with oral medications or experience significant gastrointestinal side effects [10].

Vitamin E's Role in Dementia

Vitamin E is a fat-soluble antioxidant essential for safeguarding cells against oxidative stress. It neutralizes free radicals that can damage cells and contribute to aging and numerous diseases. Vitamin E is vital for maintaining healthy skin, immune system, and eye health. It's typically present in foods such as nuts, seeds, vegetable oils, and green leafy vegetables. In relation to dementia, vitamin E is researched for its potential to protect brain cells from damage and support cognitive function, making it a promising supplement for managing oxidative stress-related conditions [11]. While research is ongoing, it is considered beneficial for overall health and well-being.

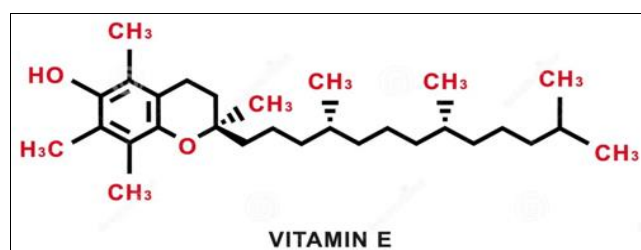


Fig 1.5: Chemical structure of vitamin E

Mechanism of Action

Vitamin E, especially alpha-tocopherol, serves as a powerful antioxidant that protects cells from oxidative stress. Oxidative stress plays a critical role in the onset of Alzheimer's disease (AD), contributing to the creation of amyloid-beta plaques and neurofibrillary tangles [11]. By neutralizing free radicals, vitamin E can potentially mitigate oxidative damage to neurons, thereby enhancing cognitive function [12].

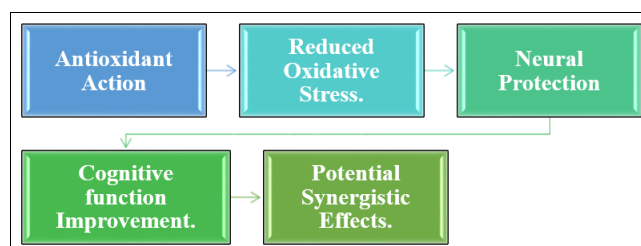


Fig 1.6: MOA of vitamin E

Clinical Evidence

The clinical evidence regarding the efficacy of vitamin E in treating dementia is varied. Some studies have indicated modest benefits, while others have found no significant effects. Here are some key findings:

- **North American and European Trials:** These trials concluded that vitamin E supplementation did not substantially slow the progression of dementia or enhance cognitive function in patients with mild cognitive impairment (MCI) or Alzheimer's disease [7, 8].
- **TEAM-AD VA Cooperative Randomized Study:** This study evaluated the impact of vitamin E and

memantine on functional decline in Alzheimer's disease. The results showed that vitamin E alone did not significantly enhance cognitive function but may have aided in managing daily activities^[13].

- **Meta-Analyses:** A meta-analysis of multiple studies indicated that a high intake of vitamin E from dietary sources and supplements was linked to a lower risk of dementia and Alzheimer's disease. However, the evidence remains inconclusive, and additional studies are necessary to verify these results^[14].

Combination Therapy: Rivastigmine and Vitamin E

Combination therapy utilizing rivastigmine and vitamin E has demonstrated potential benefits in managing dementia, particularly Alzheimer's disease (AD)^[15]. Here is an in-depth exploration of the potential synergistic effects and clinical benefits:

Potential Synergistic Effects

- **Enhanced Neuroprotection:** Rivastigmine, a cholinesterase inhibitor, elevates acetylcholine levels in the brain, enhancing neuronal communication and cognitive functions^[11, 15]. Vitamin E, known for its powerful antioxidant properties, mitigates oxidative stress by neutralizing free radicals, thereby protecting neurons from damage. The combined effects of these mechanisms provide robust neuroprotection that may decelerate the progression of AD^[11, 12, 15].
- **Improved Cognitive Function:** The combined use of rivastigmine and vitamin E can potentially offer superior cognitive benefits compared to monotherapy. Rivastigmine enhances neurotransmission by preserving acetylcholine, while vitamin E maintains neuronal health through its antioxidant effects. This combination can lead to improved cognitive outcomes for patients^[15].
- **Reduced Functional Decline:** Evidence suggests that rivastigmine combined with vitamin E can slow down the decline in daily living activities in patients with mild to moderate Alzheimer's disease. By addressing both cholinergic dysfunction and oxidative stress, this combination therapy helps patients maintain their functional independence for a longer duration^[15].

Clinical Evidence

- **TEAM-AD VA Cooperative Randomized Study:** This research evaluated the influence of vitamin E and memantine on functional decline in Alzheimer's disease^[15, 16]. Although vitamin E alone did not significantly enhance cognitive function, it showed potential benefits in managing daily activities when used with other treatments^[16].
- **Randomized Controlled Trials:** A 2014 trial involving veterans with mild to moderate AD found that vitamin E, when combined with a cholinesterase inhibitor like rivastigmine, delayed the progression of functional decline by approximately six months. This suggests that the combination therapy can enhance the quality of life for Alzheimer's disease patients^[16].
- **Meta-Analyses:** Meta-analyses of various studies have indicated that a high intake of vitamin E from diet and supplements might be associated with a lower risk of dementia and Alzheimer's disease. However, the evidence is not conclusive, and further research is

necessary to confirm these findings^[17].

Additional Insights

- **Multifaceted Approach:** Combining rivastigmine and vitamin E represents a multifaceted approach to dementia treatment^[17]. While rivastigmine addresses cholinergic deficits, vitamin E combats oxidative stress, offering a holistic treatment strategy.
- **Safety and Tolerability:** Both rivastigmine and vitamin E are generally well-tolerated. However, it is essential to monitor for potential side effects. Rivastigmine's common side effects are nausea and vomiting, and high doses of vitamin E can heighten the risk of bleeding^[9, 15]. It is crucial for healthcare providers to tailor the therapy to individual patient needs and ensure safety.
- **Future Research:** Further studies are required to fully comprehend the combined effects of rivastigmine and vitamin E. Future studies should focus on optimal dosing strategies, long-term efficacy, and potential benefits at different stages of dementia.

Future Directions and Research Needs

Examining the potential of combining rivastigmine and vitamin E for dementia management reveals several key areas requiring further research:

- **Long-term Efficacy and Safety:** More comprehensive studies are needed to explore the prolonged impacts of this combined therapy on cognitive function and overall health, including its safety over extended periods.
- **Optimal Dosing Strategies:** Research should focus on identifying the most effective dosing regimens, ensuring a balance between cognitive benefits and potential side effects. Personalized approaches based on individual patient characteristics are also crucial.
- **Mechanistic Insights:** Investigating the molecular pathways and interactions between rivastigmine and vitamin E can provide a deeper understanding of their synergistic effects and unveil new therapeutic targets.
- **Combination with Other Treatments:** Exploring how rivastigmine and vitamin E interact with other medications or lifestyle modifications could enhance overall treatment strategies for dementia.
- **Impact on Different Dementia Stages:** It is important to study the effectiveness of this combination therapy across various stages of dementia, from early to advanced stages.
- **Real-world Effectiveness:** Research in diverse clinical settings can offer valuable insights into patient adherence, quality of life outcomes, and the practical implementation of this therapy.
- **Genetic and Biomarker Studies:** Identifying genetic markers or biomarkers that predict a positive response to the therapy could facilitate personalized treatment plans, improving patient outcomes.
- **Patient and Caregiver Perspectives:** Understanding the experiences and challenges faced by patients and caregivers can inform better treatment strategies and support systems.

Addressing these research areas will enhance our understanding of the potential benefits and limitations of combining rivastigmine and vitamin E, ultimately leading to improved dementia care and patient outcomes.

Conclusion

In conclusion, combining rivastigmine and vitamin E shows considerable promise in treating dementia, particularly Alzheimer's disease. Rivastigmine works by inhibiting cholinesterase to elevate acetylcholine levels, which improves cognitive function and neural communication. Vitamin E offers potent antioxidant protection against oxidative stress, adding another layer of neuroprotection. Together, they provide a synergistic effect that could slow dementia progression and enhance patient outcomes. Nevertheless, continued research is essential to comprehensively understand the long-term benefits and safety of this combination therapy. Future studies should aim to determine the optimal dosing regimens, investigate the therapy's effects at various stages of dementia, and assess its real-world effectiveness. Additionally, gaining insights from patients and caregivers will be crucial for refining treatment protocols and improving their quality of life.

Given the increasing global prevalence of dementia, innovative treatments like the combination of rivastigmine and vitamin E are essential. This review highlights the potential advantages of this combination therapy and underscores the necessity for further research to establish its clinical utility. By advancing our knowledge of these treatments, we move closer to enhancing care and outcomes for dementia patients.

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Conflict of Interest

The authors declare that no conflict of interest of any financial or other issues.

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