

**PHARMACOLOGICAL
TREATMENT OF
ALZHEIMER'S DISEASE:
AN INTEGRATIVE
REVIEW ON THE
EFFECTIVENESS OF
CHOLINESTERASE
AND MEMANTINE
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Abstract: Introduction: Alzheimer's disease is a chronic neurodegenerative disease that affects millions of people worldwide, characterized by progressive memory loss and cognitive decline. Objective: to analyze and compare the effectiveness of different classes of drugs in the treatment of Alzheimer's disease, specifically acetylcholinesterase inhibitors and memantine. Methodology: Several relevant scientific studies were selected for the review, including randomized controlled trials, meta-analyses and systematic reviews. The database used was MEDLINE (PubMed), with inclusion criteria that considered the methodological quality of the studies and the relevance of the results, using the keywords "Alzheimer's treatment", "Cholinesterase inhibitors" and "Memantine". Results: The reviewed scientific studies provide consistent evidence that acetylcholinesterase inhibitors provide significant improvements in cognitive and behavioral functions. Memantine, in turn, demonstrated benefits in improving cognitive and functional symptoms in patients with moderate to severe Alzheimer's and in advanced stages of the disease. Discontinuation of these medications can lead to a deterioration of symptoms and cognitive decline, emphasizing the importance of continuing treatment. Conclusion: Studies have shown that acetylcholinesterase inhibitors and memantine are effective treatments for Alzheimer's disease. However, more research is needed to improve therapeutic strategies and better understand their effectiveness in different stages of the disease and in different patients.

Keywords: Pharmacological treatment; Alzheimer's disease; Cholinesterase Inhibitors; Memantine.

INTRODUCTION

Alzheimer's disease (AD) is a progressive and incurable neurodegenerative condition

that mainly affects the elderly, characterized by gradual memory loss, cognitive deficits and functional impairment. It is the most common form of dementia and represents a growing challenge to global public health. It is estimated that approximately 50 million people worldwide are affected by AD, and this number is expected to triple by 2050 (ALZHEIMER'S ASSOCIATION, 2021).

Although the exact pathogenesis of AD is still not completely understood, evidence indicates that cholinergic dysfunction and the accumulation of beta-amyloid plaques and neurofibrillary tangles are involved in the process of cognitive deterioration (Bloom, 2014; Selkoe, 2019). Based on these pathological mechanisms, currently available therapeutic approaches for the treatment of AD focus on improving cholinergic neurotransmission and modulating glutamatergic activity.

Among the therapeutic options for AD, the cholinesterase inhibitors (CI) and memantine stand out, both approved by the United States Food and Drug Administration (FDA) for the treatment of the disease. ICs, including donepezil, rivastigmine and galantamine, act by inhibiting the enzyme acetylcholinesterase, responsible for the degradation of acetylcholine, a neurotransmitter involved in cognitive function (Tariot et al, 2011). These drugs aim to increase the availability of acetylcholine in the brain and thus improve neuronal communication in areas affected by AD.

On the other hand, memantine is a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors, which regulate glutamatergic activity. Glutamatergic hyperexcitation has been associated with neurotoxicity and neuronal death, being an important pathological mechanism in AD (Parsons et al, 2007). Memantine works by blocking NMDA receptors and thus modulates glutamatergic neurotransmission, reducing

excitotoxicity and protecting neuronal cells from damage.

The aim of this article was to perform an integrative review of published scientific studies on the use of cholinesterase inhibitors and memantine in the treatment of Alzheimer's disease. Systematic reviews, randomized controlled trials, controlled trials and meta-analyses were analyzed in order to provide a critical analysis of the available evidence and assess the efficacy and safety of these therapeutic interventions. In addition, possible side effects, drug interactions, and considerations related to the administration of these drugs were explored.

METHODOLOGY

This study used a qualitative research strategy, through an integrative literature review, with the objective of relating data from previous studies, analyzing relevant issues and reviewing existing theories on the proposed topic.

Article searches were performed using the MEDLINE public platform/publisher (PubMed), including the search terms 'Alzheimer's treatment', 'cholinesterase inhibitors' and 'memantine'. Articles were selected for inclusion based on the following criteria: full text availability, publication in the last 5 years (2018-2023), written in English and targeted for systematic review, controlled and randomized trial, randomized clinical trial and meta-analyses, focused on the treatment of Alzheimer's disease. Studies covering broad topics or not directly related to the study objectives were excluded.

After applying the inclusion and exclusion criteria, each article was analyzed critically and in detail, taking into account possible differences in the study design and objectives. Then, the articles included in the integrative review were chosen, organizing the relevant data in a table with information such as the

author's name, year of publication, article title and conclusion. Preliminary, 96 searches were found in the "PubMed" data search. After applying the established inclusion and exclusion criteria, a total of 10 articles were selected to compose the integrative review. This table was compiled with the help of Excel 2016 software, and these articles were used to support the discussion of the main results found on the treatment of Alzheimer's with pharmacological therapies: cholinesterase inhibitors and memantine.

RESULTS

FIGURE 1 presents the flowchart of the process of choosing the articles that make up this integrative review. Initially, 96 articles were found following the criteria described in the methodology. Then, a thorough analysis of the articles found through the titles and their abstracts was carried out, with 15 articles being chosen for the complete reading. Finally, after a complete analysis, 10 articles were selected to compose the integrative review.

Thus, TABLE 1 presents the selected articles highlighting the authors, title of the work and main conclusions of each research.

DISCUSSION

The study by 0Dou et al (2018) presents a network meta-analysis that comprehensively compares the efficacy and tolerability between currently available cognitive enhancers approved by the "Food and Drug Administration" (FDA). Cholinesterase inhibitors result in better cognition outcomes than memantine for mild to moderate patients, among whom galantamine and donepezil are probably the interventions most strongly associated with cognitive improvements. For moderate to severe AD, combination therapy of donepezil 10 mg with memantine 20 mg is the most effective regimen, followed by donepezil 23 mg alone. Both clinical

effectiveness and adverse effects associated with cognitive enhancers have been observed to be dose-dependent. In conclusion, the authors emphasize that these results can help medical professionals in the selection of drugs directed to patients in different stages and with different clinical symptoms.

The study by Kennedy et al (2018) analyzed the association of concomitant use of cholinesterase inhibitors or memantine with cognitive decline in Alzheimer's clinical trials. Through a meta-analysis, researchers examined data from several studies and found evidence that the combined use of these drugs is associated with a decrease in cognitive decline in patients with Alzheimer's. These results suggest that combination therapy may have benefits in preserving cognitive abilities in individuals with this neurodegenerative disease.

The study conducted by Matsunaga, et al (2018) evaluated the efficacy and safety of memantine in the treatment of Alzheimer's disease. Through a systematic review, the authors concluded that memantine proved to be effective in improving cognitive and functional symptoms in patients with Alzheimer's. Furthermore, memantine was found to be safe and well tolerated, with few significant adverse effects. On the other hand, Donepezil (10 mg/day) and oral monotherapy with rivastigmine and galantamine carry the risk of some adverse events, including gastrointestinal symptoms. These results suggest that memantine may be a promising therapeutic option for the treatment of Alzheimer's disease, providing cognitive and functional benefits to patients, with a favorable safety profile.

Hong, et al (2018) examined the effectiveness of antidementia medications in patients with extremely severe Alzheimer's disease. The study was conducted over 12 weeks and involved multiple centers, being

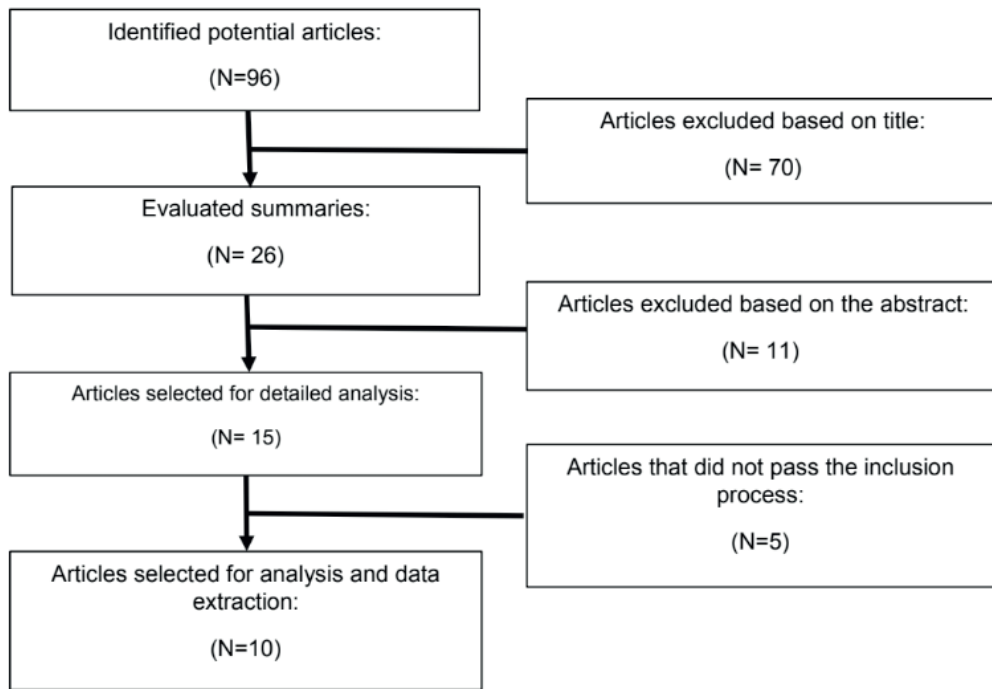


FIGURE 1: Flowchart of the process of choosing articles for the integrative review

Source: Fruchtengarten, et al (2023).

Author and Year	Study Title	Conclusions
Richard E Kennedy et al. (2018)	Association of Concomitant Use of Cholinesterase Inhibitors or Memantine With Cognitive Decline in Alzheimer Clinical Trials: A Meta-analysis	Meta-analysis has shown that concomitant use of cholinesterase inhibitors or memantine is associated with minor cognitive decline in Alzheimer's clinical trials. Combination therapy may have a synergistic effect in preserving cognitive functions and delaying disease progression.
Shinji Matsunaga et al. (2018)	The efficacy and safety of memantine for the treatment of Alzheimer's disease	Memantine has been shown to be effective in treating Alzheimer's disease, improving cognition, global function and activities of daily living. Furthermore, it was well tolerated and had few serious side effects.
Yun Jeong Hong et al. (2018)	Effectiveness of Anti-Dementia Drugs in Extremely Severe Alzheimer's Disease: A 12-Week, Multicenter, Randomized, Single-Blind Study	The study demonstrated the effectiveness of drugs for neurological disorders in treating extremely severe Alzheimer's disease over 12 weeks. The results showed significant improvements in cognitive functions, daily activities and behavioral symptoms compared to the control group.
Kai-Xin Dou et al. (2018)	Comparative Safety and Efficacy of Cholinesterase Inhibitors and Memantine for Alzheimer's Disease: A Network Meta-Analysis of 41 Randomized Clinical Trials	Both cholinesterase inhibitors and memantine are effective in treating Alzheimer's disease, with significant improvements in cognitive and functional symptoms compared to placebo. Cholinesterase inhibitors had a slightly better safety profile, with fewer side effects reported compared to memantine.
Gabriela Marucci et al. (2019)	Efficacy of Acetylcholinesterase Inhibitors in Alzheimer's Disease	The effectiveness of acetylcholinesterase inhibitors in treating Alzheimer's disease is variable, with some studies showing significant improvements in cognitive and functional symptoms, while others found no significant differences from placebo. More research is needed to conclusively assess the effectiveness of these inhibitors.

Jiaxun Guo et al. (2020)	Memantine, Donepezil, or Combination Therapy—What is the best therapy for Alzheimer’s Disease? A Network Meta-Analysis	The comparative meta-analysis concluded that combination therapy with memantine and donepezil may be the most effective treatment option for Alzheimer’s disease. However, it is important to consider individual patient characteristics when deciding on the most appropriate therapy.
Carole Parsons et al. (2021)	Withdrawal or continuation of cholinesterase inhibitors or memantine or both, in people with dementia	Results regarding withdrawal or continuation of cholinesterase inhibitors and memantine in people with dementia are variable. Some studies indicate that withdrawing these medications can lead to a deterioration in symptoms, while others have found no significant differences. More research is needed to provide clear guidance on withdrawing these medications in people with dementia.
Bago Rožanković et al. (2021)	Impact of Donepezil and Memantine on Behavioral and Psychological Symptoms of Alzheimer Disease: Six-month Open-label Study	The study demonstrated that donepezil and memantine have a positive impact on behavioral and psychological symptoms of Alzheimer’s disease. Both drugs were effective in reducing agitation, aggression and other related symptoms, improving the patients’ quality of life.
Adrian L Knorz et al. (2021)	Alzheimer’s Disease: Efficacy of Mono- and Combination Therapy. A Systematic Review	The systematic review highlighted that both monotherapy and combination therapy are effective in the treatment of Alzheimer’s disease. However, combination therapy may offer additional benefits in certain cases. More studies are needed to determine the best therapeutic approach for each patient.
Ezio Giacobini et al. (2022)	Reimagining cholinergic therapy for Alzheimer’s disease	The authors highlight the need to consider improved therapeutic strategies for Alzheimer’s disease, which aim at a selective modulation of specific cholinergic receptors. They emphasize that this approach shows promise for increasing therapeutic efficacy and reducing unwanted side effects associated with conventional cholinergic therapy.

TABLE 1: Selected studies on pharmacological treatment of Alzheimer’s disease with cholinesterase inhibitors and memantine

Source: Fruchtengarten, et al (2023).

a randomized and blinded to the evaluator. The researchers investigated the effect of antidementia medications (memantine and cholinesterase inhibitors) on patients' symptoms and functioning. The results indicated that although the medications showed a modest improvement in cognitive and behavioral symptoms, there was no significant difference from the control group. These findings suggest that, in patients with extremely severe Alzheimer's disease, antidementia medications may have a limited impact on improving Symptoms.

Marucci, et al (2019), conducted a review including randomized clinical trials, aiming to investigate the effectiveness of AChE inhibitors, such as donepezil, rivastigmine, and galantamine, in patients with Alzheimer's disease. The results consistently showed that these drugs were effective in improving cognitive symptoms compared to the control group that received a placebo. In addition, AChE inhibitors have also demonstrated improvements in patients' behavioral symptoms and functionality. The authors observed that the effectiveness of AChE inhibitors varied according to the administered dose and duration of treatment. They highlighted that the beneficial effects were most pronounced in patients with mild to moderate Alzheimer's disease, although some studies have shown benefits in patients with more advanced disease as well. In addition to clinical efficacy, the authors also discussed adverse effects associated with AChE inhibitors. The most common side effects reported were nausea, vomiting, diarrhea and loss of appetite. However, these effects were generally mild to moderate and generally disappeared with continued treatment.

A network meta-analysis study was performed by Guo, et al (2020) with the aim of investigating the effectiveness of three distinct therapies - memantine, donepezil

and combination therapy - for the treatment of Alzheimer's disease. The results showed that memantine and donepezil combination therapy was the most effective in terms of improving cognitive and functional symptoms in patients with Alzheimer's disease. Combination therapy also demonstrated a significant effect in slowing disease progression compared to memantine or donepezil alone. These results suggest that combination therapy can be considered as the best treatment option for patients with Alzheimer's disease, providing synergistic benefits compared to isolated treatments.

The study carried out by Parsons, et al (2021), analyzed the results of patients with dementia who underwent interruption or continuation of the use of cholinesterase inhibitors, memantine or both. Results showed that continuing these medications was associated with significant improvements in cognitive, functional, and behavioral symptoms compared with stopping treatment. Furthermore, continued use of the medications has also been shown to reduce the rate of cognitive decline over time. These findings suggest that continued use of cholinesterase inhibitors, memantine, or both may be beneficial for patients with dementia, providing continued improvement in symptoms and a slowing of cognitive decline. However, it is important to consider potential side effects and discuss benefits and risks with patients and their caregivers before making any decision to stop or continue treatment.

The study by Rožanković, et al (2021) was conducted over six months and involved the participation of patients with Alzheimer's disease who were treated with donepezil and memantine using various rating scales such as the Disease Rating Scale of Alzheimer-Behavior (BEHAVE-AD) and the Neuropsychiatric Scale of the International Dementia Consortium (NPI). For the authors,

treatment with donepezil and memantine led to significant improvements in the patients' behavioral and psychological symptoms. The most common symptoms, such as agitation, aggression, depression and anxiety, were reduced over the six-month period. These results indicate that both donepezil and memantine have beneficial effects in reducing the behavioral and psychological symptoms associated with Alzheimer's disease.

Korz, et al (2021), performed a systematic review to correlate the use of cholinesterase inhibitor therapy and their respective benefits for improving cognition in patients with mild to moderate Alzheimer's disease. Among cholinesterase inhibitors, galantamine and donepezil were the interventions most strongly associated with cognitive improvements. For moderate to severe Alzheimer's disease, combination therapy of donepezil 10 mg with memantine 20 mg has been identified as the most effective regimen. In addition, donepezil at a dose of 23 mg alone also showed efficacy in these patients. Results also indicated that clinical efficacy and adverse effects related to cognitive enhancers were observed to be dose-dependent. Therefore, it is important to consider the proper dosage when prescribing these drugs to patients with Alzheimer's disease. In conclusion, the systematic review showed that therapy with cholinesterase inhibitors, both in monotherapy and in combination with memantine, is effective in the treatment of Alzheimer's disease, providing improvements in cognition.

Ezio Giacobini et al. (2022) evaluated the limitations of conventional cholinergic therapy, emphasizing the need for innovative and improved therapeutic approaches. The potential of selective modulation of specific cholinergic receptors as a promising strategy to increase therapeutic efficacy and reduce unwanted side effects was discussed. In addition, recent studies were presented

that investigated new pharmacological agents and complementary therapies, such as transcranial direct current stimulation (tDCS) and cognitive stimulation, as possible adjuncts to cholinergic therapy. The results encourage the continuation of research and development of more targeted and effective cholinergic therapies, with the aim of improving the treatment and quality of life of patients with Alzheimer's disease. These findings represent significant advances in the field of neuroscience and provide valuable information for the development of more efficient and personalized therapeutic approaches for this neurodegenerative disease.

CONCLUSION

Alzheimer's disease (AD) is a devastating neurodegenerative condition that affects millions of people worldwide. In this integrative review article, we explore the role of cholinesterase inhibitors (CI) and memantine in the treatment of AD, with the aim of evaluating their efficacy and safety.

Based on the critical analysis of the included studies, it was observed that both CIs (donepezil, rivastigmine and galantamine) and memantine demonstrated significant benefits in the management of AD symptoms. CIs act by increasing the availability of acetylcholine in the brain, improving cholinergic neurotransmission and, consequently, delaying the progression of cognitive deficits. Memantine, in turn, acts as a glutamatergic activity modulator, reducing excitotoxicity and protecting neuronal cells.

Although these therapeutic interventions have been shown to be effective in improving AD symptoms, it is important to note that the results vary according to the stage of the disease and the individual response of the patient. Furthermore, both CIs and memantine can be associated with side effects such as nausea, vomiting and gastrointestinal disturbances.

It is critical that healthcare professionals carefully consider the benefits and risks of these medications when individualizing treatment for each patient with AD. Furthermore, combining different therapeutic approaches, including non-pharmacological interventions, may be a promising strategy to improve treatment outcomes.

This integrative review provided a comprehensive overview of the available

evidence on the use of CIs and memantine in the treatment of AD. However, it is important to note that research in this area remains ongoing, and new developments may occur. Therefore, it is essential that future studies further investigate the effectiveness of these drugs, especially in combination with other therapeutic approaches, in order to offer better treatment options for patients with AD.

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