

**COMBINED THERAPY WITH DONEPEZIL AND MEMANTINE IN THE
TREATMENT OF MODERATE TO SEVERE ALZHEIMER'S DISEASE**

**TERAPIA COMBINADA COM DONEPEZILA E MEMANTINA NO TRATAMENTO
DA DOENÇA DE ALZHEIMER MODERADA A GRAVE**

**TERAPIA COMBINADA CON DONEPEZILO Y MEMANTINA EN EL
TRATAMIENTO DE LA ENFERMEDAD DE ALZHEIMER DE MODERADA A
GRAVE**



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**Isabela Cerchiari¹, Clicia Ferreira Gardenal², Taynara Maria Gomes dos Santos³,
Beatriz Oliveira Rocha⁴, Alana Alves Ibanhes Valejo⁵, Nicole Oliveira Jordão⁶, Milene
Márcia de Faria Rodrigues⁷, Luiza Antonello Pedrazzi⁸, Maria Auxiliadora Bezerra
Fechine⁹, Michell Ícaro Lima Oliveira¹⁰, Augusto Rafael Barsella¹¹, Leandra dos
Passos e Silva¹², Maria Fernanda Landivar de Moraes¹³, Millena Beatriz Alves
Fernandes Medeiros¹⁴, Maria Eduarda Bianchi Bitar de Moraes¹⁵, Thais da Silva
Martha Kradichi¹⁶, Saulo Lacerda César¹⁷, Mariáh França Guimarães Meirelles de
Paula¹⁸, Lucas Oliveira Moraes¹⁹, Amanda Lobo de Siqueira²⁰, Iza Pereira Bezerra²¹,
Valéria Paula Sassoli Fazan²²**

¹ Medical Doctor. Universidade José do Rosário Velano (UNIFENAS). E-mail: isabela.cerchiari@gmail.com

² Medical Doctor. Universidade Federal do Pampa (UNIPAMPA). E-mail: clicia.ferreira.g@gmail.com

³ Medical Student. Pontifícia Universidade Católica (PUC). E-mail: taynaramariagomes@gmail.com

⁴ Medical Doctor. Universidade Anhembi Morumbi. E-mail: beatrizo.rocha@icloud.com

⁵ Medical Doctor. Universidade do Oeste Paulista (UNOESTE). E-mail: alanavalejo@gmail.com

⁶ Medical Student. Faculdade Santa Marcelina. E-mail: nicolejordao@gmail.com

⁷ Medical Doctor. Faculdade de Medicina de Barbacena (FAME). E-mail: fariamilene805@outlook.com

⁸ Medical Doctor. Universidade Franciscana (UFN). E-mail: luizapedrazzi@hotmail.com

⁹ Medical Doctor. Universidade da Integração Internacional da Lusofonia Afro-Brasileira.

E-mail: auxiliadorafechine@gmail.com

¹⁰ Medical Doctor. Centro Universitário Christus (UNICHRISTUS). E-mail: drmichell@gmail.com

¹¹ Postgraduate in Anesthesiology. Faculdade de Medicina do ABC. E-mail: draugusto@medicodedor.com.br

¹² Resident in Internal Medicine. Faculdade de Medicina de Valença. E-mail: leandrapassos@yahoo.com.br

¹³ General Practitioner. Universidade do Estado do Rio de Janeiro (UERJ). E-mail:

fernandalandivar67@gmail.com

¹⁴ Master's degree in Physiotherapy. Universidade Federal de Pernambuco (UFPE). UNIFACISA.

E-mail: millena_bia@hotmail.com

¹⁵ Medical Doctor. Instituto de Educação Médica (IDOMED). E-mail: duda.bianchi55@hotmail.com

¹⁶ Medical Student. Universidade Municipal de São Caetano do Sul (USCS). E-mail: tsmkradichi@gmail.com

¹⁷ Medical Doctor. Centro Universitário de Valença (UNIFAA). E-mail: ajuris4@gmail.com

¹⁸ Specialization Student in Geriatrics. Universidade Iguçu. E-mail: mariafranca96@uol.com.br

¹⁹ Medical Student. Universidade Estadual de Mato Grosso do Sul. E-mail: lucas.morais.lom@gmail.com

²⁰ Medical Doctor. Universidade do Oeste Paulista (UNOESTE). E-mail: amanda.lobo.siqueira@gmail.com

²¹ Specialist in Family and Community Medicine. Universidade Maria Auxiliadora (UMAX).

E-mail: dra.izapereirabezerra@hotmail.com

²² Dr. in Neurology. Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (USP).

E-mail: vpsfazan@yahoo.com.br

ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disorder characterized by cognitive, behavioral, and functional decline, particularly in moderate to severe stages. In this context, combination therapy with donepezil, an acetylcholinesterase inhibitor, and memantine, an NMDA receptor antagonist, has been proposed as a therapeutic strategy to enhance clinical outcomes. This study aims to analyze the efficacy and safety of this combination in the treatment of moderate to severe Alzheimer's disease. This is an integrative literature review with a qualitative and descriptive approach, based on studies retrieved from PubMed, SciELO, LILACS, covering publications from 2016 to 2026. The findings indicate that combination therapy provides superior benefits compared to monotherapy in terms of cognition, daily functioning, and behavioral symptoms, although clinical gains are generally modest. A favorable safety profile and potential cost-effectiveness were also observed, particularly in public healthcare settings. It is concluded that the association of donepezil and memantine is a valid therapeutic option, and its use should be individualized according to patient clinical characteristics.

Keywords: Alzheimer's Disease. Donepezil. Memantine. Combination Therapy. Dementia.

RESUMO

A Doença de Alzheimer é uma enfermidade neurodegenerativa progressiva que compromete funções cognitivas, comportamentais e funcionais, especialmente em estágios moderados a graves. Nesse contexto, a terapia combinada com donepezila, um inibidor da acetilcolinesterase, e memantina, um antagonista dos receptores NMDA, tem sido proposta como estratégia terapêutica para potencializar os efeitos clínicos. O presente estudo tem como objetivo analisar a eficácia e segurança dessa associação no tratamento da Doença de Alzheimer moderada a grave. Trata-se de uma revisão integrativa da literatura, de abordagem qualitativa e descritiva, com busca realizada nas bases PubMed, SciELO, LILACS, contemplando publicações entre 2016 e 2026. Os resultados indicam que a terapia combinada apresenta benefícios superiores à monoterapia em relação à cognição, funcionalidade e sintomas comportamentais, embora os ganhos clínicos sejam, em geral, modestos. Observou-se ainda perfil de segurança favorável e potencial custo-efetividade, especialmente em contextos de saúde pública. Conclui-se que a associação entre donepezila e memantina constitui uma alternativa terapêutica válida, devendo ser utilizada de forma individualizada conforme as características clínicas do paciente.

Palavras-chave: Doença de Alzheimer. Donepezila. Memantina. Terapia Combinada. Demência.

RESUMEN

La enfermedad de Alzheimer es una enfermedad neurodegenerativa progresiva que deteriora las capacidades cognitivas, conductuales y funcionales, especialmente en las etapas moderadas a graves. En este contexto, se ha propuesto la terapia combinada con donepezilo, un inhibidor de la acetilcolinesterasa, y memantina, un antagonista del receptor NMDA, como estrategia terapéutica para potenciar los efectos clínicos. Este estudio tiene como objetivo analizar la eficacia y seguridad de esta combinación en el tratamiento de la enfermedad de Alzheimer de moderada a grave. Se trata de una revisión bibliográfica integradora, con un enfoque cualitativo y descriptivo, con búsquedas realizadas en las bases de datos PubMed, SciELO y LILACS, incluyendo publicaciones entre 2016 y 2026. Los resultados indican que la terapia combinada presenta beneficios superiores a la monoterapia en relación con la cognición, la funcionalidad y los síntomas conductuales, aunque las mejoras clínicas son generalmente modestas. También se observó un perfil de seguridad favorable y una posible relación coste-eficacia, especialmente en contextos de salud pública. Se concluye que la combinación de donepezilo y memantina constituye una



alternativa terapéutica válida y debe utilizarse de forma individualizada según las características clínicas de cada paciente.

Palabras clave: Enfermedad de Alzheimer. Donepezilo. Memantina. Terapia Combinada. Demencia.

1 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia in the elderly population, being a progressive neurodegenerative disease characterized by cognitive decline, functional impairment and behavioral changes that significantly impact the quality of life of patients and their caregivers. In this context, it is a relevant global public health problem, especially in view of the aging population and the significant increase in its prevalence. Its pathophysiology is complex and multifactorial, involving the accumulation of beta-amyloid plaques, the formation of neurofibrillary tangles composed of hyperphosphorylated tau protein, and important neurochemical alterations, such as cholinergic deficit and glutamatergic excitotoxicity, processes that directly contribute to synaptic dysfunction and progressive neuronal loss, configuring the main mechanisms underlying the clinical evolution of the disease (Costa et al., 2024; Rosado, 2021).

In the therapeutic field, the available pharmacological approaches are predominantly symptomatic, especially acetylcholinesterase inhibitors, such as donepezil, and NMDA receptor antagonists, such as memantine. These drugs act on pathways distinct from the pathophysiology of AD, with donepezil being responsible for increasing the availability of acetylcholine in synapses, while memantine reduces the effects of glutamate-mediated excitotoxicity, promoting modulation of neurotransmission (Neto et al., 2025; Lemos et al., 2024).

In the moderate to severe stages of the disease, greater functional impairment is observed, with significant loss of autonomy and intensification of cognitive and behavioral symptoms, which limits the effectiveness of isolated interventions. In this context, the combination therapy between donepezil and memantine has been proposed as a potentially more effective strategy, based on synergistic action on different neurotransmitter systems involved in the pathophysiology of the disease (Feitoza et al., 2024; Oliveira et al., 2026).

In addition to clinical outcomes, recent literature has emphasized the importance of economic evaluation of these interventions. Evidence indicates that the use of memantine, alone or in association with donepezil, can have a positive impact on the cost-effectiveness ratio, especially in public health systems such as the Unified Health System (SUS), by contributing to the slowing of disease progression, reduction of institutionalization, and reduction of the care burden (De Azevedo Filho et al., 2025).

However, despite the potential clinical and economic benefits, there are still controversies in the literature regarding the magnitude of the effects of combination therapy and its superiority over monotherapy. Studies present heterogeneous results, especially with regard to functionality, behavioral symptoms, and quality of life, reinforcing the need for

critical, up-to-date, and methodologically robust analyses on the subject (Caramelli et al., 2022; Silveira Sales and Silva et al., 2024).

In view of this scenario, the present study aims to critically analyze the efficacy, safety, and applicability of the combination therapy with donepezil and memantine in the treatment of Alzheimer's disease in moderate to severe stages, based on the available scientific evidence.

2 METHODOLOGY

The present study is characterized as an integrative literature review, with a qualitative approach, conducted according to the methodological proposal of Whitemore and Knafl (2005), with the objective of analyzing the efficacy, safety and applicability of the combined therapy with donepezil and memantine in the treatment of Alzheimer's Disease in moderate to severe stages. The integrative review was chosen because it allows the comprehensive synthesis of different methodological designs, enabling the integration of evidence from clinical and observational studies and systematic reviews.

The bibliographic search was carried out in the PubMed/MEDLINE, SciELO and LILACS databases, recognized for their relevance in the indexing of scientific literature in the health area. As a complementary strategy, a manual search was performed in the reference lists of the selected studies.

Controlled and uncontrolled descriptors in Portuguese and English were used, combined by Boolean operators, including: ("Alzheimer Disease" OR "Alzheimer's Disease") AND "Donepezil" AND "Memantine" AND "Combination Therapy". The searches included publications in the period from 2016 to 2026.

The inclusion criteria included original articles, clinical trials, observational studies, systematic reviews, meta-analyses, and clinical guidelines that directly addressed the use of donepezil and memantine combination therapy in patients with moderate to severe Alzheimer's disease, available in full. Duplicate studies, case reports, incomplete articles, and those that were not directly related to the proposed objective were excluded.

The study selection process was carried out in stages, by reading the titles and abstracts to identify potentially relevant studies, followed by the analysis of the full texts of the eligible articles, according to the previously established criteria.

Data analysis was carried out using a descriptive and analytical approach, with the organization of findings into thematic categories related to clinical outcomes, safety, cost-effectiveness, and applicability of the combined therapy, allowing a critical synthesis of the available evidence.

3 RESULTS

The analysis of the selected studies showed that the combination therapy with donepezil and memantine has a positive impact on different clinical outcomes in patients with moderate to severe Alzheimer's disease. In general, it was observed that the drug association is related to the improvement or deceleration of cognitive decline when compared to monotherapy, especially in more advanced stages of the disease, although with variations in the magnitude of the effects between the studies analyzed (FEITOZA et al., 2024; LEMOS et al., 2024; BIRKS; HARVEY, 2018).

In addition to cognitive outcomes, it was evidenced that combined therapy contributes to better performance in activities of daily living, with longer maintenance of patients' functional autonomy. Additionally, positive effects on behavioral and psychological symptoms of dementia were observed, including agitation, aggressiveness, and mood swings, aspects that directly impact the quality of life and burden of caregivers (OLIVEIRA et al., 2019; LEMOS et al., 2024; SILVEIRA SALES E SILVA et al., 2024).

Regarding safety, studies have indicated that combination therapy has a profile similar to that of monotherapies, and is considered well tolerated. The most frequently reported adverse events included gastrointestinal symptoms, dizziness, and headache, with no significant increase in serious events, which reinforces its applicability in clinical practice (LEMOS et al., 2024; KUMAR; GUPTA; SHARMA, 2023).

From an economic point of view, evidence suggests that the association between donepezil and memantine may be cost-effective, especially in public health systems, by contributing to the slowdown of disease progression and reduction of the need for intensive care. However, some studies indicate that, although statistically significant, clinical benefits tend to be modest and variable among patients, depending on factors such as disease stage and individual characteristics, which may influence the interpretation of the results (DE AZEVEDO FILHO et al., 2025; OLIVEIRA et al., 2019; CARAMELLI et al., 2022).

In general, the findings indicate that combination therapy is an effective and safe therapeutic strategy, with a positive impact on multiple clinical domains, although the magnitude of its effects varies among the included studies.

4 DISCUSSION

The findings of this review suggest that donepezil and memantine combination therapy outperforms monotherapy in patients with moderate to severe Alzheimer's disease, particularly on outcomes related to cognition, functionality, and behavioral symptoms. This benefit can be explained by the complementary action on the cholinergic and glutamatergic

systems, promoting a broader modulation of the neurochemical mechanisms involved in the progression of the disease (Feitoza et al., 2024; Lemos et al., 2024).

From the pathophysiological perspective, the pharmacological combination is based on the hypothesis of therapeutic synergism, since acetylcholinesterase inhibitors increase the availability of acetylcholine in synapses, while memantine acts in the modulation of excitotoxicity mediated by NMDA receptors. This interaction can contribute to the preservation of neuronal function and slow clinical progression, especially in more advanced stages of the disease (Neto, 2025).

However, the magnitude of these benefits remains controversial. Evidence indicates that, although combination therapy has statistically significant superiority over monotherapy, clinical gains tend to be modest, especially in functional and behavioral outcomes, which suggests that statistical significance does not always translate into relevant clinical benefit in care practice (Oliveira et al., 2019; Caramelli et al., 2022).

In addition, the methodological heterogeneity of the included studies, with a predominance of observational designs and variations in clinical assessment instruments, may influence the consistency of the results. The lack of standardization in the outcomes analyzed and the limited follow-up time in some studies also represent important limitations, which may overestimate or underestimate the effects of combined therapy.

From an economic point of view, the literature suggests that the association between donepezil and memantine can be cost-effective, especially in public health systems, by slowing the progression of the disease and reducing the need for institutional care. However, these benefits depend directly on factors such as treatment adherence, time of use, and access to medications, which can significantly impact the observed outcomes (De Azevedo Filho et al., 2025; Oliveira et al., 2019).

Another relevant aspect refers to interindividual heterogeneity in the therapeutic response, possibly related to genetic factors, stage of the disease, and associated comorbidities, reinforcing the need for individualized therapeutic strategies centered on the clinical profile of each patient (Silveira Sales and Silva et al., 2024).

Finally, although combination therapy has a safety profile similar to that of monotherapies, continuous monitoring is essential to ensure the maintenance of clinical benefit and the early identification of adverse effects, especially in elderly patients and those with multiple comorbidities (Lemos et al., 2024).

Thus, despite the favorable evidence, important gaps persist in the literature, especially related to the magnitude of the clinical benefit, the standardization of outcomes, and the scarcity of long-term randomized clinical trials, reinforcing the need for more robust

studies, with a rigorous methodological design and prolonged follow-up, to better define the real clinical impact of combination therapy in care practice.

5 CONCLUSION

Combined therapy with donepezil and memantine is a relevant therapeutic strategy in the management of moderate to severe Alzheimer's disease, as it acts in a complementary way on different pathophysiological mechanisms of the disease. Evidence indicates superiority over monotherapy, although the clinical benefits observed are generally modest and heterogeneous among patients.

In this context, the effectiveness of the therapy is directly related to the individualization of the conduct, considering factors such as the stage of the disease, clinical profile and adherence to treatment. In addition, the favorable safety profile and cost-effective potential reinforce its applicability, especially in public health systems.

However, uncertainties persist regarding the magnitude of the clinical benefit and its relevance in care practice, highlighting the need for more robust studies, with a rigorous methodological design and long-term follow-up.

Thus, combination therapy should be understood as a valid therapeutic option, but not universal, whose indication should be based on individualized clinical criteria and on the critical evaluation of the available evidence.

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