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Multidisciplinary consensus on the combined management of Alzheimer's disease by Mexican experts: recommendations and guidelines

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Abstract

Objective: *Alzheimer's disease (AD), affecting over 55 million people globally, poses a substantial public health challenge. Early diagnosis and appropriate treatment are vital to slowing its progression and enhancing patient quality of life. The fixed-dose combination of citicoline with rivastigmine emerges as a promising strategy AD treatment.* **Methods:** *A real-time Delphi consensus was reached with the participation of 11 Mexican experts.* **Results:** *The combination offers neuroprotective benefits, enhancing neuronal regeneration and reducing glutamate levels linked to neuronal damage in AD. These effects translate into improved cognitive function and delayed cognitive decline in AD.* **Conclusions:** *The Mexican Consensus for the Combined Management of AD endorses this fixed-dose combination of rivastigmine with citicoline as a new therapeutic perspective. Its efficacy and safety make it a valuable option for the treatment of this neurodegenerative disease.*

Keywords: *Alzheimer's disease. Citicoline. Rivastigmine. Cholinesterase inhibitors. Fixed dose combination.*

Consenso multidisciplinario sobre el manejo combinado de la enfermedad de Alzheimer por expertos mexicanos: recomendaciones y lineamientos

Resumen

Objetivo: *La enfermedad de Alzheimer, que afecta a más de 55 millones de personas en todo el mundo, representa un desafío creciente para la salud pública. El diagnóstico temprano y el tratamiento adecuado son fundamentales para ralentizar su progresión y mejorar la calidad de vida de los pacientes. En este contexto, la combinación de dosis fija de citicolina con rivastigmina emerge como una estrategia prometedora en el tratamiento de la EA.* **Métodos:** *Se llevó a cabo un consenso mediante la metodología Delphi en tiempo real con la participación de 11 expertos mexicanos.* **Resultados:** *La combinación de dosis fija de citicolina con rivastigmina ofrece beneficios de neuroprotección al tiempo que aumenta la regeneración*

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neuronal y reduce los niveles de glutamato, asociado con el daño neuronal en la EA. Estos efectos se traducen en mejoras en la función cognitiva a partir de los 3 meses de iniciado el tratamiento, así como en el retraso del deterioro cognitivo en la EA. **Conclusiones:** *El Consenso Mexicano para el Manejo Combinado de la Enfermedad de Alzheimer respalda esta combinación de dosis fija de rivastigmina con citicolina como una nueva perspectiva terapéutica para la enfermedad de Alzheimer. Su eficacia y seguridad la convierten en una opción valiosa para el tratamiento de esta enfermedad neurodegenerativa.*

Palabras clave: *Enfermedad de Alzheimer. Citicolina. Rivastigmina. Inhibidores de la colinesterasa. Combinación a dosis fija.*

Introduction

According to the World Health Organization, dementia affects over 55 million people worldwide, with more than 60% residing in low- and middle-income countries; and nearly 10 million new cases reported annually. Dementia is the result of various diseases and injuries affecting the brain; Alzheimer's disease (AD) accounts for 60 to 70% of dementia cases and poses a significant economic burden, costing the global economy approximately US$ 1.3 trillion in 2019[1].

Two drug classes are approved for dementia treatment: acetylcholinesterase inhibitors for mild-to-moderate stages, and N-methyl-D-aspartate receptor antagonists which modify the function of this receptor in the brain and decrease the negative effect of overexposure to glutamate. The latter are used in moderate to severe dementia, apparently with fewer side effects[2].

Despite efforts to develop new treatments, such as biologic drugs targeting amyloid and tau proteins, there is a trend toward reevaluating existing drugs' mechanisms of action, which could be effective in various AD pathophysiological pathways[3].

Reusing pharmacological agents is as a promising strategy in AD treatment, leveraging prior knowledge about safety profiles, pharmacokinetics, dosing, and manufacturing processes. This approach, accounting for 39% of all clinical trials, is crucial for advancing AD treatment[4].

In this context, the fixed-dose combination of rivastigmine, an acetylcholinesterase inhibitor, with citicoline, an integral neuroprotectant, is proposed. This combination aims to enhance selectivity for the hippocampus and cerebral cortex by increasing acetylcholine availability in the synaptic cleft, promoting neuronal regeneration, and raising neurotransmitters levels such as serotonin-1, acetylcholine, dopamine, and norepinephrine. The combination is expected to improve memory, learning, and cognitive functions by enhancing neurotransmission and neuroprotection.

Previous studies, including CITIRIVAD by Castagna et al. in 2016, demonstrated that adding citicoline is a safe and effective option to prolong and potentiate the benefits of cholinergic therapies such as rivastigmine in patients over 65 years with mild-to-moderate AD or mixed dementia[5]. Similarly, in 2017, Gareri et al. showed in the CITICHOLINAGE study that adding citicoline acetylcholinesterase inhibitor therapy, such as rivastigmine, prolongs and enhances the beneficial effect in mild to moderate AD[6].

A multidisciplinary consensus of Mexican experts was convened to evaluate the fixed-dose combination of rivastigmine with citicoline in AD treatment. After thorough review and extensive discussion of available scientific and the benefits and possible limitations of this combination therapy, the consensus resulted in a clinical guideline providing essential recommendations for managing the disease, aiming to enhance patient and family quality of life.

Methods

Consensus was reached through a Delphi system using a real-time ad hoc platform. Eleven panelists were selected based on their expertise, using criteria adapted from those used by the California Courts to determine the expertise of a medicolegal witness[7,8].

Each expert anonymously rated 31 statements, using a five-point Likert scale (1-strongly agree, 2-agree, 3-neutral, 4- disagree, or 5-strongly disagree). *A priori* consensus was defined as agreement by 80% of the panelists on the Likert scale. Subsequently, experts could provide comments and suggestions through text boxes, which were reviewed and used to modify the statements in subsequent survey rounds. The study facilitator did not participate in the voting or comment review process.

Ethical approval was not required, as the study did not involve patient data or biological material.

The authors conducted an independent systematic review of current literature following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[9]. Articles published between 2010 and 2023 were reviewed in PubMed, Scopus, and Web of

Science databases, using keywords such as "Alzheimer disease" and supplemented with "diagnosis," "evaluation," "treatment," "therapeutic goals," "citicoline," "rivastigmine," and "cholinesterase inhibitors." Two reviewers independently selected the articles, from which the 31 questions or statements were derived.

Cronbach's alpha coefficient was used to determine the internal consistency of the assessment tool after each round[8]. This coefficient, ranging from 0 to 1, demonstrated the relationship among a set of test items as a group. The final round of consensus was defined by achieving a Cronbach's alpha > 0.80[10]. Data analysis was performed between rounds to identify statements with 80% consensus and 100% participation; those statements that did not reach these criteria were included in the next round of voting. Categorical variables were expressed as proportions (%).

Results

AD is traditionally defined as a neurodegenerative disorder characterized by a progressive decline of cognition or neurobehavioral symptoms, severe enough to impact daily activities. However, there is a shifting paradigm toward a more biological definition, utilizing precise markers to enhance diagnostic accuracy.

Loss of functionality is a key factor in distinguishing dementia from mild cognitive impairment. AD is associated with characteristic neuropathological features, including extracellular deposits of β-amyloid plaques and phosphorylated tau protein, which lead to progressive impairment of memory, learning, and executive function[11].

AD has two primary etiological types: familial and sporadic. The latter being the most common. Mutations in the amyloid precursor protein genes, presenilin-1 and presenilin-2, can cause familial AD[12].

Clinical phenotypes of AD encompass various presentations, including amnestic AD, posterior cortical atrophy, logopenic variant of primary progressive aphasia, behavioral or frontal dysexecutive variant, corticobasal degeneration, and semantic variant of primary progressive aphasia[13].

Evaluation of AD

Accurate and timely diagnosis is essential for effective management. Current diagnostic approaches for AD include clinical history, cognitive testing, imaging studies, and laboratory tests[11]. A comprehensive neuropsychological evaluation complemented by screening tests such as the mini-mental state examination or the Montreal cognitive assessment is recommended for patients with cognitive disorders.

Magnetic resonance imaging (MRI) is preferred for imaging studies in suspected AD cases, as it offers greater sensitivity in detecting characteristic cortical atrophy patterns and ruling out other causes of dementia. Medial temporal lobe atrophy on MRI is considered a biomarker for AD. Neuroinflammation is also recognized as a significant pathophysiological component in AD progression.

In Mexico, biomarkers in cerebrospinal fluid (total tau, phosphorylated tau, and amyloid b-42) can aid in confirming AD diagnosis, although their availability is limited and they are not deemed essential in routine clinical practice.

Table 1. Mechanisms of action of citicoline in AD

Enhances phospholipids synthesis in cell membrane.
Increases synthesis of acetylcholine, dopamine, and noradrenaline.
Prevents free radical generation in ischemic tissue.
Reduces apoptosis and exerts a neuroprotective effect.

AD: Alzheimer's disease.

Treatment of AD

The goal of modifying treatment in AD is to slow progression, delay cognitive and functional decline, and enhance quality of life, independence, and reduce the need for institutionalization and long-term care.

Acetylcholinesterase inhibitors such as rivastigmine, donepezil, or galantamine have demonstrated beneficial effects on cognitive function, daily activities, and global assessment in mild-to-moderate AD. Conversely, oral memantine has shown benefits in global assessment, cognitive function, daily activities, and behavior in moderate-to-severe AD.

Citicoline with its diverse mechanisms of action holds promise in AD treatment (Table 1).

The effective clinical dose of citicoline ranges from 500 to 2000 mg daily. There is evidence showing the benefit of the combination of an acetylcholinesterase inhibitor (rivastigmine, donepezil, or galantamine), together with a therapeutic potentiating agent such as citicoline in AD patients AD.

A "fixed-dose" combination refers to a blend of more than one drug in a constant ratio and a single dosage form, for the treatment of a specific condition[14]. In AD patients, the fixed-dose combination of rivastigmine and citicoline may be more effective than the use of both drugs administered in monotherapy. Citicoline has been shown to potentiate and prolong the beneficial effects of rivastigmine in AD; also, in combination with rivastigmine, it could delay cognitive decline in the disease. It has been observed that this combination may also be useful in the management of vascular dementia and mixed dementia. The benefits of this combination on cognitive function may be evident after 3 months of treatment. In addition, it may improve the administration and adherence to treatment in dementia patients.

Dosing of the fixed-dose combination is based on rivastigmine, with titration starting at 1.5 mg every 12 h, increasing to 3 mg every 12 h if the initial dose is well tolerated. Subsequent increases (4.5 and 6 mg every 12 h) are based on tolerability of the dose and are indicated after 2 weeks of treatment. The maintenance dose of the combination rivastigmine with citicoline in AD is 3 to 6 mg rivastigmine every 12 h (500-1000 mg citicoline).

Adverse events associated with the rivastigmine-citicoline combination are generally mild and predominantly related to the acetylcholinesterase inhibitor. The most frequent events include nausea, vomiting, diarrhea, anorexia, and abdominal pain.

Conclusion

AD is a highly prevalent progressive neurodegenerative disease and the most common form of dementia, impacting over than 55 million individuals globally. The diagnosis of AD is in constant evolution, with a current focus on utilizing neuroimaging techniques such as MRI and the increasing use of biomarkers to detect the disease in its early stages.

In terms of treatment, acetylcholinesterase inhibitors have been a primarily option in mild-to-moderate stages of the disease. However, the fixed-dose combination of rivastigmine with citicoline has been explored as a promising therapeutic strategy. This combination offers neuroprotection, while stimulating neuronal regeneration and reducing glutamate levels, resulting in significant improvement in cognitive function and delaying cognitive decline in AD. Future advancements in identifying accurate biomarkers are expected to enable earlier and more precise diagnosis of AD.

The fixed-dose combination of rivastigmine and citicoline could represent a valuable therapeutic choice with substantial benefits in AD patients, enhancing their quality of life and delaying disease progression. AD continues to pose a significant public health challenge, but the development of innovative treatments offers hope for a more effective management of the disease in the future.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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