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Pharmacological and Non-Pharmacological Treatments for Cognitive Impairments in Older Adults with Alzheimer's Disease: A Narrative Review

Tratamientos Farmacológicos y No Farmacológicos para las Deficiencias Cognitivas en Adultos Mayores con Enfermedad de Alzheimer: Una Revisión Narrativa

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Abstract:

Neurodegenerative disorders represent a public health problem with an increasing prevalence worldwide, with Alzheimer's disease (AD) being the most commonly diagnosed, accounting for 60-70% of cases in people over 65 years of age. AD causes problems in memory, thinking, and behaviour. Its symptoms develop slowly and worsen over time. Despite being an incurable disease, there are pharmacological and non-pharmacological treatments that can alleviate the effects of AD. The present work aimed to perform a narrative review of the main treatments used for the cognitive deficits of this disease. Among the pharmacological therapies, those indicated according to the stage of the disease are discussed, such as cholinesterase inhibitors, immunotherapy, N-methyl-D-aspartate (NMDA) antagonists, among others. Likewise, non-pharmacological treatments include strategies for cognitive stimulation and rehabilitation, reality orientation and reminiscence therapy, sensory stimulation techniques, among others. In conclusion, the combination of both treatments proves to be more effective in delaying deterioration in patients with AD. In addition, it is worth mentioning that, within the non-pharmacological treatments, cognitive stimulation is the most used strategy, either alone or in combination with others, to maintain cognitive and social functions and other activities of daily living, that is, the effectiveness of treatments may depend on the combination of appropriate actions.

Keywords:

Neurodegenerative disorders, memory, cognitive functioning, behaviour.

Resumen:

Los trastornos neurodegenerativos representan un problema de salud pública con una prevalencia que va en aumento a nivel mundial, siendo la Enfermedad de Alzheimer (EA) la más diagnosticada, ocupando entre un 60 a 70 % de los casos en mayores de 65 años. La EA causa problemas en la memoria, pensamiento y conducta, sus síntomas se desarrollan lentamente y se agudizan con el tiempo. A pesar de ser una enfermedad incurable, existen tratamientos farmacológicos y no farmacológicos que pueden paliar los efectos de la EA. El objetivo del presente trabajo fue realizar una revisión narrativa de los principales tratamientos utilizados para las deficiencias cognitivas de esta enfermedad. Dentro de los tratamientos farmacológicos se abordan aquellos que son indicados según la fase de la enfermedad como, por ejemplo, medicamentos inhibidores de la colinesterasa, inmunoterapia, los antagonistas del N-metil-D-aspartato (NMDA), entre otros. Asimismo, dentro de los tratamientos no farmacológicos se abordan estrategias que han sido utilizadas para estimulación y rehabilitación cognitiva, terapia de orientación a la realidad y reminiscencia, técnicas de estimulación sensorial entre otras. En conclusión, la combinación de ambos tratamientos resulta ser más eficaz para retrasar el deterioro en pacientes con EA, además, es preciso mencionar que, dentro de los tratamientos no farmacológicos, la estimulación cognitiva es la estrategia más utilizada ya sea sola o bien, en combinación con otras para mantener funciones cognitivas, sociales y otras actividades de la vida diaria, es decir, la eficacia de los tratamientos puede depender de la combinación de las acciones adecuadas.

Palabras Clave:

Trastornos neurodegenerativos, medicamentos, funcionamiento cognitivo, conducta.

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INTRODUCTION

The concept of aging has been studied from different approaches. For some, it can be conceptualized as a result and, for others, a process. Given this, the World Health Organization (WHO) defines aging as the result of molecular and cellular damage accumulated over time that generates a gradual decline in physical and mental capacities, leading to an increased risk of disease or death.[1] Likewise, Carrillo-Sierra et al.[2] define aging as a process of adaptation associated with a dynamic construct of biological, physiological, environmental, psychological, behavioral and social elements, together with one's perception.

Globally, the number of people already in this stage is increasing significantly, in the 90s, there were 700 million aged people, and by 2025, it is projected to be 1200 million, this population is concentrated in low- and middle-income countries.[3,4]

With these statistics, it is necessary to make visible the conditions in which people are reaching this stage. According to the WHO[1], diseases with the highest incidence are hearing loss, cataracts, refractive errors, back and neck pain, osteoarthritis, chronic obstructive pulmonary diseases, diabetes, depression, and neurodegenerative diseases such as Alzheimer's disease (AD). Currently, neurodegenerative disorders represent a serious public health problem with a rising prevalence worldwide, with around 46 million people in the world living with some form of these disorders.[5] According to Menéndez, neurodegenerative diseases are damage to the central nervous system that are associated with risk factors such as age, are characterized by being slow and progressive, and are due to protein deposits that induce cell death processes (proteinopathies), leading to a progressive decrease in the neuronal population and brain atrophy.[6]

In 2020, it was reported that there were more than 50 million people with dementia in the world, and it is estimated that by 2050, there will be 152 million, with a higher incidence in middle- and low-income countries and a concentration of 71% of all cases. Likewise, in Mexico, 3.5 million people are expected to suffer from dementia in the next 35 years, with a higher incidence and mortality rate in women.[7]

According to Villarroya-Pastor, the latter could be explained by the fact that they have a higher survival rate than men and that age is one of the risk factors for the disease, but there is evidence that a lack of estrogen during menopause could lead to the development of the disease.[8]

CHARACTERISTICS OF ALZHEIMER´S DISEASE

AD is a type of dementia that causes problems with memory, thinking, and behavior. It is characterized by an initial impairment in recording and recalling recent information (amnesia), difficulty in recognizing objects in the environment (agnosia), loss of the ability to communicate, express oneself, and understand (aphasia), its symptoms generally develop slowly and worsen over time, interfering with basic activities of daily living, There are also psychopathological changes that show diffuse neocortical involvement, with an initial temporal-parietal and limbic predominance, which is diagnosed in people over 65 years of age (late onset) and, infrequently, can appear between 30 and 40 years of age (early onset).[9,10]

It is important to note that both microscopic and functional changes in the brain begin long before signs of memory loss appear and are characterized by two types of neuronal damage: plaques and tangles of a substance called beta-amyloid that accumulate in the spaces between nerve cells, and tangles that are twisted fibers of tau-b protein, which accumulate inside cells, resulting in neurodegeneration leading to neuronal death. It is worth mentioning that the most significant damage is generated in the cortical areas related to basic cognitive processes (attention, memory, and learning) as they begin to shrink, i.e., the volume and weight of the brain decreases, acquiring a yellowish color due to an increase in lipofuscin deposits and the size of the ventricles begins to grow.[11,12]

FORMS AND SUBTYPES OF ALZHEIMER´S DISEASE

There are other forms in which the disease presents, either with a localized onset directly affecting non-amnestic domains or with a particular course. These forms are rare and, as a consequence, pose a differential diagnosis with other diseases. Some of these are mentioned:[13]

Posterior cortical atrophy: in this case, visuospatial dysfunction dominates the clinical picture, with problems in reading, writing, locating or reaching objects and disorientation. In the early stages, memory appears to be preserved, but as the disease progresses, it will decline along with other cognitive functions. In this form of AD, a differential diagnosis with Lewy body dementia, corticobasal degeneration, and frontotemporal lobar, among others, is required.[13]

Primary progressive aphasia is an early and progressive alteration of language with apparent preservation of memory and other cognitive functions.[13]

The physiological focus is mainly on the left perisylvian region, and it is responsible for language.[13]

Frontal dementia is characterized mainly by neuropsychiatric symptoms, altered behavior, personality, and social behavior. This form is commonly caused by frontotemporal lobar degeneration, progressive supranuclear palsy or corticobasal degeneration.[13]

Corticobasal syndrome is an alteration in cortical functions accompanied by parkinsonism. It has a vascular origin.[13]

Early-onset familial AD its onset is due to pathogenic variants in the β amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes, the latter (PSEN1) being the one with the highest incidence in these cases. The onset of symptoms may be before 55 years of age or even earlier if apolipoprotein E 4 (APOE ε4) is carried; the earlier the onset, the more aggressive the progression.[13]

Rapidly progressive AD. Its evolution ranges from weeks to months and a thorough clinical evaluation is required to rule out vitamin deficiencies, infections, and tumors, among others. [13]

As mentioned above, AD usually progresses slowly and progressively, affecting the person's functional capacities, and the National Institute on Aging (2021) has classified it according to its stages of progression as[14]:

Mild AD is characterized by wandering and getting lost, difficulty handling money and paying bills, repeating questions, taking longer to complete everyday tasks, and changes in personality andbehavior.[14]

Moderate AD. Damage occurs in the areas of the brain that control language, reasoning, conscious thought, and sensory processing, also affecting the ability to detect sounds and smells correctly. Memory loss and confusion worsen, and individuals have problems recognizing family and friends. Hallucinations, delusions, paranoia, and impulsive behaviour may occur.[14]

Severe AD. In this case, plaques and tangles spread throughout the brain, there is a considerable reduction in brain tissue, they can no longer communicate, and there is a total dependence on their caregiver.[14]

SYMPTOMS OF ALZHEIMER´S DISEASE

In AD, in addition to cognitive symptoms, neuropsychiatric symptoms (also considered psychological and behavioral symptoms) may occur, which may be varied and fluctuate, depending on the course of the disease.[13,15] These are described in general terms in Table 1.

DIAGNOSIS OF ALZHEIMER'S DISEASE

Currently, the definitive diagnosis of the disease is neuropathological, and it is made postmortem, only exceptionally during life. In practice, it is necessary to be guided by several recommendations, e.g., the National Institute on Aging[14] and the Alzheimer's Association[16] recommend the following:

- Assessment of the patient and a family member or friend on general health.
- Neuropsychological assessment.
- Perform biometric tests.
- DSM-V-TR diagnostic criteria.
- Review of medications used that could affect cognition.
- Serological tests.
- Biomarker testing, e.g., measurement of beta-amyloid protein (Aβ42), total tau protein (T-tau), and its phosphorylated form at position 181 (P-tau181) in cerebrospinal fluid.[17]
- Evaluation with neuroimaging, such as computed tomography (CT), magnetic resonance imaging (MRI), and other techniques.
.
- Perform complementary studies if symptoms seem to be from another disease.

PHARMACOLOGICAL TREATMENTS OF ALZHEIMER´S DISEASE

Pharmacological treatments refer to the use of any substance other than food or chemicals to diagnose, treat, or alleviate the symptoms of an illness or abnormal state and can also be called pharmacotherapy.[18]

These treatments for AD can be divided into two categories: symptomatic (having a significant impact not only on cognition but also on psychological and behavioural symptoms) and disease modifying therapies (DMT) (based on the amyloid cascade hypothesis and tau biology).[19]

Concerning this type of treatment, López-Lacanto[20] states that it should be initiated on the advice of a specialist (neurology, internal medicine, psychiatry, and geriatrics) as long as there is a caregiver who regularly monitors the patient's intake of the drug, as doses should be adjusted based on the monitoring of the probable appearance of adverse effects, it is also suggested to start with low doses and gradually increase them and to report any abnormalities during treatment to the treating physician, as well as to evaluate therapeutic efficacy by monitoring multiple domains (cognition, behavior and functionality) by specialists.

According to Pais et al.[19] and the National Institute on Aging[21], medications that could be indicated for the mild to moderate phase of the disease are galantamine, rivastigmine, and donepezil, as they are cholinesterase inhibitors, which prevent the breakdown of acetylcholine (a brain chemical important for memory and thinking), as they may help reduce or control some cognitive and behavioral symptoms. When used with the non-competitive glutamatergic receptor antagonist memantine, these medications can be employed for moderate to severe stages of the disease.

The general characteristics of these medications are described below:

Galantamine: is a tertiary alkaloid that acts on the central cholinergic system and inhibits the degradation of acetylcholine (a substance that allows nerve cells to communicate with each other) and enhances its action on nicotinic receptors; it is absorbed in the gastrointestinal tract when ingested and its maximum plasma concentration is reached in 1.2 hours; it is metabolized in the liver by 75%; it is a convenient drug to use in the elderly population. It is administered via an extended-release capsule once daily.[21] In people with AD, memory loss is related to the death of cholinergic neurons in the basal nuclei, with 20-50%. loss of high-affinity nicotinic receptors in the temporal cerebral cortex.[22] Possible side effects include nausea, vomiting, diarrhea, decreased appetite, weight loss, dizziness and headache.[21]

Rivastigmine belongs to the group of cholinesterase inhibitors and acts by blocking the enzymes that break down acetylcholine: acetylcholinesterase and butyrylcholinesterase. In terms of dosage, it can be started with a dose of 1.5 mg twice a day until it reaches 12 mg; initially, it was marketed in oral form, and now it can be administered transdermally through patches.[23] Possible side effects include nausea, vomiting, diarrhea, weight loss, indigestion, decreased appetite, anorexia, and muscle weakness.[21]

Donepezilis a reversible and selective inhibitor of brain acetylcholinesterase. Its dosage is more convenient for people with AD as it is administered daily with a dose that varies from 5mg to 10 mg a day. It has no hepatotoxic effect and is eliminated via the kidneys and liver; once treatment has started, changes in disease symptoms are noticeable after 2 to 4 months.[20,24]

Table 1. Symptoms of Alzheimer's disease.[13,15]

Symptoms		Description
Cognitive (according to their cognitive domain)	Memory	Forgetfulness of recent conversations or events, forgetfulness of objects or tasks, repetition of information, disorientation in time.
	Attention	Easily distracted by multiple stimuli, difficulty performing simultaneous or prolonged tasks requiring concentration.
	Executive functions	Difficulty in planning and executing complex sequential tasks, difficulty in understanding abstract language failure, impaired judgement, and impaired in decision-making.
	Visuospatial ability	Disorientation in outdoor spaces or even in familiar areas, problems with spatially complex tasks such as cooking, sewing, dressing, and handling cutlery, among others.
	Language	Difficulty in finding words, use of generic terms such as "that, this, that", etc. Slow, poor conversation with frequent pauses, forgetting names of people and places. Not able to follow sequential commands.
	Social cognition	It is associated with psychological and behavioral symptoms. Loss of empathy, lack of recognition of facial expression of emotions, inappropriate social behaviours.
Psychological and Behavioural		There may be disinterest, indifference, depression, anxiety, episodes of irritability, sleep disorders, insomnia or sleep, nocturnal agitation, and eating disorders, among others. In the advanced stages of the disease, there may be psychotic symptoms, delusions, hallucinations, and misidentifications. Behavioral symptoms include wandering, aggression, resistance to care, inappropriate sexual behavior, and catastrophic reactions.

Possible side effects include nausea, vomiting, diarrhea, insomnia, muscle cramps, fatigue, and weight loss.[21]

Monoclonal antibodies (such as lecanemab), which have been shown to help reduce amyloid plaques by slowing cognitive decline, are also recommended for use in early AD.[21]

Within DMT, a precise understanding of the neuropathological changes in AD is necessary to attenuate decline and preserve cognitive and functional capacity based on the amyloid cascade and cytoskeletal degeneration, i.e. tau pathology. In 2014, Cummings et al. analyzed 413 clinical trials testing 244 drugs with these characteristics (DMT), of which almost all failed, except memantine.[19]

As mentioned above, for the moderate to severe phases, a competitive N-methyl D-aspartate receptor antagonist medication may be prescribed, for example, memantine, which may help to preserve some praxes of daily life; memantine binds to the receptor and protects neurons from glutamate excitotoxicity.[25] Dosage can range from 5mg to 20 mg per day orally and is eliminated by the kidneys.[26] Possible side effects include dizziness, headache, diahrrea, constipation, and confusion.[21] Within these same phases, there may be the use of atypical antipsychotics such as brexpiprasol, which has been tested to treat the agitation associated with AD, but side effects include common cold symptoms, high blood sugar, dizziness and, stroke, as well as the use of vitamins, anxiolytics, and anticonvulsants, the latter for severe aggression.[21]

Other SMT drugs that have been used for AD, e.g., lithium (for its ability to modulate neurotrophic and protective brain responses), idalopirdine (serotonin 5-hydroxytryptamine-6 antagonist), pioglitazone (increases the body's sensitivity to insulin), however, after several controlled clinical trials, no significant cognitive improvements were observed.[19]

It is relevant to mention that some complementary medications for this treatment may also be used for other symptoms, e.g., sleeping pills, anxiolytics, anticonvulsants, and antipsychotics. However, these involve additional caution for people with AD and can only be considered after the risks and side effects of the drug have been explained and other safer options for the treatment of these symptoms have been considered, as in the case of sleeping pills, there is a risk of increased confusion and falls; for anxiolytics, they can cause drowsiness, dizziness, falls and confusion; for anticonvulsants, they can include drowsiness, dizziness, mood swings and confusion; and for antipsychotics, they can be serous and even increase the risk of death.[21]

NON-PHARMACOLOGICAL TREATMENTS OF ALZHEIMER´S DISEASE

Non-pharmacological treatments (NPT) are conceptualized as a set of strategies or activities that are applied to delay cognitive decline, assist in the maintenance of basic daily living activities, and help with behavioral and emotional symptoms to improve the person's quality of life.[27]

NPTs are non-invasive and safe, encompassing a wide range of interventions to ameliorate or delay the effects of AD in patients, reduce stress on caregivers, and improve their context. Unlike pharmacological treatments, they do not seek to influence the underlying pathophysiological mechanisms; they seek to maintain function and participation for as long as possible. Therefore, these interventions can be applied at any stage of AD, and can significantly influence neuronal plasticity. They are based on various methodologies, ranging from simple approaches like environmental interventions to more complex ones involving technological components.[28]

In recent years, various non-pharmacological treatments have been applied with the aim of evaluating their efficacy in reducing (or delaying) the cognitive impairments that certain disorders present.

Among the multiple non-pharmacological treatments, there are several types of cognitive and behavioral interventions for neurodegenerative diseases, for example, cognitive stimulation therapy, physical activity, the implementation of strategies for functional rehabilitation, the use of virtual reality, music therapy, reality orientation therapy, aromatherapy, reminiscence therapy, acupuncture, olfactory stimulation, among others.[29-45] Some of these treatments are described below:

Cognitive Stimulation Therapy is one of the main strategies used with people with AD. It consists of applying a set of structured and planned actions that impact cognitive functioning, especially attention, memory, perception, praxis, language, and executive function. It does not focus only on this; it also impacts elements such as the affective, behavioral, social and even family aspects, seeking comprehensive care to reduce dependence, in this case, of older adults. . It also recommends participation and work with the patient's relatives. Its neurological bases are cerebral reserve, neuroplasticity, and the possibility of carrying out new learning.[34]

Cognitive Rehabilitation Therapy: consists of a comprehensive program to improve cognition, including cognitive stimulation, cognitive training, and other approaches within a biopsychosocial and individualized approach to understanding dementia, and may include elements such as orientation in time and place, computer-based exercises, practical cognitive training for sustained attention, speed of visual-motor processing, cognitive and procedural motor activation through learning, manipulation of everyday objects, rehearsal of activities of daily living, among others.[36]

Physical Activity is the development of purposeful, planned physical activities that can improve cognitive function, neuropsychiatric symptoms, and quality of life of AD patients. It can even act as a protective factor and prevent destructive behavior in patients with severe AD. The effects of these interventions are prolonged in the long term if continuously practiced.[29]

Use of Virtual Reality it is an approach to user-computer interface that involves real-time simulation of an environment, scenario, or activity that allows user interaction through multiple sensory channels.[37] According to the results of the systematic review by Zhu and others, it is a beneficial non-pharmacological approach to improve cognitive and motor function in older adults with MCI or dementia, especially in attention/performance, memory, global cognition, and balance.[30]

Music therapy is a therapeutic method for development, adaptation, and rehabilitation in neurological, psychological, and physical areas.[38] In works with people with impaired cognitive function, it has been shown to increase cerebral blood flow and prefrontal cortex activity, as music activates some brain regions that govern cognitive function, affective function, and motor skills and generates neurological stimulation that can develop new neural networks.[31] Also, González-Ojea and collaborators showed positive effects of music therapy concerning the well-being of people with dementia and Alzheimer's disease, insisting on the need to implement them continuously over time, with positive results in the reduction of anxiety and depression.[32]

Reminiscence Therapy consists of recalling events in the subject's history by stimulating meaningful memories to create positive feelings.[35] Saraghi et al., in their systematic review and meta-analysis, were able to corroborate that reminiscence therapy increased cognitive functions and quality of life and decreased depression and neuropsychiatric symptoms.[39]

Acupuncture is another treatment that stood out for its effectiveness, it has been studied in recent years more frequently to verify its efficacy. It is a therapeutic procedure of Traditional Chinese Medicine that involves the insertion of needles into specific points of the skin (there are more than 365) located in a series of channels or meridians that relate to an internal organ, being recognized by the WHO in 1979 as a therapeutic means for 43 diseases.[40,41]

The results from the systematic review and meta-analysis conducted by Lin and other authors showed that treatments based on this technique improved cognitive function, self-care capacity, and muscle strength.[42] Likewise, the review by Lai et al., showed that it is a good management option in neurological diseases, demonstrated by functional magnetic resonance imaging, which states that acupuncture improves AD by suppressing the effects of oxidative stress as it reduces neuroinflammation through multiple signal transduction pathways, Aβ production, aggregation and phosphorylation of Tau.[31]

Olfactory Training. Another element that stands out for its recent research and efficacy is olfactory training, which is directly related to olfactory-based sensory stimulation therapy. It is worth mentioning that the impairment of olfactory capacity implies a loss of volume in the same brain regions. In contrast with other sensory systems activated by the thalamus, the

olfactory system expands neural projections directly to cortical areas involved in cognition and emotion.[43,44]

The results of the study by Lin and Li[45] suggest that this type of therapy can be a very beneficial intervention for dementia patients, as it is effective on blood biomarkers in addition to cognition and emotion. Likewise, Cha and collaborators state that olfactory stimulation contributes to these patient's language, memory, and emotional states. [33]

CONCLUSIONS

Although there is no cure for Alzheimer's disease, it can be concluded that there are pharmacological and non-pharmacological treatments that may be effective in delaying not only cognitive deficits but also the socio-emotional symptoms that AD brings with it. Likewise, most of the studies reviewed in this paper suggest the participation and, or involvement of primary caregivers because AD not only affects the patient, it also affects the whole family, especially the primary caregiver, if the caregiver is psychologically and physically burdened, there will be a negative impact that reduces self-cognition and quality of life assessment in these patients. Also, some interventions that include the combination of both treatments (pharmacological and no pharmacological) obtained considerable positive results. In other words, the effectiveness of treatments may depend on the combination of appropriate actions to delay the deterioration and, or maintain not only cognitive functions but also the socio-emotional functions of people diagnosed with AD.

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