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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 aim of the present work was to perform a narrative review of the main treatments used for the cognitive deficits of this disease. Among the pharmacological treatments, 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 that have been used 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 la 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, that is, for some, it can be conceptualized as a result or as a process. In view of this, the definition of the World Health Organization (WHO), which refers to ageing as the result of molecular and cellular damage that has accumulated over time, generating 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 ageing as a process of adaptation associated with a dynamic construct of biological, physiological, environmental, psychological, behavioral and social elements, as well as one´s own perception.

Globally, the number of people already in this stage is increasing significantly, in 90´s, there were 700 million aged people, is projected to 2025, 1200 million, this population 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 and 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, 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 the 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 localised onset directly affecting non-mnestic 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, frontotemporal lobar, among others, is required.[13]

Primary progressive aphasia: this 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, which is responsible for language.[13]

Frontal dementia: characterised mainly by neuropsychiatric symptoms, altered behaviour, personality and social behaviour. 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 amiloyd 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 the age of 55 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, tumours, 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: characterised by wandering and getting lost, difficulty handling money and paying bills, repeating questions, taking longer to complete normal daily tasks, changes in personality and behaviour.[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 correctly detect sounds and smells. Memory loss and confusion worsen, there are problems recognising 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 as psychological and behavioural symptoms) may occur, which may be varied and fluctuating 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 is made postmortem, only exceptionally during life. In practice, it is necessary to be guided by a number of 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), magnetic resonance imaging (MRI), among others.
- Perform complementary studies if symptoms could be better explained by 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]

With regard to 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, behaviour and functionality) by specialists.

According to Pais et al.[19] and the National Institute on Aging[21], medications 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 behavioural symptoms. When used in combination with the non-competitive glutamatergic receptor antagonist memantine, these drugs can be used for moderate to severe stages of the disease.

The general characteristics of these drugs 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 metabolised 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, together with a 20-50%. loss of high-affinity nicotinic receptors in the temporal cerebral cortex.[22] Possible side effects could include nausea, vomiting, diarrhoea, 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; it was initially marketed in oral form and can now be administered transdermally through patches.[23] Possible side effects include nausea, vomiting, diarrhoea, weight loss, indigestion, decreased appetite, anorexia and muscle weakness.[21]

Donepezil: a reversible and selective inhibitor of brain acetylcholinesterase, it has a more convenient dosage for people with AD as it is administered once a day 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 is 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, repeats or has to repeat information several times, disorientation in time.
	Attention	Easily distracted by multiple stimuli, difficulty performing simultaneous or prolonged tasks requiring concentration.
	Executive functions	Difficulty in planning and performing complex and sequential tasks, abstract language failure, loss of judgement, difficulty in decision making.
	Visuospatial ability	Disorientation in outdoor spaces or even in familiar areas, problems with spatially complex tasks such as cooking, sewing, dressing, 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	Associated with psychological and behavioural 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, eating disorders, among others. In advanced stages of the disease there may be psychotic symptoms, delusions, hallucinations, misidentifications. Behavioural symptoms include wandering, aggression, resistance to care, inappropriate sexual behaviour and catastrophic reactions.

Possible side effects include nausea, vomiting, diarrhoea, 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. analysed 413 clinical trials testing 244 drugs with these characteristics (DMT), of which almost all failed with the exception of 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, diarrhoea, 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]

There are 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 important to mention that, within this treatment, there are some complementary medications that can 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 serious 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 activities of daily living 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, as well as reduce stress on caregivers and improve their context, their aim, unlike pharmacological treatments, is not to influence the underlying pathophysiological mechanisms, but rather to maintain function and participation for as long as possible, so they can be applied at any stage of AD, although there is a greater likelihood that they can be applied at any stage of AD, do not seek to influence the underlying pathophysiological mechanisms, but rather to maintain function and participation for as long as possible, so they can be applied at any stage of AD, although there is a greater likelihood that their application in early stages will have a significant influence on neuronal plasticity. They are based on different methodologies ranging from simple approaches (environmental interventions) to more complex ones (those using 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 presents.

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 will be described below:

Cognitive Stimulation Therapy: it is one of the main strategies that has been used with people with EA, it consists in the application of a set of structured planned actions that have a direct impact on cognitive functioning, especially attention, memory, perception, praxis, language and executive function, it does not only focus on this, also impacts in elements such as the affective, behavioral, social and even family aspects, seeking comprehensive care in order to reduce dependence, in this case, of the elderly, and also recommends participation and work with the relatives of the patient with this disease. 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: the development of purposeful, planned physical activities can improve cognitive function, neuropsychiatric symptoms and quality of life of AD patients and can even act as a protective factor, as well as prevent destructive behavior in patients with severe AD. It is important to mention that the effects of these interventions can be prolonged in the long term if they continue to be practiced.[29]

Use of Virtual Reality: it can be defined as 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 defined as a therapeutic method for development, adaptation and rehabilitation in neurological, psychological and physical areas.[38] In work 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, as well as generating neurological stimulation that can develop new neural networks.[31]

Also, González-Ojea and collaborators showed positive effects of music therapy with respect to well-being for 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: it consists of recalling events in the subject's personal history by stimulating meaningful memories to create positive feelings.[35] Saraghi el 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: it is another treatment that stood out for its effectiveness, and which in recent years has been studied 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 obtained from the systematic review and meta-analysis realized by Lin and other authors showed that treatments based on this technique improved cognitive function, self-care capacity and even 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: it is 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 even shown to be effective on blood biomarkers in addition to cognition and emotion. Likewise, Cha and collaborators state that olfactory stimulation contributes to language, memory and emotional state in this population.[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, 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 person living with, it also affects the whole family, especially the primary caregiver, if the caregiver is psychologically and physically burdened, the negative impact of this, will reduce self-cognition and quality of life assessment in these patients. Also, within some interventions, includes the combination of both treatments (pharmacological and no pharmacological) obtained major positives results. In other words, the effectiveness of treatments may depend on the combination of appropriate actions, for delay the deterioration and/or maintain not only cognitive functions**,** but also the socio-emotional functions of people diagnosed with AD.

REFERENCES

[1] World Health Organization. Aging and Health [Internet]. Geneva, Switzerland: 2022. [cited 2024 March 18]. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health.

[2] Carrillo-Sierra SM, Rivera-Porras D, García- Echeverri M, Rodríguez González D. Envejecimiento e intervenciones terapéuticas desde la perspectiva psicológica a adultos mayores: una revisión descriptiva. Rev. AVFT 2020; 39(7):899-912.

[3] Parada Muñoz KR, Guapizaca Juca JF, Bueno Pacheco GA. Deterioro cognitivo y depresión en adultos mayores: una revisión sistemática en los últimos 5 años. Rev. Cient. UISRAEL 2022; 9(2):77-93.

[4] United Nations [Internet]. New York, USA: 2022. [cited 2024 Mar 18]. Available from: https://population.un.org/wpp/.

[5] Enriquez LF, Rueda A. Una revisión de técnicas básicas de neuroimagen para el diagnóstico de enfermedades neurodegenerativas. Rev. Biosalud 2018; 17(2):59-90.

[6] Menéndez-González M. Toward a new nosology of neurodegenerative diseases. Alzheimers Dement. 2022; 19(8):3731-7.

[7] Gómez-Virgilio L, Reyes-Gutiérrez GS, Silva-Lucero MC, López-Toledo G, Cárdenas-Aguayo MD. Etiología, factores de riesgo, tratamientos y situación actual de la enfermedad de Alzheimer en México. Gac. Med. Mex. 2022; 158(4):235-41.

[8] Villarroya-Pastor MT. Perfil de la enfermedad de Alzheimer en las mujeres. Rev. Neurol. 2001; 32(12):1178-81.

[9] Mancuso C, Santangelo R. Alzheimer's disease and gut microbiota modifications: the long way between preclinical studies and clinical evidence. Pharmacol. Res. 2018; 129:329-36.

[10] Amirrad F, Bousoik E, Shamloo K, Al-Shiyab H, Nguyen VV, Montazeri Aliabadi H. Alzheimer's disease: the dawn of a new era? J. Pharm. Pharm. Sci. 2017; 20(0):184–225.

[11] Carter J. Memory in shape:100 ideas simple and effective for prevent heAlzheimer's and loss memory associated with age. New York:Uranus; 2011.

[12] Mayo Foundation for Medical Education and Research. Enfermedad de Alzheimer. [Internet]. Minessota, Estados Unidos: 2023. [cited 2024 March 18]. Available from: https://www.mayoclinic.org/es/diseases-conditions/alzheimers-disease/symptoms-causes/syc-20350447

[13] Barragán Martínez D, García Soldevilla MA, Parra Santiago A, Tejeiro Martínez J. Enfermedad de Alzheimer. Med. 2019; 12(74):4338-46.

[14] National Institute on Aging. Alzheimer [Internet]. Bethesda, Maryland: 2021. [cited 2024 Mar 18]. Available from: https://www.nia.nih.gov/espanol/alzheimer.

[15] Pérez Romero A, González Garrido S. La importancia de los síntomas psicológicos y conductuales (SPCD) en la enfermedad de Alzheimer. Neurología 2018; 33(6):378-84.

[16] Alzheimer's Association. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024; 20(5):1-149.

[17] Gella Concustell A, Lladó Plarumaní A, Molinuevo Guix JL. Standardization of preanalytical aspects for the study of biomarkers of Alzheimer's disease in cerebrospinal fluid. Rev. Lab. Clin. 2016; 9(4), 184-8.

[18] National Cancer Institute. Definition therapy pharmacological. [Internet]. EEUU: 2023. [cited 2024 Mar 18]. Available from: https://www.cancer.gov/espanol/publicaciones/diccionarios/diccionario-cancer/def/terapia-farmacologica.

[19] Pais M, Martinez L, Ribeiro O, Loureiro J, Fernandez R, Valiengo L, Canineu P, Stella F, Talib L, Radanovic M, Forlenza OV. Early diagnosis and treatment of Alzheimer's disease: new definitions and challenges. Braz J Psychiatry 2020; 42(4):431-41.

[20] López- Locanto Ó. Tratamiento farmacológico de la enfermedad de Alzheimer y otras demencias. Arch. Med. Int. 2015; 37(2):61-7.

[21] National Institute on Aging. ¿Cómo se trata la enfermedad de Alzheimer? [Internet]. Bethesda, Maryland: 2023. [cited 2024 March 18]. Available from: https://www.nia.nih.gov/espanol/cuidado-medico-enfermedad-alzheimer/como-se-trata-enfermedad-alzheimer#leve.

[22] Carretero M. Galantamine. Offarm Farm. Soc. 2003; 22(8):140-2.

[23] Cruz Jentoft AJ, Hernández B. Manejo terapéutico con rivastigmina en pacientes con enfermedad de Alzheimer de leve a moderadamente grave en condiciones de práctica clínica habitual. Estudio ENTERPRISE. Neurologia 2014; 29(1):1–10.

[24] Gómez González del Tánago P, Navarro Vidal B, Panadero Carlavilla FJ. Enfermedad de Alzheimer. Panorama Actual del Medicamento. 2011; 35(347):803-8.

[25] Tanović A, Alfaro V. Neuroprotección con memantina (antagonista no competitivo del receptor NMDA-glutamato) frente a la excitotoxicidad asociada al glutamato en la enfermedad de Alzheimer y en la demencia vascular. Rev. Neurol. 2006; 42(10):607-16.

[26] McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, Maayan N, Ware J, Debarros J. Memantine for dementia. Cochrane Database Syst Rev. 2019; 3(3):CD003154.

[27] Regier NG, Hodgson NA, Gitlin LN Characteristics of Activities for Persons with Dementia at the Mild, Moderate, and Severe Stages. Gerontologist. 2017; 57(5):987-97.

[28] Zucchella C, Sinforiani E, Tamburin S, Federico A, Mantovani E, Bernini S, Casale R and Bartolo M (2018) The Multidisciplinary Approach to Alzheimer's Disease and Dementia. A Narrative Review of Non-Pharmacological Treatment. Front. Neurol. 9:1058.

[29] Liang YJ, Su QW, Sheng ZR, Weng QY, Niu YF, Zhou HD, Liu CB. Effectiveness of Physical Activity Interventions on Cognition, Neuropsychiatric Symptoms, and Quality of Life of Alzheimer's Disease: An Update of a Systematic Review and Meta-Analysis. Front. Aging Neurosci. 2022; 14:830824.

[30] Zhu S, Sui Y, Shen Y, Zhu Y, Ali N, Guo C, Wang T. Effects of Virtual Reality Intervention on Cognition and Motor Function in Older Adults with Mild Cognitive Impairment or Dementia: A Systematic Review and Meta-Analysis. Front. Aging Neurosci. 2021; 13:586999.

[31] Lai X, Wen H, Li Y, Lu L, Tang C. The Comparative Efficacy of Multiple Interventions for Mild Cognitive Impairment in Alzheimer's Disease: A Bayesian Network Meta-Analysis. Front. Aging Neurosci. 2020; 12:121.

[32] Gonzalez-Ojea MJ, Dominguez-Lloria S, Pino-Juste M. Efficacy de the programs de music therapy: un meta-analysis qualitative. Brazilian J. Occupational Therapy 2021;29:e2976.

[33] Cha H, Kim S, Kim H, Kim G, Known KY. Effect of intensive olfactory training on cognitive function in patients with dementia. Geriatr. Gerontol. Int. 2021; 22(1):5-11.

[34] Villalba Agustín S, Espert Tortajada R. Estimulación cognitiva: una revisión neuropsicológica. Therapeía 2014; 6:73-93.

[35] Irazoki E, García- Casal HA, Sánchez- Mecca J, Franco-Martín M. Eficacia de la terapia de reminiscencia grupal en personas con demencia. Revisión sistemática y metaanálisis. Rev. Neurol. 2017; 65(10):447-56.

[36] Choi J, Twamley EW. Cognitive rehabilitation therapies for Alzheimer's disease: a review of methods to improve treatment engagement and self-efficacy. Neuropsychol. Rev. 2013; 23(1):48-62.

[37] Cibeira N, Lorenzo-López L, Maseda A, López-López R, Moreno-Peral P, Millán-Calenti JC. Realidad virtual como herramienta de prevención, diagnóstico y tratamiento del deterioro cognitivo en personas mayores: revisión sistemática. Rev. Neurol. 2020; 71(6):205-12.

[38] Rodríguez-Mora Álvaro, García Ramos CM. Evaluación de la influencia de un programa de musicoterapia en los síntomas psicológicos y conductuales de las demencias (SPCD) y el estado de ánimo en una muestra de enfermos de Alzheimer. Estudio piloto. Apuntes de Psicología 2021; 38(3):167-75.

[39] Saragih ID, Tonapa YES, Yao CT, Saragih IS, Lee BO. Effects of reminiscence therapy in people with dementia: a systematic review and meta-analysis. J. Psychiatr Ment Health Nurs. 2022; 29(6):883-903.

[40] Ospina-Díaz N. Introduction to acupuncture, foundations and interest for the primary care doctor. Semergen 2009; 35(8):380-4.

[41] Arango-Vélez V, Montoya-Vélez LP. Medicina Integrativa: efectos de la acupuntura y su aplicación clínica en la medicina convencional. Rev. CES Med. 2015;29(2):283-94.

[42] Lin C-J, Yeh M-L, Wu S-F, Chung Y-C, Lee JC-H. Acupuncture-related treatments improve cognitive and physical functions in Alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. Clin. Rehabil. 2022; 36(5):609-35.

[43] Leon M, Woo C. Environmental Enrichment and Successful Aging. Front. Behav. Neurosci. 2018; 12:155.

[44] Yao L, Pinto JM, Yi X, Li L, Peng P, Wei Y. Gray matter volume reduction of olfactory cortices in patients with idiopathic olfactory loss. Chem. Senses 2014; 39(9):755–60.

[45] Lin LJ, Li KY. Comparing the effects of olfactory-based sensory stimulation and board game training on cognition, emotion, and blood biomarkers among individuals with dementia: A pilot randomized controlled trial. Front. Psychol. 2022; 13:1003325.