Alzheimer's Disease: Current Treatments and New Perspectives

Pájaro-Castro Nerlis[1]*, Bustamante-Díaz Jesús[2], Vergara-Dagobeth Edgar[3] and Ibañez-Bersinger Cristhian[4]

[1]*Associate Professor, Medical and Pharmaceutical Sciences Group, Faculty of Health Sciences, Medicine Program University of Sucre Sincelejo, Colombia*
[2]*Medico, Medical and Pharmaceutical Sciences Group, Faculty of Health Sciences, Medicine Program University of Sucre Sincelejo, Colombia*
[3]*Medico, Specialization in Breast and Soft Tissue Surgery, Candidate for Doctor of Tropical Medicine, Medical and Pharmaceutical Sciences Group, Faculty of Health Sciences, Medicine Program University of Sucre Sincelejo, Colombia*
[4]*Industrial Engineering, X semester, UNAD, Medical and Pharmaceutical Sciences Group, Faculty of Health Sciences, Medicine Program University of Sucre Sincelejo, Colombia*

*Corresponding Author: Pájaro-Castro Nerlis, Associate Professor, Medical and Pharmaceutical Sciences Group, Faculty of Health Sciences, Medicine Program University of Sucre Sincelejo, Colombia

Abstract

The global epidemiology of dementias is increasing, it is estimated a four times higher prevalence by 2050, within these is Alzheimer's disease, dementia for which there is no treatment, only drugs are available that restore, for a time, cognitive and behavioral processes at the cerebral level, for this reason, research is currently driving the development of new strategies for both pharmacological and non-pharmacological treatments. However, there are few clinical trials for the therapy of AD taking into account the magnitude of the problem. The success rate in terms of the development of new drugs is very low and the amount of drugs that pass to the regulatory review to be marketed is among the lowest found in any therapeutic area. Therefore, support and collaboration is required from the entities involved in the discovery of new medicines and those that have the budget for the execution of this process, in addition to patients and relatives, in order to obtain an adequate treatment to prevent and stop the progression of the disease.

Keywords: *Cognitive Impairment; Therapy; Neurodegenerative Disease; Treatment; Alzheimer's Disease*

Introduction

Dementia is a syndrome characterized by a progressive decline in memory, executive functions, language and other areas of cognition, associated with behavioral symptoms. Primary dementias are not curable at present and produce progressive and irreversible damage to the brain. The most representative causes of this group include: Alzheimer's disease (AD), responsible for 50 to 60% of the total cases, vascular dementias, dementia due to Lewy body disease and frontotemporal degeneration [1].

Alzheimer's disease has become a growing problem of a medical, psychiatric, neurological, epidemiological, social and economic order, particularly in countries with high life expectancy [2,3]. The disease is associated with neurodegenerative processes that involve loss of synapse and cholinergic, glutaminergic and gabaergic neurons [4], which is why dementia with the greatest cause of failure of brain function in old age is considered [5].

In addition to the neurodegenerative stages typical of Alzheimer's disease, evidence has shown that the disease is a "protein folding disorder" that exhibits common malformation characteristics [5]. The two main lesions in the disease are: extracellular filament deposits (amyloid plaques) and intracellular deposits (neurofibrillary tangles). The latter are mainly formed by an abnormal form of the Tau protein [6-8]. Extracellular filaments are found mainly in the cortex, while neurofibrillary tangles are intracellular and extracellular [9-11].

Together, the presence of extracellular beta amyloid plaques, intracellular neurofibrillary tangles and gliosis, activated glial cells, in the brain lead to progressive neural death, neuroinflammation and gliosis and ultimately, cognitive impairment, which generates clinical expression typical of the disease [12,13]. Although promising treatments have been developed in recent years, it is necessary to make an early diagnosis of the disease, and design new medications focused on the prevention and arrest of the disease, so it is necessary to carry out clinical trials of course modifying drugs evolutionary disease [14].

A 2011 study estimated that social costs amount to approximately € 14500 per year in patients at home with a high level of autonomy, but they amount to € 72500 per year in patients in need of residential care [15-17]. Current treatments are based on medications that slow the progression of the disease provide symptomatic relief, but do not achieve a definitive cure. This lack of understanding about the pathogenic process may be the probable reason for the lack of availability of a treatment [18,19].

Current treatments

Research on therapy for Alzheimer's disease has been at least partially successful in terms of developing symptomatic treatments but has also had several failures in the development of treatments that modify the disease. Many clinical and experimental studies are ongoing, but we must recognize that a treatment is unlikely and that the approach to drug development for this disorder should be reconsidered [20].

Future therapies should address multiple aspects of Alzheimer's disease, for example, different pathogenic mechanisms and the convergence of symptoms that may occur during the course of dementia [21]. The following describes the current approaches to treating the disease.

Non-pharmacological treatments

The cornerstone in the treatment of dementias and Alzheimer's disease is to gain the trust and participation of the family. The family must learn to know and provide comprehensive care to the patient [22].

Non-pharmacological interventions can be promising because older adults may prefer them to maintain cognitive function and independence, they have less risk than pharmacological ones (i.e. the low probability of contraindications or problems that occur with polypharmacy). In fact, non-pharmacological interventions that address cognitive function and its impact on daily life have been widely studied in a variety of clinical populations [23].

The use of these types of therapies has some fundamental indications as a whole: "Daily care of patients with dementia, intention of a partial reversal of symptoms and control of agitation through behavior modification therapies" Although, non-pharmacological interventions They tend to be complex, multimodal, as defined by the Medical Research Council. The main of these interventions are cognitive training interventions [24,25]. Additionally, non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation and transcranial electrical stimulation, are increasingly being investigated for their potential to improve Alzheimer's disease symptoms [26].

Pharmacological treatments

The pharmacological treatment of AD is classified as: increasing the availability of neurotransmitters, actions on pathogenic mechanisms, treatment of stages of agitation and other psychiatric manifestations and associated diseases [22].

Cholinergic neurons are the main site of pathological abnormalities in Alzheimer's disease [22]. First-generation acetylcholinesterase inhibitors such as physostigmine and tacrine, and second-generation inhibitors, such as donepezil, rivastigmine and reminyl, increase the local concentration and duration of acetylcholine in the synaptic cleft, therefore, These medications are effective in mild and moderate forms of the disease (Table 1) [22].

Drug	Mechanism of action	Observations	Reference
Donepezil Rivastigmine Galantamine	Cholinesterase (IC) inhibitors, to improve cholinergic transmission and delay the degradation of acetylcholine between the synaptic cleft.	In the early stages of the disease a loss of acetylcholine neurons occurs, of the enzymatic function for the synthesis and degradation of acetylcholine.	27
Memantine	N-methyl-D-aspartate antagonist.	For the treatment of moderate to severe disease. This drug is a non-competitive, moderate-affinity antagonist of N-methyl-D-aspartate (NMDA) that is believed to protect neurons from excitotoxicity.	27
Tramiprosate- 3APS- (In clinical trial, phase III)	Aβ aggregation inhibitor.	Designed to interfere with the binding of glycosaminoglycans and Aβ. It will be marketed as a brand nutraceutical. However, recent data suggest that tramiprosate promotes abnormal aggregation of tau protein in neuronal cells.	27
Colostrinin (In clinical trial, phase II)	Inhibits Aβ aggregation and neurotoxicity in cellular assays and improves cognitive performance in animal models.	Proline-rich polypeptide complex derived from sheep colostrum.	27
Phenothiazine, methylene blue (MB) or methylthioninium chloride	Tau aggregation inhibitors.	Promising results have emerged from a phase II clinical trial that tests MB as a potential therapy for the disease.	
Pioglitazone (NCT01931566; Phase III)	PPARγ agonist that acts as a β-secretase inhibitor: inhibits the first protease necessary for the production of Aβ.	This drug is in a phase III clinical trial study.	15
Solanezumab	Anti-Amyloid Monoclonal Antibody.	A humanized monoclonal antibody that binds to amyloid, failed to improve cognitive or functional ability.	15
Gantenerumab	Anti-Amyloid Monoclonal Antibody.		15
Huperzine-A	Acetylcholinesterase inhibitor, Modulates the processing of APP by increasing the soluble secretion of APPα.	Approved in China for the mild to moderate stages of the disease. Dietary supplement in some countries.	20

Table 1: *Drugs reported for the treatment of Alzheimer's disease.*

To date, there are only symptomatic treatments for AD. Current studies focus on the search for drugs that can block the progression of the disease, that is, drugs that interfere with the pathogenic mechanisms responsible for clinical symptoms, including the deposition of extracellular amyloid β plaques and the formation of intracellular neurofibrillary clews, inflammation, oxidative damage, iron deregulation and cholesterol metabolism [27].

Immunotherapy is one of the strategies that most pharmaceutical companies are studying, based on the mechanisms of the immune response within which are the direct disassembly of plaques by selective antibodies, activation induced by microglial cell antibodies and phagocytosis. of pathological protein deposits and immunoglobulin M-mediated hydrolysis (IgM) [27].

A recent review has presented the case to exploit AβOs (beta amyloid oligomer) as a therapeutic target [28]. Recent discovery efforts concern vaccines that target AβO, the search for the relationship between AβO, toxin receptor antagonists, inflammation and insulin signaling, and intriguing findings of behavior modification [29]. Another route in the development of new drugs, is the search for molecules capable of interacting with the CDK5 protein at the level of its active site, so they could act as inhibitors of this kinase, which opens a future therapeutic window in the treatment of the disease, through in silico evaluation [30]. In addition, other pharmacological targets are gamma-secretase and beta-secretase inhibitors, amyloid antiplatelet therapies, metal chelators, therapies directed against tau protein, among others [31].

New insights

At present, several aspects should be considered with respect to the pharmacological treatment of Alzheimer's disease, including: diagnosis, individualized study, the use of evidence-based prescription, and the need for investment in the health system and access policies [15]. Additionally, the analysis of family-centered patient protocols for drug treatment has not yet been developed.

The search for disease modifying interventions has mainly focused on compounds directed to the Aβ pathway. To date, many treatments aimed at this route, such as tarenflurbil, tramiprosate and semagacestat, have not been successful in demonstrating efficacy in the final clinical stages of the test [27,32]. Therefore, it is extremely important to propose strategies whose main objective is to prevent or stop the progression of the disease.

Prevention strategies pursue different objectives: eradicate the disease, postpone its onset and communicate with people at risk. Current research advocates the potential effects of prevention on dementia through the adoption of healthy lifestyles, early interventions in public health, early diagnosis and adequate treatment of chronic diseases [1].

Therefore, it is recommended to: minimize the intake of saturated fats and trans fats; consider vegetables, legumes, fruits and grains as main sources of the diet and consider vitamin B intake. The role of aluminum, the usefulness of antioxidant vitamins, huperzine A, resveratrol, Ginkgo biloba and the available nutraceuticals are discussed [3].

A more real goal is to postpone the clinical onset of dementia to increasingly advanced ages: a year of delay in the clinical onset of dementia would result in a reduction of 12 million fewer cases worldwide by 2050 and a reduction considerable cost [1]. In addition, it is widely accepted that the disease is associated with genetic and environmental factors, therefore, there is a growing interest in scientific research related to those factors that are modifiable [1]. Most of the anti-aging interventions that increase life expectancy or duration of health in animal models have a therapeutic action in Alzheimer's disease [33].

The pharmacological evaluation of new biologically active molecules should be promoted by the government, public and private institutions, EA associations and the pharmaceutical industry through improvements in the clinical development infrastructure that allow to increase clinical research [15]. The diagnosis and treatment of associated conditions, neuropsychiatric symptoms and psychosocial

deterioration are key elements to improve the quality of life of patients and their families. Changes in lifestyle, exercise and nutritional support may play a role in all phases of the disease, but more research is needed to guide the implementation of intervention programs [15]. The worrying thing is that, according to the Clinicaltrials.gov database, relatively few clinical trials are conducted for the therapy of the disease taking into account the magnitude of the problem. The success rate to advance from one phase to another is low, and the amount of compounds that progress to the regulatory review is among the lowest found in any therapeutic area. The drug development ecosystem for Alzheimer's disease requires support and collaboration from the entities involved in the discovery of new drugs and those that have the budget for the execution of this process, in addition to the patients and relatives, in order to obtain an adequate treatment to prevent and stop the progression of the disease [34].

There are 105 agents in the treatment development line for AD, of which 25 agents are in 29 trials in phase I, 52 agents are in 68 trials in phase II and 28 agents are in 42 trials in phase III. 70% of medications are therapies that modify the disease, 14% are symptomatic cognitive enhancers and 13% are symptomatic agents that address neuropsychiatric and behavioral changes [35].

Conclusion

Alzheimer's disease is a pathology for which there is no treatment for prevention or to stop the progression of the disease. Current treatments only temporarily improve symptoms of memory loss and problems with thinking and reasoning. The development of new medicines is a slow and meticulous process. The pace can be especially frustrating for people with Alzheimer's and their families who are waiting for new treatment options.

Acknowledgment

Bibliography

1. Llibre RJ and Gutiérrez HRF. "Demencias y enfermedad de Alzheimer en América Latina y el Caribe". *Revista Cubana de Salud Pública* 40.3 (2014): 378-387.

2. Menéndez S., *et al*. "Péptido beta amiloide, proteína Tau y enfermedad de Alzheimer". *Revista Cubana Invest Biomed* 21.4 (2002): 253-261.

3. Arizaga R., *et al*. "Dieta y prevención en enfermedad de Alzheimer". *Neurología Argentina* 10.1 (2018): 44-60.

4. Rockenstein E., *et al*. "Neuro-peptide treatment with Cerebrolysin improves the survival of neural stem cell grafts in an APP transgenic model of Alzheimer disease". *Stem Cell Research* 15.1 (2015): 54-67.

5. Wang H., *et al*. "Heat Shock Proteins at the Crossroads between Cancer and Alzheimer's Disease". *BioMed Research International* (2014): 239164.

6. Oviedo D., *et al*. "Deterioro cognitivo leve y enfermedad de Alzheimer: Revisión de conceptos". *Investigación y Pensamiento Crítico* 4.2 (2016): 64-81.

7. Bernhardi R. "Neurobiological mechanisms of Alzheimer's disease". *Revista chilena de neuro-psiquiatría* 43.2 (2005): 123-132.

8. Aggleton JP., *et al*. "Thalamic pathology and memory loss in early Alzheimer's disease: moving the focus from the medial temporal lobe to Papez circuit". *Brain* 139.7 (2016): 1877-1890.

9. Bazzocchini V. "Mecanismos etiopatogénicos, fisiopatológicos y moleculares de la Enfermedad de Alzheimer". *Revista Bionanálsis* 24 (2008): 6-13.

10. Sarria S., *et al.* "Reproducibility of qualitative assessments of temporal lobe atrophy in MRI studies". *Radiología* 57 (2015): 225-228.

11. Vázquez J., *et al.* "Inflammatory amyloid angiopathy". *Neurologia* 29 (2014): 254-256.

12. Frost G and Li Y. "The role of astrocytes in amyloid production and Alzheimer's disease". *Open Biology* 7.12 (2017).

13. Zhang X., *et al.* "Near-infrared fluorescence molecular imaging of amyloid beta species and monitoring therapy in animal models of Alzheimer's disease". *Proceedings of the National Academy of Sciences of the United States of America* 112.31 (2015): 9734-9739.

14. Valls-Pedret C., *et al.* "Diagnóstico precoz de la enfermedad de Alzheimer: fase prodrómica y preclínica". *Revue Neurologique* 51.8 (2010): 471-480.

15. Winblad B., *et al.* "Defeating Alzheimer's disease and other dementias: a priority for European science and society". *The Lancet Neurology* 15.5 (2016): 455-532.

16. Prada S., *et al.* "Costo monetario del tratamiento para la enfermedad de Alzheimer en Colombia". *Acta Neurológica Colombiana* 30.4 (2014): 247-255.

17. Vargas E., *et al.* "Prevalence of dementia in Colombian populations". *Dementia and Neuropsychologia* 8.4 (2014): 323-329.

18. Kumar A., *et al.* "A review on Alzheimer's disease pathophysiology and its management: an update". *Pharmacological Reports* 67.2 (2015): 195-203.

19. Alzheimer's Association. "De Alzheimer y de Demencia de Alzheimer: El Diario de la Asociación de Alzheimer" 2 (2010): 158-194.

20. Mangialasche F., *et al.* "Alzheimer's disease: clinical trials and drug development". *The Lancet Neurology* 9.7 (2010): 702-716.

21. Blesa R., *et al.* "Strategies for Continued Successful Treatment in Patients with Alzheimer's Disease: An Overview of Switching Between Pharmacological Agents". *Current Alzheimer Research* 15.10 (2018): 964-974.

22. Llibre J and Guerra M. "Actualización sobre la enfermedad de Alzheimer". *Revista Cubana de Medicina General Integral* 18.4 (2002): 264-269.

23. Chung CS., *et al.* "Cognitive rehabilitation for executive dysfunction in adults with stroke or other adult non-progressive acquired brain damage". *Cochrane Library: Cochrane Reviews* 4 (2013): CD008391.

24. Rodakowski J., *et al.* "Non-pharmacological interventions for adults with mild cognitive impairment and early stage dementia: An updated scoping review". *Molecular Aspects of Medicine* 43-44 (2015): 38-53.

25. Olazarán J and Muñiz R. "Mapa de Terapias No Farmacológicas para Demencias Tipo Alzheimer". Fundación Maria Wolff y el International Non Pharmacological Therapies Project (2009).

26. Buss SS., *et al.* "Therapeutic noninvasive brain stimulation in Alzheimer's disease and related dementias". *Current Opinion in Neurology* 32.2 (2019): 292-304.

27. Yiannopoulou KG and Papageorgiou SG. "Current and future treatments for Alzheimer's disease". *Therapeutic Advances in Neurological Disorders* 6.1 (2013): 19-33.

28. J Folch., *et al.* "Review of the advances in treatment for Alzheimer disease: strategies for combating β-amyloid protein". *Neurología* 33.1 (2018): 47-58.

29. Viola KL and Klein WL. "Amyloid β oligomers in Alzheimer's disease pathogenesis, treatment, and diagnosis". *Acta Neuropathologica* 129 (2015): 183.

30. Pájaro-Castro Nerlis., *et al*. "Identificación in silico de moléculas potencialmente inhibidoras de CDK5, proteína relacionada con la enfermedad de Alzheimer". *Revista Habanera de Ciencias Médicas* 16.3 (2017): 325-336.

31. Scarpini E., *et al*. "Treatment of Alzheimer's disease current status and new perspectives". *The Lancet Neurology* 2.9 (2003): 539-547.

32. Dos Santos Picanç L., *et al*. "Alzheimer's disease: A review from the pathophysiology to diagnosis, new perspectives for pharmacological treatment". *Current Medicinal Chemistry* 23.999 (2016): 1-1.

33. Alonso G., *et al*. "Terapias antienvejecimiento aplicadas a la enfermedad de Alzheimer". *Revista Española de Geriatría y Gerontología* 53.1 (2018): 45-53.

34. Cummings J., *et al*. "Alzheimer's disease drug-development pipeline: few candidates, frequent failures". *Alzheimer's Research and Therapy* 6 (2014): 37.

35. Cummings J., *et al*. "Alzheimer's disease drug development pipeline". *Alzheimer's and Dementia: Translational Research and Clinical Interventions* 3.3 (2017): 367-384.