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THE EFFECT OF DONEPEZIL IN THE COGNITIVE FUNCTION IN ELDERLY WITH ALZHEIMER'S DISEASE: AN INTEGRATIVE REVIEW

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ABSTRACT

Introduction: Considered as a neurodegenerative dementia, Alzheimer's is directly related to aging through the establishment of cognitive deficits. The main drugs used in the treatment of the aforementioned disease are acetyl cholinesterase inhibitors. Considered as a reversible acetyl cholinesterase inhibitor, Donepezil is the second medication most commonly used by elderly people with Alzheimer's disease because it is well tolerated and has beneficial effects on the cognition of affected patients. **Objective:** Study's goal has been to analyze the scientific production about Donepezil's effect in the cognitive function of elderly carriers of Alzheimer's. **Methods:** This is an integrative literature review, with a bibliographic and documental approach that addresses the pharmacological treatment in the use of Donepezil in elderly people affected by Alzheimer's disease. The data gathering has been performed during the period of June to august of 2019 in the LILACS - Latin American and Caribbean Health Sciences Literature database, Scientific Electronic Library Online (SciELO), Pubmed database. The search strategy used by the Health Sciences Descriptors (HSD) in the Lilacs and SciELO database: "Alzheimer" AND "elderly" AND "cognitive" AND Donepezil. Pubmed database accordingly with the Medical Subject Headings (MeSH): Alzheimer" AND "elderly" AND "cognitive" AND "memory" AND "Donepezil". Without limitations of studies periods. With the goal of minimize a possible publication bias, the research did not have a temporal limitation, not even the publication or size of the sample's type. **Results:** The observed articles addressed the pharmacological properties of donepezil in the treatment of the elderly with Alzheimer's disease, as well as in the identification of mechanism of action, therapeutic effects, pharmacokinetic aspects, adverse effects and drug interactions of donepezil and in the understanding of the use of donepezil in the treatment of Alzheimer's disease. **Conclusion:** The role of the cholinergic system in cognition and the identification of cholinergic deficits in Alzheimer's disease allowed the development of drugs that restored cholinergic function, such as donepezil, which is a central action acetylcholinesterase inhibitor that acts, especially with the purpose of increasing the intrasynaptic availability of acetylcholine, leading to a decrease in the cognitive, functional and behavioral symptoms of Alzheimer's disease.

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INTRODUCTION

The World Health Organization has stated an estimated amount of 47 million people in the world with dementia (WORLD, 2015). Within the types of dementia Alzheimer's Disease (AD) stands out, which one of the main clinic symptoms is the recent memory impairment, however, there are other symptoms associated with the disease, such as depressive mood, the decrease of social interaction, appetite alterations, sleep and psychomotor swings as well as irritability, fatigue and feelings of worthlessness (Vital *et al*., 2015 & Cruz *et al*., 2015). Epidemiologically, studies point to the prospective increase scenario of people with AD, representing a significant global impact, specially within the population over 70 years old (Zidan, 2012; Dias, 2013; Viegas Júnior, 2014). The socioeconomic impact from the Alzheimer's Disease outlay is quite a relevant factor, the care and treatment costs affect the lives of those who carry the

disease and their relatives'. The AD carriers' spendings with caretakers, special needs and pharmacotherapy exceed 25 billion dollars per year (DIAS, 2013). The main drugs used for the disease's mentioned above treatment are the acetyl cholinesterase inhibitors (Forlenza, 2010). The Donepezil considered as a reversible acetyl cholinesterase inhibitor is the second most used medication in the United States since 1997 for the elderly with Alzheimer's Disease because it is such a well received drug and it presents benefits over the affected patient's cognition (Vital *et al*., 2015). Over the years, many psychoactive substances have been being used in pharmacological treatments with the intent of preserving the elderly with Alzheimer's cognition, behavior and functional abilities, and this procedure is known as symptomatic treatment. However, the study of Donepezil as a drug in this disease's treatment aims identifying if it limits the disease's natural evolution allowing its stabilization or if it's capable of presenting an improvement, even if temporary in the elderly that is a carrier of AD. Considering the importance of the evaluation of the available evidences in literature, this study's goal has been to analyze the scientific production about Donepezil's effect in the cognitive function of elderly carriers of Alzheimer's.

MATERIALS AND METHODS

Source of information and search strategy: An integrative review of literature has been made following the subsequent recommendations suggested by PRISMA (Moher *et al*., 2015). The data gathering has been performed during the period of june to august of 2019 in the LILACS - Latin American and Caribbean Health Sciences Literature database, Scientific Eletronic Library Online (SciELO), Pubmed database. The search strategy used by the Health Sciences Descriptors (HSD) in the Lilacs and SciELO database: "Alzheimer" AND "elderly" AND "cognitive" AND Donepezil. Pubmed database accordingly with the Medical Subject Headings (MeSH): Alzheimer" AND "elderly" AND "cognitive" AND "memory" AND "Donepezil". Without limitations of studies periods. With the goal of minimize a possible publication bias, the research did not have a temporal limitation, not even the publication or size of the sample's tipe.

Criterias of inclusion and exclusion: The integrative review included papers that followed the following criteria's: a) studies published in English, portuguese and spanish b) studies available in their entirety; c) articles published in the Lilacs and SciELO database. As an exclusion criterion were used: a) project documents, congresses, conference, monographies and theses; b) articles that do not approach as a main subject the effect of Donepezil in the cognitive function in elderly with Alzheimer's Disease.

Codification of results and information analysis: It has been elaborated a manual of codification to register the variables and a synoptic chart with the following information's of every study: research name; authors name; publishing year, place of study (country), study type, sample, instrument used for data gathering, measured parameters and main results. The articles with methodological misconceptions that also did not follow the study's goal have been deleted by the researchers. Considering the study has been made through the consultation of indexed articles in scientific databases without involving human beings, it wasn't necessary to be committed to the Ethics Committee in Research. The presentation of the results was performed in a figure, chart, shape and descriptive form making possible to the reader the evaluation of its applicability.

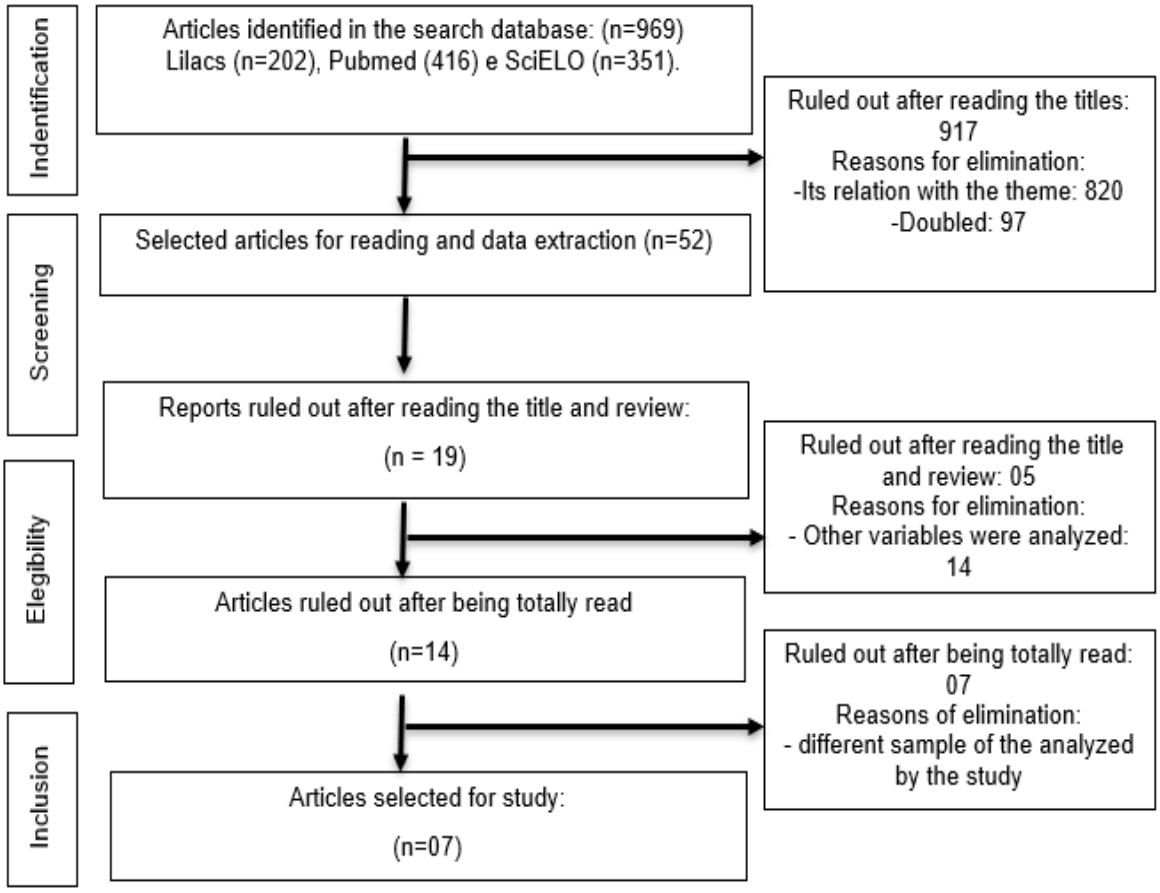
RESULTS

The study sample was composed by 1685 patients that have used Donepezil. There have been identified on the initial search of databases 969 articles, of which only 07 have been selected for study (image 1). It's found on chart 1 a summary of analyzed works that have a direct approach o the authors and year of publishing, as well as the study's location, population studied, and the study's main results used for the presentation's construction. In the matter of the origin of the publications, the countries that stood out by the number of publications were Brazil (Viegas *et al*., 2011; Bottino *et al*., 2012; Noetzli *et al*., 2015) and Europe (Persson *et al*., 2009; Commings *et al*., 2010; Coin *et al*., 2016). The main results found about the effect of Donepezil on elderly with Alzheimer's Disease are related to: I) Elderly with Alzheimer's Disease that use Donepezil; II) To identify cognitive domains separated in the tools of standard evaluation on patients with AD in treatment the drug Donepezil; III) Relation between the concentrations of Donepezil and the CYP2D6 and CYP3A4 activities on elderly patients with Alzheimer's Disease; V) Higher concentration of Donepezil and long-term memory on patients with a light stage and advanced stage of AD.

DISCUSSION

Classified as a neurodegenerative dementia, Alzheimer's Disease is associated with aging and cognitive deficit. The referred disease generates a significant global impact according to epidemiological data, specially to the subjects that are older than 70 years old (Aprahamian *et al*., 2009; Zidan *et al*. 2012; Dias *et al*., 2013; Viegas-Júnior *et al*., 2014).

Elderly with Alzheimer's Disease and Donepezil: The age is considered as a main risk factor for the development of Alzheimer's Disease. Given this fact, it's observed that every five years added on age increasement the disease's prevalence doubles starting on 65 years old (Talmelli *et al*., 2013). The family history elevates the risk of involvement. There are still predisposing factors such as cranioencephalic trauma, gender (feminin), ethnicity (caucasian), exposure to aluminum and atherosclerosis, they are still questioned in the literature according to scientific evidences (Bottino *et al*., 2012). Throughout the development of Alzheimer's Disease many changes relating to the family's everyday life tend to show up, bringing, consequently, considerable shocks and emotional distresses to the members of such family, which makes the referred disease a family involvement (Freitas *et al*., 2016). The family plays a fundamental role in the control and maintenance of the drug treatment of the elderly with AD. The treatment with Donepezil is initiated with a daily dose of 5mg/day, increasing to 10mg/day according with the patient's tolerability. The drug presents a half-life of intermediary elimination of approximately 7 hours (Engelhardt *et al*., 2016; Forlenza, 2015). With aging the renal function tend to decrease, it is emphasized that the use of Donepezil is safe even in patients that present a deficit in the renal function (Persson *et al*., 2009).



Picture 1. Flow chart based in the PRISMA model with the results of the articles' selection

Chart 1. Description of the scientific works included in the present study about the effect of Donepezil in elderly with Alzheimer's Disease (AD)

Nº	Authors/Year of publishing	Place of study	Studied population	Main results
1	Persson, C.M.; Wallin, A.K.; Levander, S.; et al. (2009)	Fulfilled in 10 memory clinics on Switzerland, administered from the Memory Clinic in U-MAS, in Malmö, Switzerland.	421 patients with AD, however, the study was finished with 158 patients that stayed for analysis for the course of 3 years.	There has been a cognitive improvement with the use of Donepezil in 6 months, followed by a linear decrease in time for the three followed by a linear drop over time for the threecommands.
2	Commings et al. (2010)	Study fulfilled by the Research Group in Memory Disorders at the Neurology Department of Copenhagen, Denmark.	The data was grouped from four clinical trials with Donepezil. (n=904).	It was observed as a result of the benefits of Donepezil the cognitive function of patients with severe AD, including the ones that have been more damaged. The size of the treatment's effect and the correlation in the improvements in the scores of the Beneficiary Information System (BIS) and measurements of global functional results suggest that the differences between the placebo and this drug are clinically significant.
3	Viegas, F.P.D.; Simões, M.C.R.; Rocha, M.D.; et al. (2011)	Federal University of Alfenas / Minas Gerais.	54 patients with indication of cholinesterase's inhibitors.	Between the four most used drugs in the AD treatment, Donepezil is the one that stands out for being considerably less toxic than Tacrine, becoming 1250 times more selective for AChE than BuChE. The Donepezil brings about little side effects to the patient, still it presents a linear absorption hitting a maximum plasmatic concentration in 3-5 hours after its administration.
4	Bottino, C. M. C. et al. (2012)	Third Age Project (PROTER), Institute and Department of Psychiatry of Hospital of Clinics (HC). São Paulo.	06 patients diagnosed with a light AD, according to the diagnosis criteria of CID-10 and NINCDS-ADRDA.	At the end of monitoring there was: stabilization of discrete improvement of the cognitive deficits and of the patients' daily life activities; stabilization or decrease of the depression and anxiety on the patients or relatives.

Continue ……..

5	Yang, Y.H.; Chen, C.H.; Chou, M.C.; et al. (2013)	Cognitive Abilities Screening Instrument, in Taiwan.	37 patients with AD of light stage recently diagnosed taking Donepezil 5 mg/d.	Between the 9 cognitive domains in the Cognitive Abilities Screening Instrument, the long-term memory domain presented the biggestrate of improvement (81,1%) in comparison with the other domains. A higher plasmatic concentration of Donepezil [average (DP), 75,14 (32,16) ng / mL] has been significantly associated to the long-term memory improvement (P = 0,045; odds ratio, 0,959; confidence interval of 95%, 0,920-0,999) after adjustment for age, gender, education and genotype of apolipoprotein E.
6	Noetzli, M.; Guidi, M.; Ebbing, K.; et al. (2015)	Scientific department of Cognitive Neurology and Aging of Brazilian's Academy of Neurology, in Rio de Janeiro.	It was made a pharmacokinetic population study including data of 129 sick elderly treated with Donepezil.	The average debug of Donepezil was of 7,3 l h (-1) with a interindividual variability of 30%. Gender influenced markedly the debug of Donepezil (P <0,01).
7	Coin, A.; Pamio, M.V. et al. (2016)	University of Padova, Italy.	It was used for this study a sample of 54 patients affected by a likely AD in therapy with D 10 mg /for at least 3 months.	A significant correlation was found between the plasmatic levels of D and the variations in the MEEM scores after 9 months of therapy (r_2 = 0,14; p =0,006). Nor the metabolites D concentrations or the metabolic reasons of CYP2D6 and CYP1A4 have showed any correlations whatsoever with the cognitive variations.

Chart 2. Features of the selected studies

STUDY	METHODOLOGY OF STUDY	PERIODIC
1	Prospective and continuous multicenter	*BMC Neurology*
2	Experimental	Journal of Alzheimer's Disease
3	Literature research	Virtual Magazine of Chemistry
4	Exploratory, quantitative	Arq Neuropsychiatry
5	Experimental	Journal of Clinical Psychopharmacology
6	Experimental	Eur. J. Clin. Pharmacol
7	Literature research	Eur J Clin Pharmacol

A big advantage of Donepezil, that guarantees its efficiency in the treatment of a neurodegenerative disease, is its good penetration through the blood-brain barrier, indicating a wide peripheral distribution, arriving in the brain in a concentration about 6 to 7 times bigger than plasma's. For this reason, Donepezil is considered an inhibitor of central action (Forlenza 2015; Persson *et al*., 2009). According to Noetzli *et al* (2015), so the Donepezil can work its inhibitory effect on the acetylcholinesterase's enzyme, it tends to accommodate in the enzyme's active site through an extended conformation. It's observed that the main intermolecular interactions that have as a goal guaranteeing the drug's through the enzyme, are done with amino acids TRP 279 and TRP 84. The inhibitor drugs of cholinesterase (IChE) are the main drugs approved for the specific treatment of AD. Its use bases itself in the increase of acetylcholine synaptic's disponibility, through the inhibition of enzymes acetylcholinesterase and butyrylcholinesterase (BChE) (Lima, 2014; Neotzli, 2015).

The drug Donepezil that belongs to the reversible inhibitors of acetylcholinesterase, has the drug Donepezil Belonging to the reversible acetylcholinesterase inhibitors, has as a purpose inhibit the acetylcholine's hydrolysis (Cutuli *et al*., 2013), avoiding its inactivation and increasing the levels of this neurotransmitter in the synaptic cleft in frontal regions of the brain (MOLINO *et al*., 2013) with the goal of compensating the cholinergic deficit typical of Alzheimer's Disease (Noetzli *et al*., 2015). Viegas *et al*., (2015) e Coin (2016), support that the adverse effects of Donepezil can be classified in relation with its incidence rank, in more common, less common, rare and unknown incidence. Like every other medication the Donepezil also presents side effects, that at first are related to the intensification of the cholinergic transmission provided by its action mechanism.

Within the side effects associated with Donepezil on clinical trials, nausea, vomit, dyspepsia, anorexia, weight loss, diarrhea and abdominal pain stand out. It's important to put emphasis that these side effects are dose-dependent and of transitional character, with the possibility of being reduced with the administration during the meals and reduction of the dose. (CUNHA *et al*., 2016; VIEGAS *et al*., 2014).

II) Cognitive domains separated in the standard evaluation tools on patients with AD in treatment with the drug Donepezil: On a study performed by Persson *et al*. (2009), it was possible to characterize cognitively, a group of patients as not-advanced in AD. In the same study it was realized that the analysis of homogeneity of MMSE and ADAS-Cog take to understand that: the items are reasonably homogenic, which limits the chance to identify cognitive profiles of individuals based on these indexes. The instruments, MMSE particularly, function better for groups that are more advanced in its cognitive reduction of the current group that was in the study. According to Rockwood (2007), it can be proposed definitions of fast cognitive decline in patient with Alzheimer's Disease having as a base the Assessment Scale-Cognitive subscale (ADAS-Cog), although, these measurements are not always correlated to the clinical decline obtained through other instruments, thus, it's interesting to build indexes of separated cognitive declines instead of summarizers. With what has been exposed, Soto (2015) believes that the best criteria's can be established, for example, for "fast declines".

Relation between the concentrations of Donepezil and activity of CYP2D6 and CYP3A4 on elderly patient with Alzheimer's Disease: The Donepezil is metabolized in the liver, specially by the isoenzymes CYP450 2D6 and 3A4, responsible for the metabolism of many other drugs, which

could indicate a great potential for the occurrence of clinically relevant drug interactions. However, studies reveal low drug affinity for such enzymes. It's estimated that the level of plasmatic concentration obtained therapeutically for the Donepezil can be 280 times smaller than the minimum inhibitory concentration for CYP450 2D6. What can be 800 times smaller when compared to the CYP450 3A4 (Neotzli *et al*., 2015). This fact is significant in the clinical practice, considering that the low affinity of Donepezil by CYP450 2D6 and 3A4 minimizes the possibility of occurrence of a vast list of drug interactions with the classes of drugs metabolized by both enzymes (Persson *et al*., 2009). Studies affirm that the administration of Donepezil can be done with safety on elderly with cardiovascular comorbidities, as long as some precautions are taken, including electrocardiographic monitoring (basal and in every increase of dose), of the blood pressure and attention to the possible drug interactions, of which can occur, for example, with drugs with negative chronotropic effect (bradycardia), hypertension and hypotension. So, the Donepezil has been chosen as first drug choice in the treatment of patients with Alzheimer's Disease, by virtue of its pharmacokinetics profile and its smaller toxicity in comparison to the other inhibitors of acetylcholinesterase (Cunha *et al*., 2016; Viegas *et al*., 2015).

Higher concentration of Donepezil and long-term memory in patients with light and advanced stage of AD: The main goal of the AD's treatment with Donepezil consists on providing the stabilization of the cognitive commitment, of the behavior and achievement of the daily-life routine (or modify the disease's manifestations), with a minimum amount of adverse effects. The use of the adequate dosage of the referred drug entails in the reduction of the disease's progression and improvement of memory and attention (BRASIL, 2013). Some systematic reviews reveal that there is no difference in the efficiency between the three most used drugs in treatment of AD, so it is possible the substitution of it according to the patient's tolerance (BRASIL, 2013; BRASIL, 2014). The adequate use of Donepezil consists in the prescription of pills of 5 and 10 mg, of which must be initiated with 5 mg/day orally. According with the level of AD, this dose can be increased to 10 mg/day after 4-6 weeks, and it must be taken by the patient when lying down, however, it's worth mentioning that a high concentration of this drug can cause nausea, vomit, diarrhea, anorexia and muscular weakness (KNOPMAN, 2012). Recently, it was observed in some studies that the stabilization of the cognitive stabilization starts appearing only after the thirtieth week of use of the anticholinesterases of second generation (Palmer, 2012). Though with advantages, it is still debatable if this group is effectiveness in interfering with the disease's progression, once this effectiveness can be quite modest or even nonexistent for a minority of patients (Ramos & Montano, 2011).

Conclusion

Still having found a lot regarding Alzheimer's Disease in the past few years many studies have found themselves on an advanced stage about the pathogenesis of the referred disease, there is still much to comprehend in a precise manner regarding its mechanisms of instauration, development and risk factors, whether they are genetic or environmental. The role of the cholinergic system in cognition and identification of cholinergic deficits in the Alzheimer's Disease has allowed the development of drugs that restored the cholinergic function, such as Donepezil, that consists on being an inhibitor of acetylcholinesterase in the central action that acts, specially with the means to increase the intrasynaptic disponibility of acetylcholine, resulting in the decrease of the cognitive, functional and behavioral symptoms of Alzheimer's Disease. The Donepezil is considered a first-line treatment for light and moderated, for presenting good and few side effects. tolerability, ease of administration. However, despite its positive characteristics, the pharmacotherapy with Donepezil is insufficient in providing the cure for Alzheimer's Disease, showing us that there is still much to be done in the camp of development of new drugs that are as safe as Donepezil, but that in the other hand have a bigger effectiveness in the control of the disease's progression.

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