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Cardiovascular effects of cholinesterase inhibitors for the treatment of elderly patients with dementia

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Marina Mamede Pozo
Neurologist, title of specialist by AMB, Professor and advisor of the Union of Colleges of the Great Lakes, sub-specialized in neuromuscular diseases.
E-mail: dramarinamamedepozo@hotmail.com

Claudio Humberto Diogo Jorge
Fellow in Clinical Arrhythmia
Specialist in Cardiology by SBC
Faculty of Medicine, University of São Paulo
Faculty of Medicine of São José do Rio Preto
E-mail: dr.claudiojorge@hotmail.com

Anna beatriz Oliveira Teixeira
Training area:
graduating in medicine from UNILAGO (Union of Colleges of the Great Lakes).
Current institution: UNILAGO (Union of Colleges of the Great Lakes).
E-mail: anna_beatriz.t@hotmail.com

Livia Mazzi Jorge Racy
Higher academic background and area of training: MBA in sustainable construction from UNICID (Universidade Cidade de São Paulo).
Training area: Architecture and urbanism by MACKENZIE University.
Current institution: UNILAGO (Union of Colleges of the Great Lakes), undergraduate in medicine.
E-mail: limjracy@gmail.com

Bruna Natyele Marcon de Farias
Training area:
graduating in medicine from UNILAGO (Union of Colleges of the Great Lakes).
Current institution: UNILAGO (Union of Colleges of the Great Lakes).
E-mail: bruna.nmarcon@live.com

Fernanda Marins Assis Palma
Training area:
graduating in medicine from UNILAGO (Union of Colleges of the Great Lakes).
Current institution: UNILAGO (Union of Colleges of the Great Lakes).
E-mail: fernandamarins22@yahoo.com

Bruna Souza Carvalho
Training area: undergraduate student of the 12th period in medicine at UNILAGO (Union of Colleges of the Great Lakes).
Current institution: UNILAGO (Union of Colleges of the Great Lakes).
E-mail: brunascarvalho1999@gmail.com

Luiz Carlos Gomes da Rocha Junior
Training area: graduating from the 7th period in medicine at UNILAGO (Union of Great Lakes Colleges).
Current institution: UNILAGO (Union of Colleges of the Great Lakes).
E-mail: lc.juninho@live.com

ABSTRACT

Cholinesterase inhibitors are drugs used against hallucinations, providing high concentrations of the neurotransmitter acetylcholine, which will act by stimulating communication between cells and helping in the memory process, but which requires risk assessment for their use, especially cardiovascular risks . The objective was to highlight the cardiovascular effects resulting from the use of cholinesterase inhibitors as a treatment for elderly patients with dementia. This is a bibliographical research, of the integrative literature review type, carried out through research in the databases: Scientific Electronic Library Online, Medical Literature Analysis and Retrieval System Online and Latin American and Caribbean Literature in Health Sciences, through of Health Sciences Descriptors (DeCS): “Cholinesterase inhibitors”; “Dementia”; "Elderly"; “Cardiovascular System”, associated with the Boolean AND operator. A total of 6 documents were reached to compose the review. Among these cardiovascular risks, we mention: signs and symptoms of bradycardia, effects of blood pressure decay, postural hypotension and syncope, in addition to the development of other pathologies, such as: Stroke, Systemic Arterial Hypertension and Arrhythmias.

That is, there are several complications related to the Cardiovascular System, requiring constant evaluation of the patient and his health condition, adapting the therapy based on his previous history of pathologies, complaints and the evolution of his health status.

Keywords: Dementia, Elderly, Cholinesterase Inhibitors, Cardiovascular System.

1 INTRODUCTION

Considering the theory of demographic transition, there is a decrease in fertility and mortality rates and an increase in life expectancy. This increase in expectations generated an aging population and consequently, an increase in the rates of Chronic Non-Communicable Diseases (NCDs), since around 80% of the elderly public has at least one chronic disease (SANTOS; BESSA. XAVIER, 2020).

Among these NCDs, dementia stands out because it is the pathology of the nervous system of the neurodegenerative type, with higher mortality among the elderly, described as a mental syndrome that affects the full cognitive and memory functioning, causing forgetfulness, mental decline, aphasia, mood swings, agnosia, incontinences and several other signs and symptoms, which together trigger problems in social relations (SANTOS *et al*., 2020).

Therefore, these elderly require an adequate treatment, which includes drugs that have the function of increasing brain transmission, citing as an example cholinesterase inhibitors: Donepezil, Galantamine, Rivastigmine Quinazoline and Tacrine, focusing on the first three, being described by the Ministry of Health (MS) as the first line for the treatment of dementia and Alzheimer's (BRAZIL, 2010).

These cholinesterase inhibitors are drugs used in the face of alzheimer's disease, providing high concentrations of the neurotransmitter acetylcholine, which will act by stimulating communication between cells and assisting in the memory process (HAINES, 2020).

Despite the various benefits, it is valid to consider the complications and side effects of its use, being primarily related to the cholinergic system and cardiovascular effects, due to the destruction of acetylcholine in the heart, including: bradycardia, Systemic Arterial Hypertension (SAH), Arrhythmias, postural hypotension and syncope, thus requiring electrocardiographic monitoring, blood pressure monitoring, perception and listening to the signs and symptoms described by the elderly and constant analysis of the general health picture, to avoid the appearance of later complications (SRIVASTAVA; AHMAD; Khare, 2021).

Thereby This study aimed to highlight the cardiovascular effects resulting from the use of cholinesterase inhibitors as a treatment for elderly patients with dementia.

2 METHODOLOGY

The present work is a bibliographic research, of the integrative literature review type. This type of review is done through six stages, as described by Ercole, Melo and Alcoforado (2014), starting with

the definition of the theme and the problem question, followed by the choice of eligibility criteria, selection of documents, evaluation of materials, interpretation and discussion of results and presentation of the review.

As stipulated above, along with the theme, the definition of the problem question is carried out, this being: " What are the andcardiovascular findings of cholinesterase inhibitors in elderly people with dementia?", considering the PICo strategy, where (P): population; (I): intervention and (Co): context, being addressed and associated the issue in table 1.

Table 1 – PICo Strategy for defining the guiding question, 2022.

Population (P)	Elderly with dementia
Intervention (I)	Cardiovascular effects of cholinesterase inhibitors
Background (Co)	It refers to the scientific evidence identified on the cardiovascular effects of cholinesterase inhibitors in the elderly public with dementia.

Source: Own authorship, based on PICo, 2022.

To obtain the materials to be used, searches were performed in the following databases: *Scientific Electronic Library Online* (SciELO), *Medical Literature Analysis and Retrieval System Online* (MEDLINE) and Latin American and Caribbean Literature in Health Sciences (LILACS), the last two being via the Virtual Health Library (VHL), through the Health Sciences Descriptors (DeCS): "Cholinesterase Inhibitors"; "Dementia"; "Elderly"; "Cardiovascular System".

The search in the databases with the descriptors occurred in a associated with the Boolean operator *AND*, presenting the following crossover and search strategy: (Cholinesterase inhibitors) AND (Dementia) AND (Elderly) AND (Cardiovascular system).

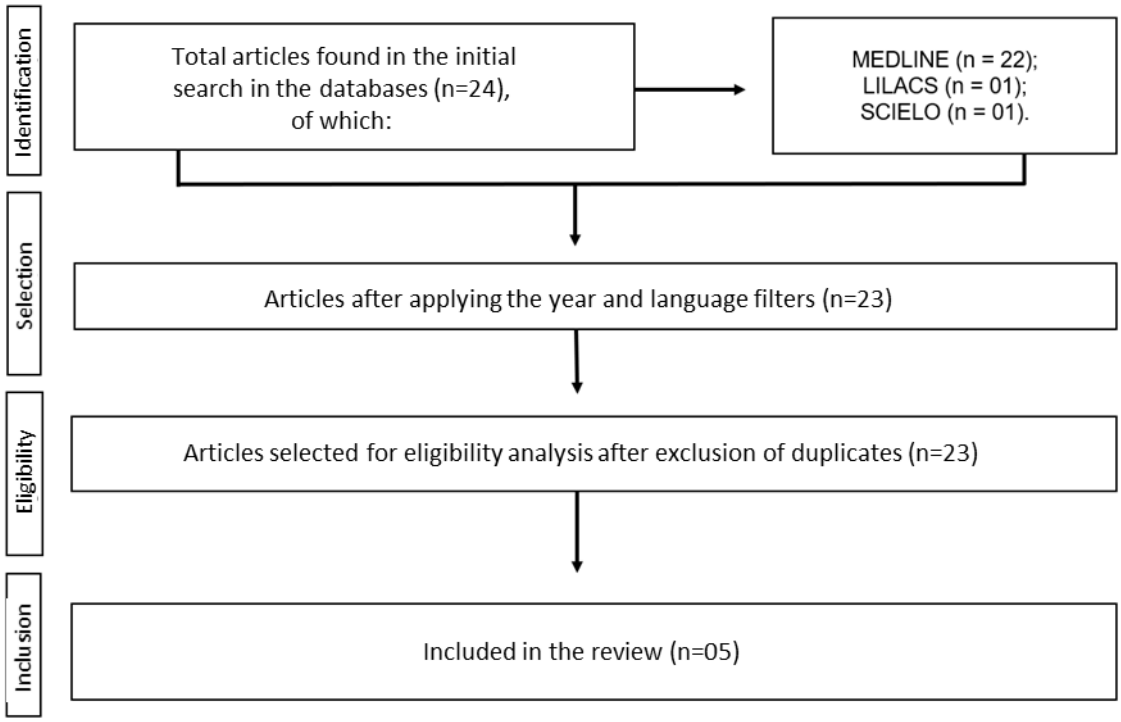
Following the order established for the creation of an integrative review, eligibility criteria should be selected, including the inclusion criteria and the exclusion criteria. Regarding the inclusion criteria, the following are mentioned: Works published in the Portuguese language, English or Spanish, from the last 10 years and that answered the problem question.

Regarding the exclusion criteria, materials that are not fully available, paid, will be disregarded, prior to the period of search and reviews published in annals of events.

3 RESULTS

After searching the databases, with the previously selected descriptors, the titles were carefully read initially, followed by the reading of the abstracts and finally, reading the complete materials, for the proper selection of those that would compose the present review, this whole process was exemplified in a flowchart, for better understanding (FIGURE 1).

Figure 1 – Flowchart of the search process, 2023.



Source: Own authors, 2023.

These five documents were organized in a table (CHART 2) to categorize the findings, presenting the author(s), year of publication, language of publication, database, journal and objective of the study.

Table 2 – Categorization of findings, 2023.

AUTHOR(S)	YEAR	LANGUAGE	DATABASE	PERIODIC	GOAL
Dias *et al.*	2013	English	Medline	Current Alzheimer Research	To evaluate the systemic actions that may affect the cardiovascular autonomic nervous system from treatment for dementia with cholinesterase inhibitors.
Kroger *et al.*	2015	English	Medline	Annals of Pharmacotherapy	To describe the adverse drug reactions (ADRs) induced by cholinesterase inhibitors (ChEI) in Alzheimer's disease and characterize their severity as reported by the national pharmacovigilance systems to VigiBase.
Pinheiro, Carvalho and Luppi	2013	Portuguese	Lilacs and Scielo	Brazilian Journal of Geriatrics and Gerontology	To investigate possible drug interactions in order to identify probable adverse events related to the pharmacotherapy of dementia syndromes.
Secnik *et al.*	2017	English	Medline	Diabetes Care	To investigate the differences in clinical features and

					pharmacological treatment associated with the presence of diabetes in a large cohort of patients with dementia.
Tan *et al.*	2018	English	Medline	Alzheimers Dement	To investigate the association between the use of acetylcholinesterase inhibitors (AChEI) and the risk of ischemic stroke and death in people with dementia.

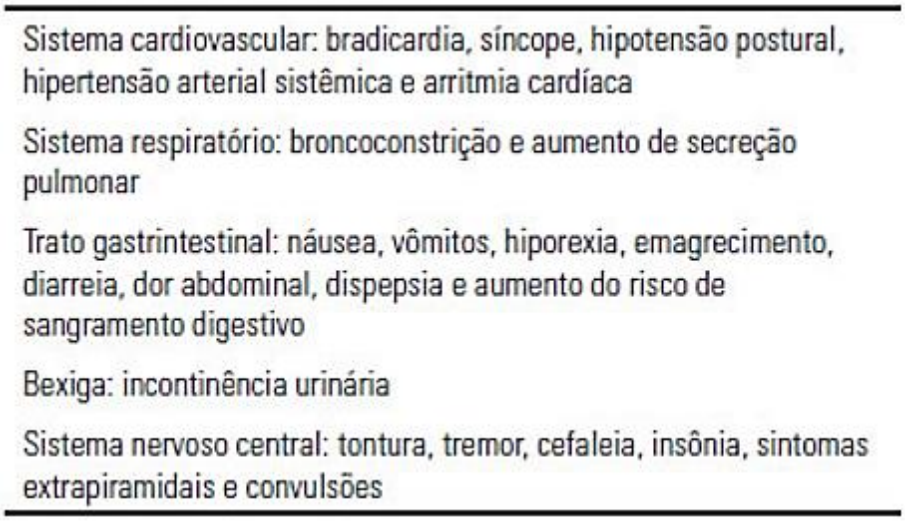
Source: Own authors, 2023.

Regarding the year of publication, the initial idea was to research in the last five years, to obtain more current results, however, it was necessary to increase the search period, since few studies addressing the theme were found. By increasing the period, this problem remained, with few studies on the subject in question, this means that it is scientifically relevant the development of new current studies on the subject.

4 DISCUSSION

Cholinesterase inhibitors are the prominent drugs in the treatment of Alzheimer's Disease and Dementia, however, despite their various benefits, it is necessary to evaluate the possible side effects arising from the use of these drugs, highlighting the gastrointestinal, cardiovascular, neurological and other general symptoms (PINTO *et al*., 2015)., as shown in Figure 1.

Figure 1 – Main side effects of cholinesterase inhibitors on the various organs and systems.



Source: Cunha *et al*. (2008)

The knowledge of these complications resulting from cholinesterase inhibitors allows the constant evaluation of the health status and the rational management for the decision to interrupt the therapies, based on the need and situation of each patient (PINTO *et al*., 2015).

Confirming this statement above, Tan *et al*. (2018) states that cholinesterase inhibitors are extremely effective in people with dementia, but that it may present an increased risk of brain and cardiovascular events, requiring evaluation and special attention to patients who already have some type of history of cardiovascular problem, that is, cardiovascular risk factors.

According to Bargagli *et al.* (2019, p. 2076), in relation to the elderly with dementia undergoing polypharmacy due to the treatment of the pathology:

> The following cardiovascular risk factors were considered, identified through hospital admissions in the 2 years prior to the date of enrollment: lipid metabolism disorders, hypertension, ischemic heart disease (including previous cardiac revascularization), heart failure, cerebrovascular diseases (including cerebrovascular revascularization).

In addition to the relevance of analyzing cardiovascular factors, Bargagli *et al*. (2019) also points to socioeconomic factors as something of prominence. This association of predictive factors of response to cholinesterase inhibitors is exemplified in the research of Miranda (2015), when pointing out that patients with socioeconomic problems tend to discontinue treatment, affecting the evolution of health status. With this, it is a factor considered by professionals, where the prescription is usually avoided in these cases (CALDAS *et al*., 2021).

Within the most commonly used medications, it is evident the Rivastigminaa and Donepezil (Kroger *et al*., 2015). The recommendation report of the Ministry of Health and the National Health Surveillance Agency (ANVISA), points out that Rivastigminaa can trigger sinoatrial or atrioventricular block in people with defects in their conduction, in addition to other general effects such as dehydration resulting from vomiting and diarrhea, in addition to weight loss (BRASIL, 2016).

Already the drug Donepezil, it is described as one of the main drugs for Alzheimer's disease, along with Galantamine, being the most effective without causing hepatotoxicity, unlike Tacrine, the first compound used in cases of dementia and Alzheimer's, but which was soon withdrawn from circulation due to its toxic side effects (SOUZA; SILVA; Smith, 2014). Figure 2 shows the differentiation between the characteristics of cholinesterase inhibitors available in the market.

Figure 2 – General characteristics of cholinesterase inhibitors.

	Tacrina	Donepezil	Rivastigmina	Galantamina
Disponível no ano	1993	1997	1998	2000
Classe química	Acridina	Piperidina	Carbamato	Alcalóide fenantreno
Seletividade cerebral	Não	Sim	Sim	Sim
Tipo de inibição da colinesterase	Reversível	Reversível	Pseudo-irreversível	Reversível
Modulação alostérica de receptor nicotínico	Não	Não	Não	Sim
Enzimas inibidas[1]	AchE BuChE	AChE	AchE BuChE	AChE

1 AchE: acetil-colinesterase; BuChE: butiril-colinesterase.

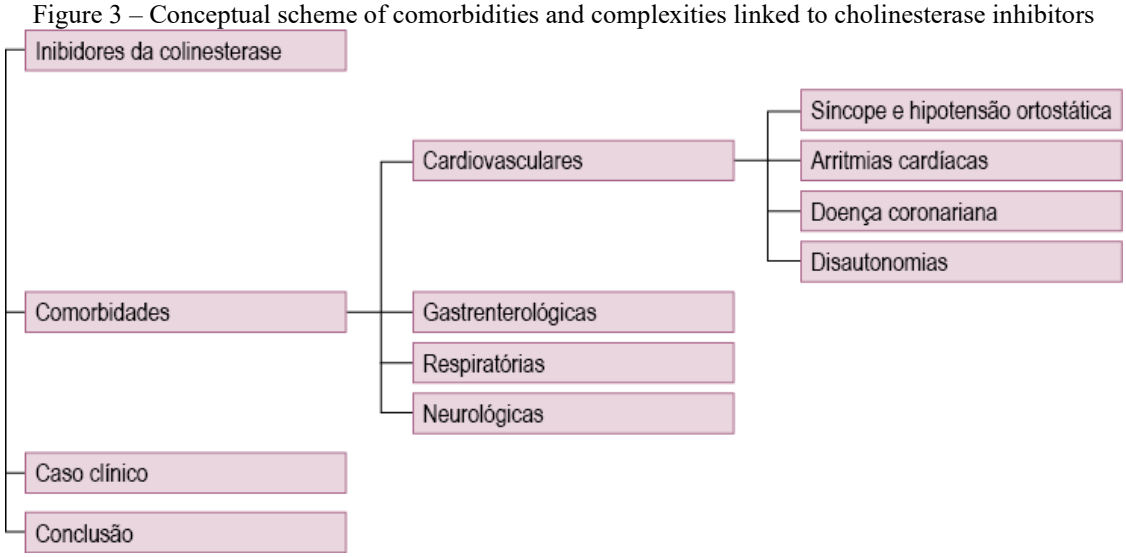
Source: Forlenza (2005)

That is, at the time of choosing the drug, the professional needs to have adequate knowledge about the inhibitors, thus reducing the possibility of triggering adverse effects during their use (MOHSIN; AHMAD, 2020).

In general, considering the adverse reactions to the use of medications, neuropsychiatric disorders were the ones that reported the greatest adverse effects and in relation to severity, cardiovascular complications were considered the most serious. Considering that the elderly patient with dementia is a patient who has high frailty due to several factors, such as age, pathology and frequent use of medications, the importance of assessing the cardiovascular risks associated with the use of medications (KROGER is confirmed. *et al*., 2015).

The main side effects related to the cardiovascular system were: bradycardia, postural hypotension, syncope (SRIVASTAVA; AHMAD; Khare, 2021), reduction in blood pressure (DIAS *et al*., 2013) and the development of other pathologies such as Systemic Arterial Hypertension (SAH) by cerebral mechanism, Arrhythmias (SRIVASTAVA; AHMAD; KHARE, 2021) and Stroke or Stroke (BARGAGLI *et al*., 2019), visualizing some of these factors in Figure 3.

Figure 3 – Conceptual scheme of comorbidities and complexities linked to cholinesterase inhibitors



Source: Barbosa *et al*. (2013)

In contrast to these findings, some authors refer to different results, such as the reduction of the risk for the development of Stroke, however, the author states that to occur this reduction, it is necessary more than 1 daily dose, about 1.33, a factor that can exacerbate the risk for other problems (NHS *et al*., 2018)

Another factor presented differently is blood pressure, the author above described hypertension, that is, increased pressure. Already for Days *et al*. (2013), the use of inhibitors provides a considerable reduction in blood pressure, especially in the orthostatic one.

Understanding such complexity, Days *et al*. (2013) conducted a study with 39 patients with Alzheimer's and Dementia, where they underwent evaluation with Electrocardiogram (ECG) and Spectral Analysis of Heart Rate Variability (HRV) through Holter recording, before and after the introduction of cholinesterase inhibitors.

Thus, it is perceived that there are several cardiovascular complications and that they differ among the authors, requiring more studies on the given theme, also considering the costly costs of including this therapy in the daily lives of patients, since they will need constant monitoring of their health status and the performance of this medication (PINHEIRO; OAK; LUPPI, 2013; SENIK *et al*., 2017).

5 CONCLUSION

It was possible to conclude that cholinesterase inhibitors are classified as efficient drugs in the face of situations of patients diagnosed with dementia or Alzheimer's disease, however, their use requires risk assessment, especially cardiovascular risks, due to their such complexity.

Among these cardiovascular risks, the following are mentioned: signs and symptoms of bradycardia, effects of blood pressure decay, postural hypotension and syncope, in addition to the development of other pathologies, such as: Stroke, Systemic Arterial Hypertension and Arrhythmias. That is, there are several complications related to the Cardiovascular System, requiring constant evaluation of the patient and his health condition, adapting the therapy based on his previous history of pathologies, complaints and the evolution of health status.

Among the limitations experienced when writing the work, we highlight the absence of studies that addressed the selected theme, where it was necessary to broaden the search For the last 10 years and even so, few materials were obtained, mainly in the Portuguese language. This highlights the need for the development of new research, confirming its justification in the scientific aspect.

REFERENCES

BARGAGLI, Anna Maria *et al*. Determinants of antipsychotic drugs prescription among community-living older adults with dementia: a population-based study using health information systems in the Lazio Region, Italy. Clinical Interventions in Aging, v. 14, p. 2071-2083, 2019.

BARBOSA, Maira Tonidandel *et al*. Uso de inibidores da colinesterase para o tratamento de demência em idosos com comorbidades clínicas. Secad Artmed, 2013.

BRASIL. Ministério da Saúde. Secretaria de Atenção à Saúde. Portaria nº 491, de 23 de setembro de 2010. Brasília: Ministério da Saúde, 2010.

BRASIL. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Rivastigminaa via transdérmica (adesivo) para o tratamento de pacientes com demência leve e moderadamente grave do tipo Alzheimer - Relatório de recomendação. Brasília: Ministério da Saúde, 2016.

CALDAS, Geovanna Renaissa Ferreira Caldas *et al*. Determinantes e condicionantes da saúde x patologias. Research, Society and Development, Vargem Grande Paulista, v. 10, n. 11, p. 1-8, 2021.

CUNHA, Ulisses Gabriel de Vasconcelos *et al*. Uso de inibidores da colinesterase em idosos com comorbidade clínicas. Geriatria & Gerontologia, v. 2, n. 4, p. 162-166, 2008.

DIAS, Filipi Leles da Costa *et al*. Cholinesterase inhibitors modulate autonomic function in patients with Alzheimer's disease and mixed dementia. Current Alzheimer Research, v. 10, n. 5, p. 476-481, 2013.

FORLENZA, Orestes V. Tratamento farmacológico da doença de Alzheimer. Archives of Clinical Psychiatry (São Paulo), v. 32, n.3, p. 137-148, 2005.

HAINES, Paul. Estudo abrangente avalia o uso de inibidores da colinesterase. Neurodiem, 30 jul. 2020.

KROGER, Edeltraut *et al*. Adverse drug reactions reported with cholinesterase inhibitors: an analysis of 16 years of individual case safety reports from VigiBase. Annals of Pharmacotherapy, v. 49, n. 11, p. 1197-1206, 2015.

MIRANDA, Luís Felipe José Ravic de. Fatores preditivos de resposta aos inibidores da colinesterase, dosagem da concentração plasmática de Donepezilaa e avaliação farmacogenética em pacientes com Doença de Alzheimer e Demência mista: estudo naturalístico. 2015. 212 f. Tese (Doutorado em Ciências Clínicas) – Faculdade de Medicina da Universidade Federal de Minas Gerais, Belo Horizonte, 2015.

MONSIN, Noor ul Amin; AHMAD, Matloob. Donepezila: A review of the recent structural modifications and their impact on anti-Alzheimer activity. Brazilian Journal of Pharmaceutical Sciences, v. 56, n. 18325, p. 1-16, 2020.

PINHEIRO, Juliana Souza; CARVALHO, Maristela Ferreira Catão; LUPPI, Graziela. Interação medicamentosa e a farmacoterapia de pacientes geriátricos com síndromes demenciais. Revista Brasileira de Geriatria e Gerontologia, v. 16, n. 2, p. 303-314, 2013.

PINTO, Renato Sousa *et al*. Doença de Alzheimer: Abordagem farmacoterapêutica. Boletim Informativo Geum, Piauí, v. 6, n. 1, p. 16-25, jan./mar., 2015.

SANTOS, Camila de Souza dos; BESSA, Thaíssa Araujo de; XAVIER, André Junqueira. Fatores associados à demência em idosos. Ciência & Saúde Coletiva, v. 25, n. 2, p. 603-611, 2020.

SANTOS, Adriene Roberta Costa dos *et al*. Produção científica sobre o idoso com demência na atenção primária à saúde. Research, Society and Development, v. 9, n. 10, p. 1-16, 2020.

SECNIK, Juraj *et al*. Diabetes in a large dementia cohort: clinical characteristics and treatment from the Swedish dementia registry. Diabetes care, v. 40, n. 9, p. 1159-1166, 2017.

SOUZA, Neliane Duarte de; SILVA, Cristiane Rodrigues da; SILVA, Vinicius Barreto da. Donepezila no tratamento da doença de Alzheimer. Estudos, Goiânia, v. 41, n. 4, p. 755-766, out./dez. 2014.

SRIVASTAVA, Sukriti; AHMAD, Razi; KHARE, Sunil Kumar. Alzheimer's disease and its treatment by different approaches: A review. European Journal of Medicinal Chemistry, v. 216, p. 113-120, 2021.

TAN, Edwin CK *et al*. Acetylcholinesterase inhibitors and risk of stroke and death in people with dementia. Alzheimer's & Dementia, v. 14, n. 7, p. 944-951, 2018.