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CARDIOVASCULAR EFFECTS OF CHOLINESTERASE INHIBITORS FOR THE TREATMENT OF ELDERLY PATIENTS WITH DEMENTIA

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ABSTRACT:
Objective: The study aimed to raise awareness of the potential cardiovascular hazards associated with cholinesterase inhibitor therapy in elderly dementia patients.
Background: Cholinesterase inhibitors, which increase levels of the neurotransmitter acetylcholine, are commonly used to treat Alzheimer's disease. These medications aid memory and promote cell-to-cell contact, but they also pose significant cardiac-related risks.
Methods: A bibliographic search utilizing the Boolean operator AND was conducted as part of an integrative literature review. Databases searched included Cholesterol Inhibitors, Dementia, Older people, and the cardiovascular system; an Online Scientific Electronic Library; and an Online Medical Literature Analysis and Retrieval System (MEDLINE).
Results: Six papers were identified and reviewed. The findings highlighted various cardiovascular issues linked to cholinesterase inhibitor use, including arrhythmias, stroke, systemic arterial hypertension, syncope, postural hypotension, and bradycardia.
Conclusions: The review underscores the necessity for continuous evaluation of patients undergoing cholinesterase inhibitor therapy. Adjustments in treatment should be made considering the patient's medical history, current health status, and evolving conditions to mitigate cardiovascular risks.

KEYWORDS: Dementia; Cardiovascular System; Cholinesterase Inhibitors; Neurology; Elderly.

INTRODUCTION:

The demographic transition theory states that fertility and mortality rates decrease as life expectancy increases. This increase in expectations has led to an aging population and an increase in the incidence of chronic non-communicable illnesses (NCDs), as 80% of the elderly population has a minimum of one chronic ailment. Dementia stands out among these non-communicable disorders in particular. Full cognitive and cognitive function is affected by this neurodegenerative nervous system disorder, which leads to a lack of memory, cognitive impairment, aphasia, fluctuating emotions, agnosia, incontinence, and a host of additional signs and symptoms that combined produce problems in social connections (Havreng-Théry et al., 2024; Shahim et al., 2024). Dementia also has a higher mortality rate among the elderly. As a result, these elderly patients require proper care, which may involve medications that increase brain transmission. Cholinesterase inhibitors are one example; the Ministry of Health currently describes donepezil, galantamine, rivastigmine, quinazoline, and tacrine. The primary line of treatment for dementia and Alzheimer's disease is health (MS). These anti-Alzheimer medications, known as cholinesterase inhibitors, deliver high amounts of the neurotransmitter acetylcholine, which promotes cell-to-cell contact and aids in memory formation. Despite the many advantages, it is important to consider the risks and adverse effects of using it (Nham et al., 2024; Zhang, Sun, Hu, Yao, & Wang, 2024). These are primarily related to the cholinergic system and cardiovascular effects because of the destruction of acetylcholine in the heart. Bradycardia, systemic arterial hypertension (SAH), arrhythmias, postural hypotension, and syncope are just a few of the symptoms that can occur.

Table 1: Demographic Transition and Aging Population

Aspect	Description	Reference
Demographic Transition Theory	States that fertility and mortality rates decrease as life expectancy increases, leading to an aging population and increased incidence of chronic non-communicable diseases (NCDs).	Havreng-Théry et al., 2024; Shahim et al., 2024
Chronic Ailments in the Elderly	80% of the elderly population has at least one chronic ailment.	Havreng-Théry et al., 2024; Shahim et al., 2024
Prevalence of Dementia	Dementia affects memory, cognition, emotions, and social connections, and leads to various symptoms.	Havreng-Théry et al., 2024; Shahim et al., 2024

Table 2: Treatment of Dementia and Alzheimer's Disease

Aspect	Description	Reference
Primary Treatment	Health interventions are primary for dementia and Alzheimer's disease.	Nham et al., 2024; Zhang et al., 2024
Cholinesterase Inhibitors	Medications include donepezil, galantamine, rivastigmine, quinazoline, and tacrine, which increase acetylcholine transmission and aid in memory formation.	Nham et al., 2024; Zhang et al., 2024

Table 3: Risks and Adverse Effects of Cholinesterase Inhibitors

Aspect	Description	Reference
Cholinergic System Effects	Destruction of acetylcholine in the heart leads to various cardiovascular symptoms.	Elhalag et al., 2024; Huang et al., 2024
Cardiovascular Complications	Symptoms include bradycardia, systemic arterial hypertension (SAH), arrhythmias, postural hypotension, and syncope.	Elhalag et al., 2024; Huang et al., 2024
Prevention and Monitoring	Requires electrocardiograms, blood pressure checks, awareness of symptoms, and ongoing evaluation of health conditions.	Elhalag et al., 2024; Huang et al., 2024

To prevent these complications, electrocardiograms, blood pressure checks, awareness of and attentive listening to elderly patients' signs and symptoms, and ongoing evaluation of overall health

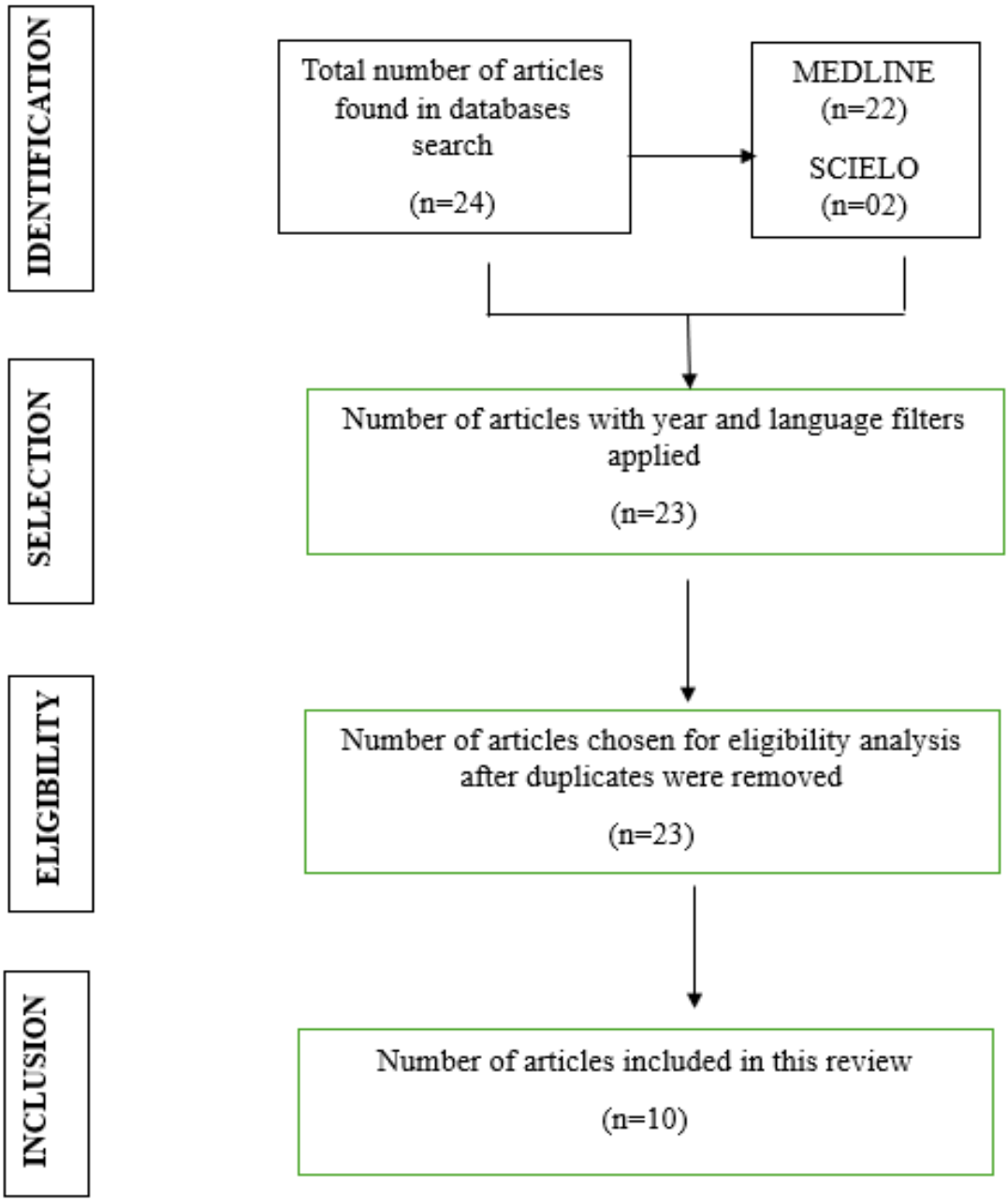
conditions are necessary. This drew attention to the cardiovascular implications of treating senior dementia patients with cholinesterase inhibitors (Elhalag et al., 2024; Huang, Meir, Frishman, & Aronow, 2024).

METHODOLOGY: This work is an integrative literature review-style bibliographic investigation. This review involves six stages, as Ercole, Melo, and Alcoforado outlined. These stages include defining the theme and the problematic question, selecting documents, evaluating materials, interpreting and discussing the findings, and presenting the review (Yilmaz, 2024).
The following definition of the problematic question and topic is provided: what are the cardiovascular consequences of drugs that inhibit cholinesterase in elderly individuals having dementia?" Taking into account the PICo approach, which is discussed and connected to the problem in Table 1 and where (P) refers to population, (I) represents intervention, and (Co) represents context (Szilcz et al., 2024; N. Zhang et al., 2024).

Population (P)	Seniors suffering from dementia
Intervention (I)	Cholinesterase inhibitors' impact on the cardiovascular system
Context (Co)	Discusses the scientific data about cholinesterase inhibitors' impact on the circulatory system in senior dementia patients.

PICo's technique for defining the driving question is shown in Table 1.
To locate the required materials, the subsequent databases were searched: Medical Material Analysis and Retrieval System Online (MEDLINE), Scientific Electronic Library Online (SciELO), and the latter two via the Virtual Health Library (VHL) utilizing the Health Sciences Descriptors (DeCS): "Cholesterol inhibitors," "Memory loss," "Elderly," along with "Cardiovascular system." The databases holding the descriptors were searched using the subsequent crossing and search method, which made use of the Boolean operator AND: (Cholinesterase inhibitors) AND (Cardiovascular system) AND (Dementia) AND (Elderly) (Carotenuto, Andreone, Amenta, & Traini, 2024; Zuliani et al., 2024).
The inclusion, exclusion, and eligibility criteria must be chosen to generate an integrative review. The following are mentioned about the inclusion criteria works from the past ten years that addressed the difficult subject and were published in English. In terms of the exclusion criteria, reviews published in event annals and materials that are not completely available or paid for before the study period will not be considered (Ip et al., 2024; Possemis, Verhey, Prickaerts, Blokland, & Ramakers, 2024).

RESULTS:
Following a search in the databases using the pre-selected descriptors, a thorough examination of the titles was done first. The abstracts were read, and lastly, the full materials were read to ensure that an appropriate selection of those that would comprise for the sake of better comprehension, the full review process is represented in a flowchart (FIGURE 1) (Talwar et al., 2024; Toribio-Fernandez et al., 2024).



The research process flowchart is shown in Figure 1.

To categorize the results, these five documents have been arranged in a table (TABLE 2) that includes the publication year, author(s), database, and work purpose (Deblier, Dossche, Vanermen, & Mistiaen, 2024).

AUTHOR(S)	DATABASE	YEAR	PERIODIC	GOAL
Secnik et al.	Medline	2017	Diabetes Care	This study aims to examine the variations in clinical traits and pharmacological interventions linked to diabetes in a sizable group of dementia patients.
Dias et al.	Medline	2013	Current Studies on Alzheimer's	To assess the potential systemic effects of Alzheimer's inhibitor-treated dementia on the cardiovascular autonomic nervous system.

				Cholinesterase.
Pinheiro, Carvalho e Luppi	Scielo	2013	The Journal of Geriatrics and Gerontology	Examine potential drug interactions to determine the most likely side effects associated with the pharmacotherapy of dementia disorders.
Kroger et al.	Medline	2015	Annals of Pharmacotherapy	Using data from national pharmacovigilance systems, explain the harmful effects of drugs caused by cholinesterase inhibitors (ChEI) in Alzheimer's disorder and assess their seriousness.
Tan et al.	Medline	2018	Alzheimer's Disease	Examine whether using acetylcholinesterase inhibitors (AChEI) increases a person's chance of having an ischemic stroke or dying from dementia.

Results are categorized in Table 2.

Nevertheless, since only a few studies addressing the subject were found, it was imperative to extend the search period. The persistence of this issue over time and the paucity of studies on it make the development of new, current studies on the topic scientifically relevant (Arjmandi-Rad, Vestergaard Nieland, Goozee, & Vaseghi, 2024; Reuben, Kremen, & Maust).

DISCUSSION:

The most crucial drugs for treating dementia and Alzheimer's disease are cholinesterase inhibitors. Despite the many benefits they offer, it is crucial to evaluate the possible negative consequences that could result from using these drugs, with particular attention to unfavorable effects on the nervous system, gastrointestinal tract, heart, and other general symptoms, as shown in Figure 1 (Joseph, Cameron-Carter, & Akinyemi, 2024; Park, Choi, Jang, Kim, & Ham, 2024).

DRUG	SIDE EFFECTS
Tacrine	Nausea, vomiting, diarrhea, dyspepsia, myalgia, anorexia, dizziness, confusion, insomnia, rare agranulocytosis, reversible hepatotoxicity manifested by elevated transaminases
Donepezil	Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia, dizziness, abdominal pain, myasthenia, rhinitis, weight loss, anxiety, syncope
Rivastigmine	Nausea, vomiting, anorexia, dizziness, abdominal pain, diarrhea, malaise, fatigue, asthenia, headache, sweating, weight loss, somnolence, syncope. Rarely, severe vomiting with esophageal rupture
Galantamine	Nausea, vomiting, diarrhea, anorexia, weight loss, abdominal pain, dizziness, tremor, syncope

According to Yaari et al. 2008

The primary adverse effects of cholinesterase inhibitors on many organs and systems are shown in Figure 1.

Understanding these cholinesterase inhibitor-related side effects enables ongoing health assessment and well-reasoned decision-making regarding therapy discontinuation, depending on the requirements and circumstances of each patient. Tan et al. confirm the above statement by stating that although cholinesterase inhibitors are very effective in treating dementia, they may also increase the risk of cerebral and cardiovascular events. As such, patients who already have a history of cardiovascular problems or cardiovascular risk factors should receive extra evaluation and care (Joshi, Patel, & Gopalakrishnan, 2024; Khalid, 2024).

The following cardiovascular risk factors, which were identified through hospital admissions in the two years before the enrollment date, were taken into consideration: the breakdown of lipids

disorders, elevated blood pressure, an ischemic cardiovascular disease (which includes prior cardiac revascularization), heart failure, and cerebral artery disease (such as cerebrovascular revascularization). Bargagli et al. discusses older adults with dementia who have undergone polypharmacy for the treatment of the pathology. In addition to analyzing cardiovascular parameters, Bargagli et al. stress the importance of socioeconomic determinants (Gajendra, Pratap, Poornima, Shantaram, & Ranjita, 2024; Odenigbo et al., 2024).

Miranda's research demonstrates the correlation between elements that predict a patient's reaction to cholinesterase inhibitors and the tendency for patients with socioeconomic problems to stop their therapy, which can have an impact on how their health condition changes over time. Professionals consider this, and in most cases, the prescription is avoided. Two medications that are frequently utilized include donepezil and rivastigmine. The National Health Surveillance Agency (ANVISA) and Ministry of Health's recommendation report emphasize that rivastigmine can cause atrioventricular block or sinoatrial block in individuals with conduction defects, in addition to other side effects like weight loss and dehydration from vomiting and diarrhea (Liu et al., 2024; Nematillayevna & Temirpulotovich, 2024; Riemma et al.).

In contrast to tacrine, which was originally used for Alzheimer's and dementia but swiftly removed due to its toxic adverse effects, donepezil is considered one of the primary medications for Alzheimer's disease, alongside galantamine. It is deemed the most productive without inducing hepatotoxicity. Figure 2 illustrates the differentiation of distinctive characteristics among marketed cholinesterase inhibitors (Crestini et al., 2024; Mok et al., 2024).

	Donepezil	Rivastigmine	Galantamine	Clinical Relevance
1. Elimination half-life (hr)	70–80	0.6–2*	7–8	Easier to switch from drug with shorter half-life
2. Metabolism	Liver	By AchE	Liver	Liver metabolism involves P450 system: potential for drug interaction
3. Protein binding	96%	40%	8%	Potential for interaction with drugs having high protein binding
4. Food interaction	No	Yes	No	Need to take the drug with meals if food interaction
5. Dosing	Once daily	Twice daily	Twice daily	Compliance issues
6. Pricing	2 Level	Flat rate	3 Level	Cost implications
7. BuChE inhibition	No	Yes	No	Unknown
8. Nicotinic modulation	No	No	Yes	Unknown
9. Specific AchE subtype inhibition	No	Yes	No	Unknown
10. Titration	1 Step	2–4 Steps	2–3 Steps	Complex titration may influence decisions in busy practices

* Enzyme inhibition significantly outlasts elimination half-life.

Note: BuChE = butyrylcholinesterase; AchE = acetylcholinesterase.

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Figure 2 - General features of cholinesterase inhibitors.

The general properties of cholinesterase inhibitors are shown in Figure 2.

In another way, the professional must select the medication with a sufficient understanding of the inhibitors to lower the risk of experiencing side effects when using it. When it comes to medication side effects, neuropsychiatric illnesses typically reported the worst consequences, while cardiovascular issues were thought to be the most significant in terms of severity. Given that the elderly patient who has dementia is highly vulnerable because of a variety of characteristics, including age, pathology, and frequent drug use, it is imperative to assess the cardiovascular risks associated with drug use (Agewall, 2024; Akhtar, Singh, Kaushik, Awasthi, & Behl, 2024).

Bradycardia, postural hypotension, syncope, blood pressure drops, and the emergence of additional pathologies, including cerebral arrhythmias, cerebral vascular accidents, and systemic artery hypertension (SAH), were the primary adverse effects linked to the cardiovascular system (ACVA) or cerebrovascular accident (CVA), figure 3 illustrates a few of these elements (Beigh et al., 2024).

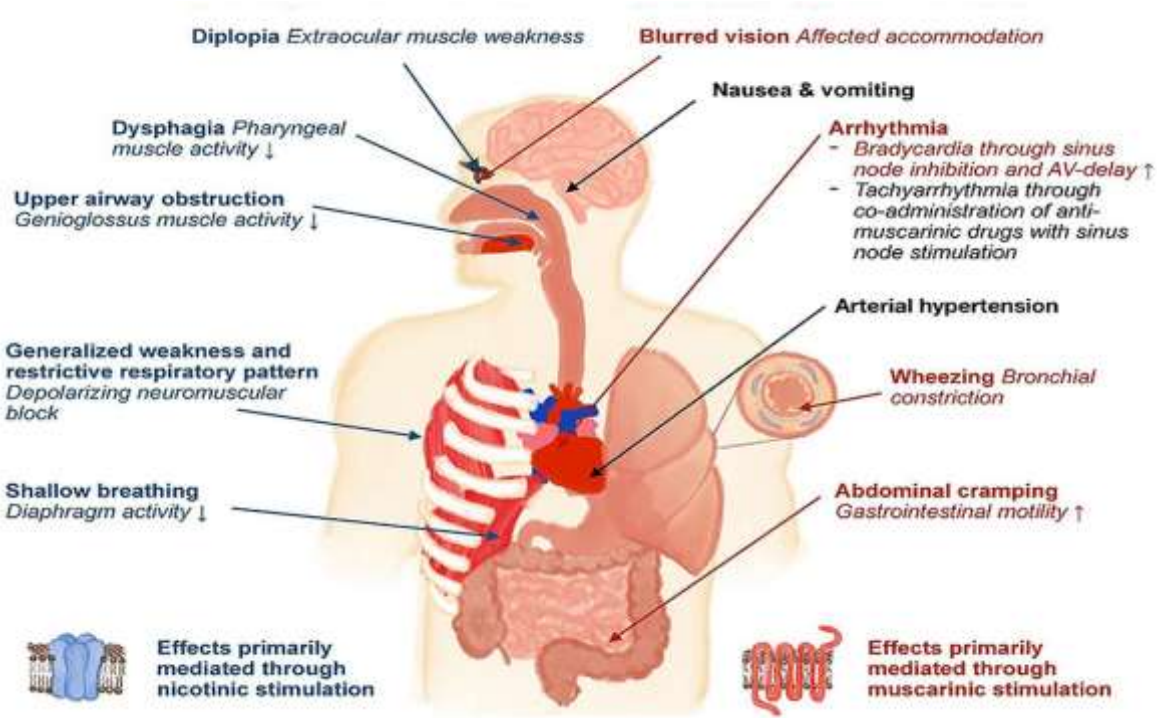

Figure 3 – Conceptual diagram of comorbidities and complexities related to cholinesterase inhibitors

Figure 3: Conceptual diagram of cholinesterase inhibitor-related comorbidities and complications

Some authors, however, report different results, such as reducing the risk of cerebrovascular accidents (CVA). The author claims that more than one daily dose of roughly 1.33 is required for this reduction, which may increase the risk of other issues. Blood pressure is another aspect that is given differently. The author previously discussed hypertension or elevated pressure. According to Dias et al., using inhibitors lowers blood pressure significantly, particularly orthostatic blood pressure. Considering this complexity, Dias et al. conducted a study involving 39 patients with dementia and Alzheimer's (Alageel, Hughes, Alwhaibi, Alkeridy, & Barry, 2024; Pinto, 2024).

Before and after introducing cholinesterase inhibitors, the patients underwent evaluation with an electrocardiogram (ECG) and spectral analysis of heart rate variability (HRV) using Holter recording. Therefore, it is evident that there are many different types of cardiovascular complications, which vary from author to author. This calls for more research on the subject and considers the high costs associated with incorporating this therapy into patients' daily lives, as it eliminates the need for constant health monitoring. Health circumstances and the medication's effectiveness (Fantuzzi, 2024; Muğlu et al., 2024; Riemma et al.).

CONCLUSION:

It was feasible to conclude that cholinesterase inhibitors are categorized as beneficial medications in cases when patients have been diagnosed with dementia or Alzheimer's disease; nonetheless, because of their complexity, their usage necessitates an evaluation of hazards, particularly cardiovascular risks. These cardiovascular concerns include bradycardia symptoms and indications, blood pressure lowering effects, syncope and postural hypotension, and the development of other diseases such as arrhythmias, stroke, and systemic arterial hypertension.

As stated differently, many cardiovascular-related difficulties necessitate ongoing assessment of the patient and his condition, with the therapy being modified to consider the patient's history of diseases, illnesses, and changes in his state of health. One of the primary challenges encountered in creating this study was the absence of studies on the selected issue; this required extending the investigation to the past ten years, and even then, only a limited number of materials, primarily in

Portuguese, could be found. This emphasizes the necessity of conducting additional studies to support its scientific basis.

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