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SCIENTIFIC EVIDENCE ON THE USE OF PROTON PUMP INHIBITORS AND RISK OF DEMENTIA

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Abstract: Proton Pump Inhibitors (PPIs) are among the most prescribed drugs worldwide, considered safe and effective, and are used to treat a range of diseases. Recent studies have associated its use with some adverse effects, including reports of dementia. Based on this, we sought to synthesize evidence obtained from research on the relationship between the use of PPIs and dementia. This is a systematic review in which scientific articles published in the Pubmed database, in the years 2022 and 2023 were selected. according to the recommended guidelines of PRISMA. A total of 25 articles were found, of which 9 met the selection criteria and are therefore included in this study. The studies found were heterogeneous in terms of results. Some authors found a higher risk of dementia associated with the use of PPIs, with no differences regarding subtypes. And among those who described an association, prolonged chronic use was more evident, with a possible cumulative effect. As possible proposed mechanisms, the interaction with the cholinergic pathway through the choline acetyl-transferase enzyme and interactions with the APOE ε4 genotype were raised. This systematic review corroborates updates on the use of PPIs found in the current literature, contributing to the establishment of personalized therapy for patients with dementia.

Keywords: Clinical Pharmacology, Proton Pump Inhibitors, Choline Acetyltransferase, Cognitive Decline, Adverse Effects.

INTRODUCTION

Proton Pump Inhibitors (PPIs) are among the most prescribed drugs worldwide, being considered safe and effective (BAIK; FUNG; MCDONALD, 2022). PPIs are used to treat Gastroesophageal Reflux Disease (GERD), Peptic Ulcer Disease (PUD) and Helicobacter pylori infections, and for the prophylaxis of stress-induced PUD and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (KIM, 2021). However, the frequent use of PPIs, whether through medical prescription or the ease of purchase in pharmacies, has drawn the attention of the scientific community to sporadic reports of possible side effects.

Recent studies have associated the use of PPIs with some adverse effects, such as an increased risk of osteoporosis-related fractures due to interference with the absorption of calcium and vitamin D, intestinal infections by Clostridium difficile, malabsorption of vitamins and minerals such as vitamin B12 and iron., in addition to reports of dementia (PERRY et al., 2020)

Dementia has been of particular relevance, as this is a syndrome of cognitive decline that affects around 50 million people globally, it is estimated that by the year 2050 it will affect approximately 131 million (PONJOAN et al., 2019). The increased prevalence of this syndrome worries patients and their families, in addition to increasing public health spending. Dementia, prevalent in elderly individuals, is the main cause of disability, affecting behavior, thinking and memory (AARSLAND, 2020).

The risk of developing dementia is associated with several factors such as age, gender and alcohol intake. However, some studies indicate that dementia may also be associated with the use of PPIs, but there is no consensus on this, as pointed out by the study by CHINZON et al. (2021), who report that such an adverse effect is a consequence of the low quality of scientific evidence, often resulting from observational and retrospective studies with heterogeneous samples. These studies generally represent low-quality evidence (CHINZON et al., 2022). Corroborating with Chinzon et al. (2022), (WANG; TIAN; YAN, 2022), suggest that PPIs do not increase the risk of dementia.

Thus, the purpose of this integrative review was to synthesize evidence obtained from research on the relationship between the use of Proton Pump Inhibitors (PPIs) and dementia, in a systematic, orderly and comprehensive manner, contributing to the deepening of knowledge on the subject.

METHODOLOGY

For the development of the work, a careful search was carried out for original scientific articles published in the PubMed databases, using the descriptors "proton pump inhibitors" and "dementia" combined through the Boolean AND operator, in accordance with the recommended guidelines of the PRISM.

As inclusion criteria, original studies were considered, which presented the descriptors in the title or abstract and written in English. Articles written in languages other than English were excluded, in addition to those whose title or abstract/abstract did not suit the proposed theme. Comments, books, literature reviews and articles unavailable for free access were also excluded. The survey of bibliographic data between 2022 and 2023 resulted in a total of 25 scientific articles. After extensive analyses, only 9 papers met all selection criteria and were included in this study, as shown in figure 1.

RESULTS

After using the inclusion and exclusion criteria, it was found that PubMed has 9 manuscripts that address the topic of using PPIs for dementia. The studies included in this review include: 01 experimental *in silico* study, 01 cross-sectional study, 01 nested case-control study and 06 prospective cohort studies. Tables 1 shows a summary description of the works included in this study, highlighting the type of study, place of execution and main findings.

OVERALL RISK FOR DEVELOPING DEMENTIA AND ITS SUBTYPES

AHN et al. (2022) showed that the use of PPIs increased the risk for developing dementia in up to 10 years, through a study with 2,698,176 people in Germany. Participants were classified according to their use of PPIs into two groups: users (n=674,544) and non-users (n=2,023,632), matched for the presence of comorbidities and risk factors for the disease. The first group included those using at least 56 defined daily doses (DDDs) of any inhibitor and consecutive use being defined if the participant repeated the treatment in less than 30 days. The diagnosis of dementia was confirmed by documenting one of the codes included in the International Classification of Diseases (ICD-10) related to the disease for at least two consecutive times. The authors identified 4.4% of cases of dementia among users and 1.3% among non-users, comparing the two groups after 01 year of use, which demonstrates a *hazard ratio* (HR) of 1.54 (95%; CI 1.51-1.58). In this study, it was not possible to analyze the risk of developing specific dementias, since many individuals were classified into different subtypes of dementia.

With regard to subtypes, the use of PPIs was associated with a higher risk of developing nonspecific dementia (ID), Alzheimer's disease (AD) and vascular dementia (DV), according to ZHANG et al. (2022). From 501,002 individuals with no previous diagnosis of dementia, the authors identified 53,735 participants using PPIs and 447,267 participants not using them. Diagnoses were confirmed through the presence of corresponding ICD-10 codes in hospital admission records and death certificates. At the end of the study, 2,505 cases of ID, 932 cases of AD and 524 cases of DV were identified. After adjusting for comorbidities, the HRs of the incidence of dementia for

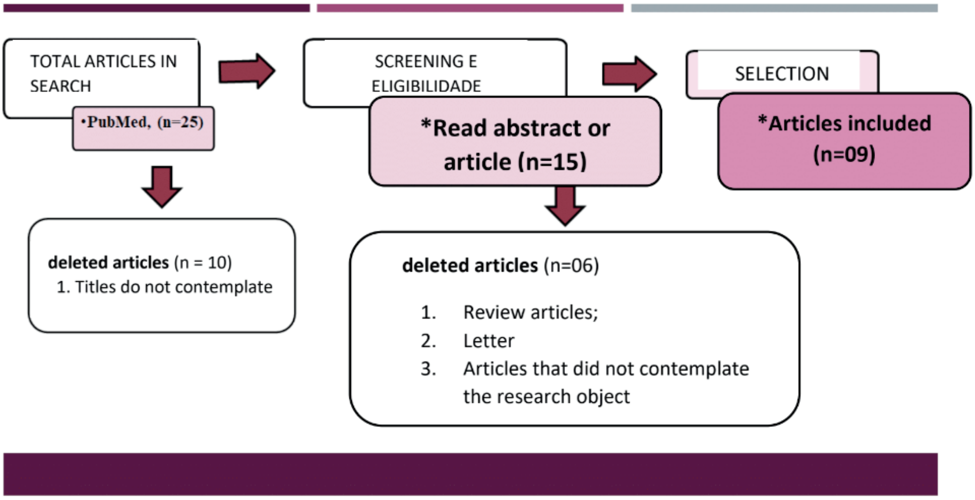

Figure 1: Bibliographic search evidence retrieval and selection diagram according to PRISMA guidelines.

Source: Own elaboration.

Title	Country	Sample/Study Method	Results	Reference
Mechanistic insight into the inhibition of choline acetyltransferase by proton pump inhibitors.	Índia	Experimental in silico study with PPI molecules and choline acetyltransferase (ChAT). It analyzes the mechanics of molecular interactions between PPIs and ChAT through molecular coupling and molecular dynamics simulators.	The PPIs showed an affinity equal to or greater than the classic ChAT inhibitor for the enzyme's catalytic site. The IBP-ChAT complexes remained stable over the simulation time, where the pyridine ring interacted mainly with the amino acid residue Hys324.	Baidya *et al.* (2023)
Signal and noise: Proton pump inhibitors and the risk of dementia?	Canadá	Prospective cohort study using data from the *Manitoba Population Research Data Repository*. It investigates, for up to 22 years, the risk of developing dementia due to the cumulative use of PPIs, in participants of different age groups and without a previous diagnosis of dementia.	Participants with long-term use of PPIs were not more likely to develop dementia than non-users after adjusting for comorbidities and other variables.	Friesen *et al.* (2023)
The effects of proton pump inhibitors on neuropsychological functioning.	EUA	Prospective cohort study with data from the *Wisconsin Registry for Alzheimer's Prevention Study*.Avalia for 12 years the neuropsychological function (working memory, verbal memory, psychomotor speed and cognitive flexibility) of participants with different patterns of PPI use, with or without the APOE ε4 genotype and without signs of previous cognitive decline.	No significant effects of the use of PPIs and their association with polymorphisms in the APOE ε4 gene on memory decline or psychomotor speed were found. Discontinuing the use of PPIs may be a protective factor for changes in cognitive flexibility among non-APOE ε4 carriers. H2 antagonists were also not associated with changes in any of the neuropsychological tests.	Collin *et al.* (2022)

Regular proton pump inhibitor use and incident dementia: Population-based cohort study.	China	Prospective cohort study with UK Biobank data. Compares the incidence of nonspecific dementia (ID), Alzheimer's disease (AD) and vascular dementia (DV) over 9 years in participants with or without PPI use and without a previous diagnosis of dementia. It also compares the influence of APOE ε4 genotypes among those using PPIs.	It is shown that the use of PPIs is associated with a higher risk for the development of the three types of dementia studied. The risk remained significant after adjusting for other comorbidities, especially VD. Using lansoprazole, female participants and heterozygous carriers of the APOE ε4 genotype had a higher incidence of DI.	Zhang *et al.* (2022)
Neuropsychological assessment after long-term omeprazole treatment.	Brasil	Cross-sectional study with 60 patients assisted by the health services of ''Universidade Feevale'', in Novo Hamburgo, Brazil.It is investigated cognitive alterations (memory, attention, executive functions) in participants without previous diagnoses of neurological or psychiatric disorders who make or do not make chronic use of omeprazole	Greater cognitive alterations were found in participants in chronic use of omeprazole in terms of selective attention, short-term episodic memory, verbal fluency and executive functions, especially inhibitory control. Such alterations were more expressive the longer the treatment time.	Haefliger *et al.* (2022)
Associations between proton pump inhibitors and Alzheimer's disease: A nested case-control study using a Korean nationwide health screening cohort.	Coréia do Sul	Nested case-control study with data from the Korean *National Health Insurance Service-Health Screening Cohort*. Verifies the probability of developing AD dependent on previous use of PPIs for 1 year before diagnosis, comparing diagnosed participants to a control group for sex, age, income and region.	Previous use, regardless of current exposure, duration of use or generation of PPIs used, increased the likelihood of developing AD, being more significant as time of use increased.	Choi *et al.* (2022)
Emulating a target trial of proton pump inhibitors and dementia risk using claims data.	Alemanha	Prospective cohort study with administrative data from a large state health insurer. Determines the 10-year risk of developing dementia in participants with or without PPI use and no previous diagnosis of dementia.	The use of PPIs increased the risk of developing dementia, even in cases of intermittent use. There was no divergence in risk between PPIs and H2 antagonists as well as difference for subtypes of dementia	Ahn *et al.* (2022)
Chronic omeprazole use in the elderly is associated with decreased risk of dementia and cognitive decline.	Israel	Prospective cohort study with data from an Israeli health insurer. Assesses for 10 years the risk of developing dementia or cognitive decline of participants with or without use of PPIs and without previous diagnoses of these conditions	It was not possible to confirm the association between the use of PPIs and the development of dementia or cognitive decline. In contrast, it was observed that PPI use was associated with a few years delay in incidence compared to patients who did not use PPIs.	Weiss *et al.* (2022)
Gastric acid suppressants and cognitive decline in people with or without cognitive impairment.	EUA	Prospective cohort study with data from *National Alzheimer's Coordinating Center*. Estimates the 5-year risk of progression to mild cognitive impairment or dementia in participants with no previous disorders, with or without use of PPIs or H2 antagonists. It also estimates the speed of long-term memory decline in participants with mild or moderate AD using these drugs.	No differences were found between the two classes for the risk of developing dementia or declining cognitive function in patients without previous alterations. However, H2 antagonists were more associated with the early development of dementia in patients with cognitive impairment and the rapid deterioration in memory performance in patients diagnosed with Alzheimer's.	Wu *et al.* (2022)

Table 1: Clinical trials addressing the correlation of PPI use and dementia.

Source: Own elaboration.

PPI users were 1.20 (95%; CI 1.07-1.35), 1.23 (95%; CI 1.02-1.49), and 1.32 (95% CI 1.05-1.67), respectively. For the authors, the method chosen to confirm the diagnoses can lead to inaccuracies, as they usually cover more advanced stages of the disease, which demonstrates an underdiagnosis of this condition.

CHOI et al. (2022) aimed to verify the probability of developing AD dependent on previous PPI use. In this nationwide study, 17,225 individuals diagnosed with AD were matched with a control group of 68,900 people and investigated for PPI use in the year prior to diagnosis (confirmed in those treated more than twice for the disease). Participants were classified according to exposure as non-users, previous users (without a prescription in the last 30 days) and current users (with a prescription in the last 30 days). The risk was significant in both experimental groups, determining *odds ratio* (OR) of 1.36 (95%; CI 1.26-1.46) for those in current use and 1.11 (95%; CI 1.04-1.18) for those with only previous use. This result points out that the probability of developing AD does not depend on current exposure to PPIs.

On the other hand, according to FRIESEN et al. (2023), the risk of dementia must not be considered an important factor in prescribing PPIs. In their study of 207,380 people, participants using the medication over the long term were not more likely to develop dementia than non-users. To achieve the result, five different models were created from the combination of the type of exposure (previous use or during the cohort) with the analysis of variables. Furthermore, the authors divided the participants into three age groups and into three degrees of PPI use (in DDDs). The diagnosis of dementia was made through a validated algorithm involving: prescription of at least one specific medication; hospital diagnosis; or at least three medical records with the corresponding ICD, with a maximum interval of 2 years between records. The models showed significant relationships only before adjusting for comorbidities, however, PPI users had higher rates of morbidities such as the cardiovascular disease, diabetes mellitus and depression (being more expressive in those with a higher degree of use). Such conditions are individual risk factors for the development of dementia and after adjustment, none of the models showed significant results.

WEISS et al. (2022) also showed that the use of PPIs does not imply an increased risk for the development of dementia. A study was conducted with 48,632 elderly people over 10 years, where the experimental group consisted of participants who received at least 11 PPI prescriptions per year (chronic use). The outcome occurred with the diagnosis of dementia or cognitive decline, through recent history, validated mental status scales or imaging tests. From the sample collected, the incidence of dementia was similar in both groups, with 18.6% among users and 18.1% among non-users. Comparing the two groups, the risk was up to 0.77 (95% CI 0.73-0.81) after adjusting for variables, with a significant p-value. The evidence of a lower risk among the experimental group is explained by the authors as a result of the methodology used to diagnose the conditions and the short period between use and the diagnosis of dementia.

For comparison purposes, WU et al. (2022) aimed to estimate the risk of progression to cognitive impairment or dementia in participants using PPIs or H2 antagonists (other antisecretory drugs). The authors conducted a study with 43,746 individuals, divided into two groups (normal cognition or mild cognitive alterations), and followed up for 5 years until one of the expected diagnoses was described. The participant was classified with mild cognitive impairment based on the Petersen criteria and they were classified with dementia based on the symptoms presented (functional and cognitive decline), their influence on their daily life activities and the exclusion of psychiatric diseases that could explain these symptoms. At the end of the study, no differences were found between the two classes for the risk of developing dementia or decline in cognitive function in patients without previous alterations, also confirmed by COLLIN et al. (2022).

USE OF PPIS AND NEUROPSYCHOLOGICAL DECLINE

Two articles evaluated the decline in neuropsychological functions as an outcome of PPI use. HAEFLIGER et al. (2022), in their cross-sectional study with 60 individuals, investigated changes in memory, attention and executive functions in participants without previous diagnoses of neurological or psychiatric disorders, regarding the chronic use of omeprazole. To be included in the experimental group (n=30), participants must have used the drug for at least 6 months (mean duration equal to 9.57 years), while in the control group (n=30) participants never used it. There were no significant differences between groups regarding socioeconomic variables.

The alterations were accessed through validated neuropsychological instruments, among them: o *Rey Auditory-Verbal Learning Test*, o *Sentence-word Span test*, o *Psychology Battery Test of Attention*, o *Verbal Fluency Subtest*, o *Five Digit Test* e o *Hayling Test*. Significant differences were observed between the two groups in all applied tests. Participants who made chronic use of omeprazole showed less expressive results in phonemic and categorical fluency tests (which assess lexical-semantic memory and speech planning). They had longer times to complete the reading and numerical counting sections (which assess automatic attention and inhibitory control). They were inefficient in tests of short-term episodic memory and attention, and also obtained prolonged verbal processing speeds and greater verbal inhibition.

For COLLIN et al. (2022) found no significant influence of PPI use on memory decline or psychomotor speed. During four visits spanning 10 to 15 years, 1,573 subjects were assessed for changes in working memory, verbal memory, psychomotor speed, and cognitive flexibility. These were performed through the *Verbal Intelligence Quotient*, *Mini-Mental State Examination*, *Digit Span Subtest, Auditory Verbal Learning Test*, *Trail Making Test* and the *CESD Scale*. In this study, participants who did not use PPIs, started during the study, stopped during the study or used them continuously did not show any difference in the results of the applied instruments.

The authors stated that the study was limited by including individuals with above-average levels of verbal intelligence and by relying on self-reported data regarding the use of medications, in addition to not detailing the exact period of use. In continuity, for Haefliger et al. (2022), the limitation included the small sample size, which was insufficient to determine whether omeprazole was the reason for the identified changes. Another point to be highlighted is the type of study of each article, which have different levels of evidence and do not allow further comparisons.

INFLUENCE OF PATTERN OF USE AND TYPE OF PPI

Few studies have sought to assess the influence of the pattern of PPI use. in this context, CHOI et al. (2022) evaluated the duration of treatment based on three time groups: less than 30 days; between 30 and 90 days; greater than 90 days. At the end of the study, the short-term use group had an OR equal to 1.13 (95%; CI 1.07-1.19), the intermediate use group had an OR equal to 1.18 (95%; CI 1.10-1.27) and the long-term use had OR equal to 1.26 (95%; CI 1.14-1.36). This finding evidences a possible cumulative effect of the use of PPIs for the development of AD. HAEFLIGER et al. (2022), brings similar results by showing that the magnitude of cognitive changes were worse in those patients who underwent longer treatments with omeprazole. And AHN et al. (2022) also points out that intermittent use does not reduce the risk for developing dementia by class use (HR 1.56; 95%; CI 1.50-1.63).

Regarding the type of PPI, CHOI et al. showed that both 1st generation drugs (omeprazole, lansoprazole and pantoprazole) and 2nd generation drugs (rabeprazole, esomeprazole and ilaprazole) were associated with a higher probability of AD, not showing significant differences between generations. HRs of 1.51 (95%; CI 1.40-1.64) for omeprazole, 1.58 (95%; CI 1.40-1.79) for lansoprazole and 2.12 (95%; CI 1.82-2.47) for esomeprazole have been described. Therefore, the effects of use on cognition would be intrinsic to the class and not specific to a single drug. However, ZHANG et al. (2022) described that the relationship between different PPIs and dementia may differ, with lansoprazole being more associated compared to the others. The explanation for the lack of further studies on this fact may be due to the change in prescription between different drugs in very short time intervals, or even the simultaneous prescription of two PPIs, as explained by AHN et al. (2022).

MECHANISMS PROPOSED FOR THE ASSOCIATION

In order to propose a mechanism that could explain the risk of developing dementia after the use of PPIs, BAIDYA et al. (2023) analyzed the mechanistic transduction pathways of molecular interactions between PPIs and the enzyme choline acetyl transferase (ChAT) through molecular coupling simulators and molecular dynamics. This enzyme is responsible for the biosynthesis of acetylcholine, a neurotransmitter involved in cognitive functioning (memory, learning and sleep) as well as in neuromotor function. As proof of this, there is evidence of loss of central cholinergic neurons in the brain of patients diagnosed with Alzheimer's, as the authors explain.

Previously, these same authors had reported the inhibition of ChAT activity through the use of PPIs in in vitro enzymatic kinetics tests. In their new study, using molecular coupling programs in silico, different drugs of this class were linked to the active site of the enzyme, showing strong interaction of the pyridine ring of PPIs, with the residue of the amino acid Hys324. The tested molecules showed greater affinity with ChAT when compared to a classic inhibitor of the enzyme, and the IBP-ChAT complexes remained stable during all molecular dynamics tests. One of the advantages of PPIs is that they easily cross the blood-brain barrier, enhancing their effects at a central level. This mechanism is associated with others already evidenced in the literature, such as vitamin B12 deficiency and increased secretion of β-amyloid peptides, which can also cause cognitive decline and interference in the cholinergic pathway (WANG, H.; TIAN, L.; YAN, X, 2022).

Regarding the epigenetic role of PPIs, COLLIN et al. (2022) and ZHANG et al. (2022) investigated the risk of use regarding polymorphisms in the APOE gene, especially the ε4 allele. Carriers of this genotype exhibit lower levels of acetylcholine and higher concentrations of neurofibrillary tangles in the CNS, causing neuronal dysfunction and cell death. Therefore, by combining these risk factors, the propensity for developing dementia becomes greater. ZHANG et al.

(2022) confirmed this theory only among heterozygous carriers of the ε4 allele, characterizing HR of 1.46 (95% CI 1.22-1.75) for nonspecific dementia, 1.40 (95%; CI 1.06-1.86) for Alzheimer's disease and 1.69 (95% ; CI 1.20-2.39) for vascular dementia.

In the study by COLLIN et al. (2022), the association of PPI use (short- and long-term) among carriers of the APOE ε4 genotype did not show greater cognitive decline in any of the tests performed. However, discontinuing use had a protective factor against reduced cognitive flexibility among non-carriers of the APOE ε4 genotype. Anyway, the cognitive effects of PPIs were different between carriers and non-carriers of the studied genotype.

CONCLUSION

This systematic review corroborates updates on the use of PPIs found in the current literature, contributing to the establishment of personalized therapy for patients with dementia. The studies discussed here were heterogeneous in terms of results, similarly to other existing reviews. Some authors found a higher risk of dementia associated with the use of PPIs, with no differences regarding subtypes. And among those who described an association, prolonged chronic use was more evident, with a possible cumulative effe3ct.

For deeper investigation on the subject, it is still necessary to assess the dose-dependent risk, standardize the diagnostic confirmation form, deepen studies with different drugs of the class and carry out experimental studies that corroborate the clarification of the possible molecular mechanisms involved.

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