REVIEW ARTICLE

Proton pump inhibitors: the impact on cognitive health in older adults

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ABSTRACT

Proton pump inhibitors (PPIs) are the most potent drugs to inhibit gastric acid secretion, being used in the treatment of most inflammatory conditions of the gastric mucosa. They are among the most prescribed and overprescribed medications worldwide; for example, in the United States, according to the National Health and Nutrition Examination Survey, they almost doubled their use in adults aged 40 years and older from 4.9 % to 8.3 % between 1999 and 2012. Although they are generally considered well tolerated, some epidemiological studies extracting information from large databases have reported a number of adverse effects associated with their prolonged use, including cognitive impairment, chronic kidney disease, myocardial infarction, stroke, bone fractures and even death, among others.

The objective was to conduct a narrative review of the literature on the effects of chronic use of PPIs on cognitive impairment in older adults. Articles were reviewed based on a search in the PubMed, Scopus and SciELO databases using both English and Spanish keywords and related MeSH/DeCS terms.

Neurological side effects induced by chronic PPI use may be indirectly related to secondary systemic disorders (magnesium and vitamin B12 deficiency) or to direct effects on neuronal functioning after passing through the blood-brain barrier. Although several neurobiological mechanisms by which PPIs could favor the development of dementia—which involve Tau protein function, beta-amyloid [βA] accumulation and cobalamin deficiency, among others—have been described, most of the available clinical evidence has not shown a significant association between PPI use and the risk of dementia or cognitive impairment.

To establish the adverse clinical effects of chronic PPI use more clearly, especially on brain functioning, well-designed cohort studies with large sample sizes and long follow-up periods, with a reliable method to adjust for standardized confounders, as well as subgroup analyses are needed.

Keywords: Omeprazole; Esomeprazole; Lansoprazole; Pantoprazole; Dementia; Cognitive Dysfunction; Depression (Source: MeSH NLM).

INTRODUCTION

Proton pump inhibitors (PPIs) are the most potent drugs to inhibit acid gastric secretion, being used in the treatment of most inflammatory conditions of the gastric mucosa [(1)].

They are among the most prescribed and overprescribed medications worldwide. According to the National Health and Nutrition Examination Survey in the United States of America, between 1999 and 2012, the percentage of adults aged between 40 and 60 years taking a PPI almost doubled from 4.9 % to 8.3 %. On the other hand, various studies have demonstrated that 50 %-70 % of the patients who are prescribed a PPI do not have the correct indication, particularly hospitalized older adults [(2)].

While PPIs have been considered generally well tolerated, some epidemiological studies drawing information from large databases have reported a number of adverse effects associated with their prolonged use, such as the development of cognitive impairment, chronic kidney disease, myocardial infarction, stroke, bone fractures, fluid and electrolyte disorders, and even death, among others [(3-5)].

In many cases, the quality of the evidence underlying these associations is low because these studies, due to their design, cannot establish a cause-effect relationship; nevertheless, they generate hypotheses. Despite the foregoing, in many contexts, both health professionals and patients have decided not to use PPIs in clinical situations where they are clearly indicated, e.g., to prevent and treat complications of different forms of acid-peptic disease.

In contrast to the above, some neuroprotective properties of PPIs have recently been described, as will be mentioned below.

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It is intended, then, to conduct a narrative review that includes the noteworthy pharmacological aspects of PPIs, in order to understand, from a biological standpoint, the possible mechanisms that could influence brain functioning and, ultimately, to contrast them with the available clinical evidence regarding the chronic use of these drugs and cognitive impairment.

SEARCH STRATEGY

A literature search was conducted to answer the question: What is the effect of chronic use of PPIs on cognitive impairment in older adults? The search keywords were neurological adverse effects, dementia, depression, cognitive impairment, and PPIs (omeprazole [OPZ], esomeprazole, pantoprazole and lansoprazole [LPZ]). The databases consulted were PubMed, Scopus and SciELO, which included both English and Spanish articles. The search was not limited to any specific time period. The information found in the selected studies was carefully evaluated and is described below.

PROTON PUMP INHIBITORS (PPIs)

To understand the mechanism of action of PPIs, it is important to know physiological aspects of acid secretion in gastric parietal cells starting from the enzyme hydrogen-potassium-adenosine triphosphatase (H^+/K^+-ATPase), which creates a 1-million-fold concentration gradient of hydrogen ions (H^+) in the gastric lumen compared to the interior of the parietal cell. The enzyme that normally remains in a resting state in tubulovesicular form in the cell cytoplasm, upon being activated by different ligands, such as acetylcholine (neural stimulus), histamine (paracrine stimulus) or gastrin (endocrine stimulus)—mainly as a response to food intake—undergoes conformational changes that lead to the intracellular release of second messengers such as calcium and cyclic adenosine monophosphate (cAMP), which produce acid secretion as the common final pathway. The enzyme H^+/K^+-ATPase exchanges H^+ for K^+ (expelling H^+ and introducing K^+), while basolateral secretion of bicarbonate (HCO_3) occurs to maintain intracellular electroneutrality. The enzyme H^+/K^+-ATPase binds to magnesium-adenosine-5'-triphosphate (MgATP), which provides it with the energy to fuse with the apical microvilli at the luminal membrane of the secretory canaliculus of the parietal cell (active pump).

Structurally, H^+/K^+-ATPase is a heterodimer with an α-subunit and a ß-subunit. It contains 28 cysteine (CYS) molecules located in different regions of the enzyme, with 10 of these molecules being the binding site of PPIs once the pump is active, especially CYS 813 [6].

PPIs are prodrugs that require activation in an acidic environment once they have been absorbed. They are the most potent acid secretion inhibitors, achieving a daily basal and stimulated decrease in secretion between 80 % and 95 %. Such inhibitors are weak bases and labile to the acidic environment; therefore, they need a coating to protect them from the acidic environment and allow their absorption in a more alkaline environment, i.e., the small intestine. PPIs share a very similar basic structure that combines a benzimidazole ring and a pyridine ring through a sulfinyl linkage. To chemically bind to the CYS portion of the ATPase, the sulfinyl group must derive energy from the acidic environment within the parietal cell, i.e., the PPI must be activated, which occurs by the addition of two protons to the nitrogen on each side of the sulfinyl group. Once activated, PPIs can inactivate the proton pump by binding to the CYS molecules in the ATPase to form disulfide bonds. PPIs can bind to different CYS sites on the enzyme, depending on the rate at which they are activated. This difference in binding sites explains some of the pharmacodynamic differences among PPIs according to those with reversible binding and those that are inaccessible to the reduction of disulfide bonds, e.g., the inhibition of acid secretion by OPZ can last up to 24 hours and by pantoprazole up to 46 hours [1,6,7].

Although PPIs produce relatively few adverse effects and have a good safety profile, prolonged inhibition of gastric acid secretion leads to prolonged hypergastrinemia, which can result in enterochromaffin-like cell hyperplasia, carcinoid tumor formation, vitamin B12 deficiency, iron deficiency, hypomagnesemia, necrotizing enterocolitis, osteoporosis, atrophic gastritis and increased infections due to changes in the intestinal microbiota, among others [4,6,8].

COGNITIVE IMPAIRMENT

Cognitive impairment consists of the progressive loss of higher mental functions, on a spectrum ranging from mild cognitive impairment to dementia. The boundaries defining the separation between these are based on the preservation or loss of independence in daily life. Dementia consists of a progressive loss of higher mental functions, affecting one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual-motor function, social cognition), which variably limits the ability to think, memorize, reason and perform activities of daily living, which results from a disorder in brain functioning. They may also be accompanied by changes in personality, mood and behavior, but without alteration of the level of consciousness [9,10].

Most dementias are due to neurodegenerative disorders, such as Alzheimer's disease (AD, 60 %-80 % of the cases), Lewy body dementia, frontotemporal dementia, Parkinson's disease dementia and, in rarer cases, progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy and Huntington's disease. It may be also associated with a vascular cause (the second most frequent

cause), especially in black patients and in patients with diabetes, hypertension and other cardiovascular risk factors. Other less common etiologies include alcohol-related dementia, chronic traumatic encephalopathy, normal pressure hydrocephalus, chronic subdural hematoma, and other central nervous system (CNS) diseases such as prion diseases and HIV infection, among others. Mixed dementia occurs frequently and refers to the coexistence of more than one pathology underlying dementia, most commonly found with AD and vascular dementia [11-15].

Although dementia mainly affects older people, there has been an increase in cases diagnosed in individuals under 65 years. The global prevalence of dementia is estimated to increase from 43.8 million patients at present to about 100 million by 2050. There are 10 million new cases per year worldwide. It is estimated that the number of people with dementia will nearly double every 20 years, with the majority of cases occurring in rapidly developing middle-income countries. In Latin America, an increase of between 134 % and 146 % can be expected [16-18].

Currently, the diagnosis of AD is based on neuropsychological tests (cognitive criteria), neuroimaging (nuclear magnetic resonance and amyloid deposits found by positron emission tomography) and the presence of tau/amyloid proteins in the cerebrospinal fluid (biomarker criteria), which rule out other causes of dementia. However, a definitive diagnosis can only be confirmed histopathologically by the extensive presence of beta-amyloid (ßA) and neurofibrillary tangles (NFTs) of tau protein in the neocortex of postmortem brain tissue [19].

PPIs AND COGNITIVE IMPAIRMENT

Pathophysiological mechanisms

The following is a description of the pathophysiological mechanisms that can explain the effects of PPIs on brain functioning, considering the neurobiological bases described in AD.

There is evidence of H^+/K^+-ATPase proton pump activity in the CNS, with specific isoforms (P-type ATPases) that have various physiological functions in neurons and contribute to acid-base and potassium homeostasis and also create the proton gradient required for neurotransmitter packaging in synaptic vesicles. Recently, it has been described that the vesicular H^+/K^+-ATPase proton pump also plays an important role in both exocytosis and endocytosis processes in nerve terminals [17].

P-type ATPases (Ca^{2+}-ATPase, Na^+/K^+-ATPase and H^+/K^+-ATPase) share similarities in their primary structure: the α-subunit of gastric H^+/K^+-ATPase shows 98 % homology) and the catalytic subunit (63 % homology) and of the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (25 % homology).

As stated above, PPIs effectively block acid secretion by covalent binding to CYS residues of the activated H^+/K^+-ATPase pump in gastric parietal cells, particularly at CYS 813. Considering the high homology between P-type ATPases, PPIs could possibly inhibit other ion pumps in various organs and induce systemic physiological changes. The CNS can be affected considering the presence of facilitating conditions, i.e., various pathological states that result in reduced pH levels in the brain, cerebrospinal fluid and blood (metabolic stress).

Pharmacokinetic studies have revealed that the blood-to-brain distribution coefficient of OPZ following a single intravenous dose is 0.15, i.e., 15 % of this drug can reach the CNS and potentially affect brain functioning with acute or prolonged use [14]. It has also been demonstrated through in vitro and in vivo studies that LPZ can penetrate the blood-brain barrier (BBB) as well [20].

Thus, it has been reported that some PPIs, such as LPZ, esomeprazole and pantoprazole, may cause adverse neurological effects, mainly headaches and dizziness/vertigo and, to a lesser extent (< 1 %), depression, diplopia, sleep disorders, drowsiness, insomnia, nervousness, tremor and sensory-perceptual abnormalities (hallucinations) and delirium [21].

These neurological side effects induced by chronic use of PPIs may be indirectly related to systemic alterations secondary to their use (magnesium and vitamin B12 deficiency) or direct effects on neurons after passage through the BBB. However, the exact mechanisms within brain circuits have not been fully described [20].

Pathophysiological effects of PPIs on dementia

PPIs may facilitate tau and ßA protein-induced neurotoxicity, potentially accelerating the progression of AD and cognitive impairment. Moreover, prolonged use may lead to the development of vitamin B12 deficiency, which plays an important role in cognitive function [17, 22].

Beta-amyloid

One of the main characteristics of AD is the extracellular accumulation of ßA plaques, which cause oxidative and inflammatory damage in the brain. PPIs increase the production of ßA. ßA is produced by an abnormal cleavage of the amyloid precursor protein (APP), which is an integral protein of cell membranes. When the APP is cleaved by α-secretase, which is the normal pathway, the resulting product is a soluble peptide that is then easily eliminated by the body; nevertheless, in AD, the consecutive cleavage of APP first by ß-secretase and then by γ-secretase prevails. Subsequently, insoluble ßA is formed, which neurons excrete to their exterior and glia cells (astrocytes and microglia) try to eliminate without success. Therefore, an inflammatory process is generated, which, together

with the toxic effect of βA itself, contributes to neuronal damage [23].

Recently, Badiola et al. investigated the effect of PPIs on the production of βA using cellular and animal models. They suggested that PPIs act as inverse α-secretase (iGSM) modulators, shifting the cleavage site towards γ-secretase, thus resulting in increased levels of type 42 βA, which is the main pathological amyloid species. On the other hand, PPIs alter the pH of the environment, amplifying the activity of other proteases, such as memprin-β, resulting in the generation of other Aβ2 peptides (Aβ2-37, Aβ2-40 and Aβ2-42) [24].

It has also been demonstrated that PPIs can cross the BBB and inhibit the vacuolar proton pumps (V-ATPases) in microglia and macrophages. These pumps normally acidify the lysosomes by pumping protons from the cytoplasm into the lumen of the vacuoles, allowing an acidic environment in the lysosomes necessary for the degradation of fibrillar βA. By blocking this effect, PPIs would reduce the degradation of fibrillar βA, thus leading to a decrease in its clearance [25].

Tau protein

Tau protein plays an important role as a microtubule-associated protein in neuronal axons as it stabilizes microtubules and induces their assembly. NFTs are intraneuronal formations resulting from the hyperphosphorylation of tau proteins, which in this state are unable to bind to and stabilize microtubules. Thus, paired helical filaments (PHFs) are formed, indicating the destruction of microtubules and neurofilaments. Subsequently, the affected neurons undergo degeneration, leading to cell death [26,27].

According to the neuroimmunomodulation theory of AD, initial CNS changes prior to the clinical onset (presence of symptoms) result from a chronic inflammatory response. This causes abnormal tau protein phosphorylation which, in turn, induces the formation of PHFs and tau protein aggregates [28].

Several studies have found that NFTs correlate with cognitive impairment and severity in AD, positioning tau NFTs as suitable targets for potential therapy and diagnosis in patients with AD [20].

It has been discovered that benzimidazole derivatives and quinoline have a high affinity for tau protein, particularly for NFTs in neural plaques [29]. Some PPIs contain a benzimidazole ring in their structure, as is the case with LPZ. It has been found to have a high affinity for tau NFT compounds and, being lipophilic and capable of passing through the BBB, its usefulness as a radiotracer for positron emission tomography (PET) imaging has been researched. However, this usefulness has not been documented in all cases, possibly indicating that affinity varies depending on the type of tau protein isoform expressed in the CNS, according to the microtubule-binding domains, which may vary under different pathological conditions [30]. Further research is needed to specifically understand the interactions between PPIs and tau protein.

Vitamin B12 deficiency

Vitamin B12 (cobalamin), which is obtained from different food sources—especially animal sources such as meat, fish, dairy products and some fortified cereals—requires gastric acidity for absorption. In humans, total cobalamin reserves (2-5 mg) are much greater than daily requirements, suggesting that body reserves are sufficient to meet them for 3 to 4 years after a period of low intake or malabsorption of vitamin B12 [31].

During the digestion process, vitamin B12 binds to salivary R proteins (cobalophilins). Then, in the small intestine, it binds to intrinsic factor, a high-affinity glycoprotein under acidic pH conditions produced by gastric parietal cells of the fundus and cardia. It continues its journey to the terminal ileum, where it is absorbed. On the other hand, vitamin B12 is tightly bound to proteins in food; thus, it requires acid-activated proteolytic digestion. Since PPIs promote the development of hypochlorhydria, they decrease the absorption of this vitamin B12 because it remains tightly bound to the proteins in the stomach and does not bind efficiently to intrinsic factor [31].

Vitamin B12 is required for one-carbon transfer reactions, such as methylation, which are necessary for the processing and producing of nucleotides, phospholipids and monoamine neurotransmitters. It is involved in the production of methionine from homocysteine: a methyl group from tetrahydrofolate is removed, producing methylcobalamin plus a methyl group, which is then transferred to homocysteine and by the action of methionine synthase, produces methionine. Based on the foregoing, vitamin B12 deficiency is one of the main causes of hyperhomocysteinemia. Both hyperhomocysteinemia and B12 deficiency are considered risk factors for cerebral atrophy, cognitive impairment and dementia [32-34].

Hyperhomocysteinemia can activate several protein kinases—such as glycogen synthase kinase 3β (GSK-3β), cyclin-dependent kinase 5 (Cdk-5), c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase p38 (MAPK)—and inhibits protein phosphatase 2A (PP2A). All of them are key enzymes in the regulation of the phosphorylation state of tau protein [32].

Therefore, vitamin B12 is one of the inhibitors of tau polymerization and its deficiency is linked to

the inactivation (decreased methylation) of protein phosphatase (PP2A), which plays a crucial role as the main serine/threonine phosphatase enzyme in the CNS. It catalyzes dephosphorylation reactions, thereby promoting hyperphosphorylation of tau protein, leading to its aggregation, production of NFTs and neurodegeneration [35,36].

Alternative mechanisms linking AD with vitamin B12 deficiency have also been described, which are different from PP2A inactivation. Cobalamin can bind directly to tau protein via CYS residues in such protein and inhibits its fibrillation and aggregation [35].

In animal models, hyperhomocysteinemia, in addition to inducing hyperphosphorylation of tau protein, can increase ßA production. However, supplementation with folate/vitamin B12 can attenuate these effects [37].

While the association between decreased B12 absorption and the use of PPIs has been described in short-term studies, this association has not been evident in all studies involving patients with prolonged use of PPIs. It should be noted that most of these studies demonstrate an association rather than causality. There are likely other contributing factors to these findings besides acid-suppressive therapy with PPIs [22].

Considering, as described above, that PPIs do not completely inhibit gastric acid secretion and that physiological reserves of vitamin B12 are generally sufficient in the general population, routine serum checks of B12 levels in patients using PPIs may not always be necessary. However, it is an aspect to be considered depending on the patient's clinical context.

To conclude this section, various mechanisms have been described to explain the effects of vitamin B12 deficiency on dementia. Nevertheless, intervention studies with folic acid, vitamin B12 and/or B6 supplementation compared to placebo in older adults with cognitive impairment secondary to AD have not shown benefit [34].

More clinical trials are needed to understand this relationship more precisely and to determine whether vitamin B12 deficiency is a causal factor or merely an associated factor in dementia (Figure 1).

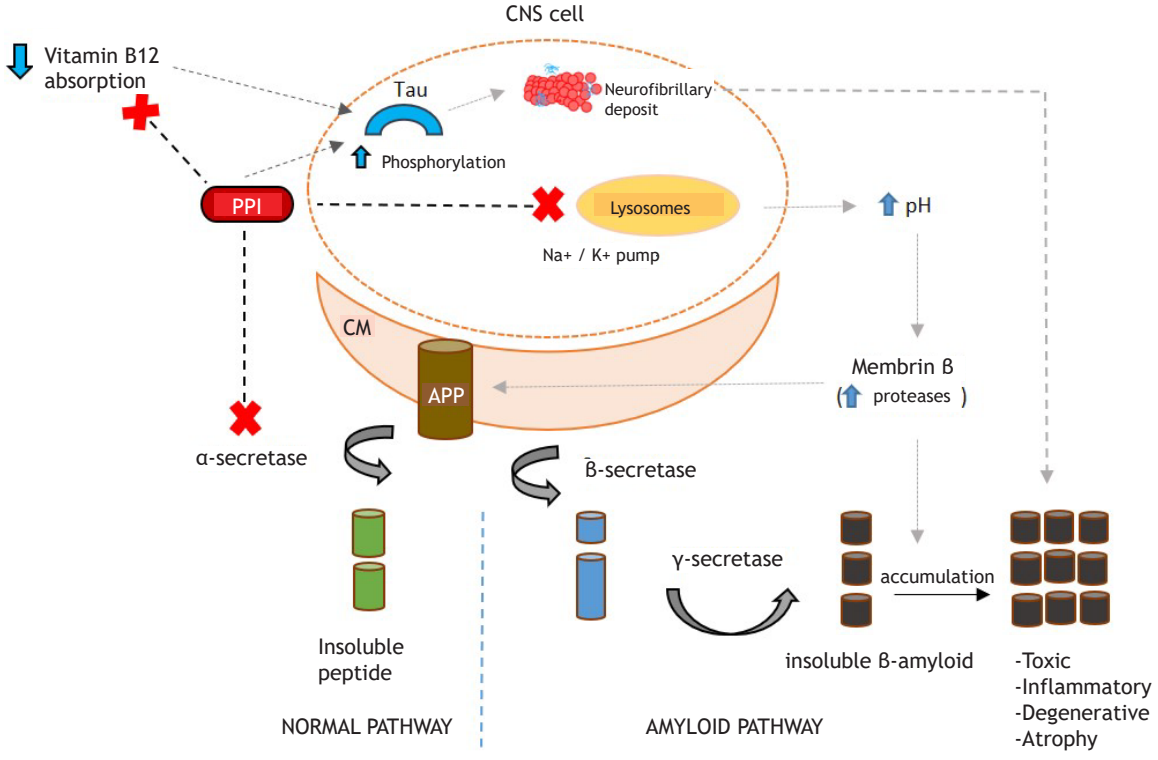

Figure 1. Postulated mechanisms of PPIs on the CNS and their relationship with cognitive impairment
CM: central membrane; APP: amyloid precursor protein; PPI: proton pump inhibitor; CNS: central nervous system.

The figure shows the normal pathway of the APP metabolism, which is integral to cell membranes and mediated by α-secretase, an enzyme blocked by PPIs, consecutively triggering the amyloid generation pathway through the action of ß-secretase and γ-secretase on the APP, which produces ß-amyloid peptide. Such peptide is insoluble and not adequately cleared by glial cells. Therefore, it accumulates and causes direct toxic effects on neuronal cell membranes, inflammation, neuronal degeneration and cerebral atrophy. Another mechanism of PPIs involves direct effects on tau protein hyperphosphorylation and indirect effects mediated by vitamin B12 deficiency due to malabsorption caused by gastric hypochlorhydria. Finally, the inhibition of the Na^+/K^+ pump in lysosomes increases the pH of the environment, which leads to the activation of proteases such as membrin ß, which degrade other proteins including APP, resulting in the accumulation of insoluble peptides.

Experimental studies showing potential benefit from PPIs

As mentioned above, a neuroprotective effect of PPIs has been recently reported, but at an experimental level.

To research whether PPIs have anti-inflammatory effects on microglia, the effect of LPZ and OPZ on the toxic action in cell cultures of human microglia and THP-1 monocytes exposed to SH-SY5Y neuroblastoma cells was studied. Thus, the production of the proinflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) was measured. Both PPIs significantly reduced TNF-α secretion from stimulated THP-1 cells in a concentration-dependent manner, with a trend towards a reduction in IL-6. The authors concluded that PPIs have anti-inflammatory effects and can decrease human microglial and monocytic neurotoxicity [38].

Considering that several inflammatory processes, including astrocytic activation, have been involved in the pathogenesis of different neurodegenerative diseases, including AD, and that interferon (IFN)-γ-induced astrocytic neurotoxicity is mediated, at least in part, by phosphorylation of the signal transducer and activator of transcription (STAT3), a study was conducted using human astrocytes cell cultures exposed to SH-SY5Y neuroblastoma cells in order to assess the effects of PPIs on IFN-γ-induced neurotoxicity through STAT3 activation. It was found that both LPZ and OPZ significantly inhibited IFN-γ-induced phosphorylation by STAT3 activation, but not by STAT1. In addition, secretion of IFN-γ-inducible T-cell α chemoattractant was significantly reduced. These results suggest that PPIs attenuate IFN-γ-induced neurotoxicity of human astrocyte by inhibiting the STAT3 signaling pathway. The authors conclude that PPIs possess anti-neurotoxic properties and may be a useful treatment option for AD and other neuroinflammatory disorders associated with activated astrocytes [39].

Clinical studies that found an association with cognitive impairment

Various studies have reported an association between the use of PPIs and cognitive impairment. Below, we include those considered most noteworthy.

In the German Study on Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe), a longitudinal multicenter cohort study among 3,327 elderly patients aged 75 years or older, participants were followed up to 72 months with intervals of every 18 months. During such period, 431 developed incident dementia, with 260 of them diagnosed with AD. Time-dependent Cox regression was used to estimate hazard ratios for the incidence of any dementia and AD. Potential confounders included in the analysis were age, sex, education, apolipoprotein E4 (ApoE4) allele status, polypharmacy, and comorbidities such as depression, diabetes, ischemic heart disease and stroke. Patients receiving PPIs had a significantly higher risk of any dementia (hazard ratio [HR] 1.38, 95 % confidence interval [CI]: 1.04-1.83) and AD (HR 1.44, 95 % CI: 1.01-2.06) compared to those not using PPIs [40].

In another prospective cohort study assessing the association between the use of PPIs and the risk of incident dementia in the elderly, data were obtained from Germany's largest health insurer, Allgemeine Ortskrankenkassen (AOK), for the years 2004 to 2011, among both inpatients and outpatients, regarding medication prescriptions, diagnoses and incident dementia, using time-dependent Cox regression adjusted for age, sex, comorbidities, and polypharmacy. A total of 73,679 participants aged 75 years or older and free of dementia at baseline were analyzed. Patients receiving regular PPI medication (n = 2,950; mean age 83.8 years [SD: 5.4]; 77.9% were females) had a significantly increased risk of incident dementia compared to patients not receiving such medication (HR = 1.44, 95 % CI:1.36-1.52]; $p < 0.001$) [41].

A third study conducted to examine this association in Asian population included patients without a history of dementia initiating PPI therapy between January 1, 2000 and December 31, 2003. These patients were identified from Taiwan's National Health Insurance Research Database. The outcome of interest was all-cause dementia. Similarly, Cox regression models were applied to estimate the HR of dementia. The cumulative PPI dosage was stratified by quartiles of defined daily doses and adjusted for disease risk score. Data from 15,726 participants aged 40 years or older and free of dementia at baseline were analyzed. PPI users (n = 7,863; average follow-up for 8.44 years) had a significantly higher risk of dementia over non-PPI users (n = 7,863; average follow-up for 9.55 years) (adjusted HR [aHR] 1.22; 95 % CI: 1.05–1.42). Subgroup analysis showed

an excess frequency of dementia in PPI users diagnosed with depression (aHR 2.73 [1.91–3.89]), hyperlipidemia (aHR 1.81 [1.38–2.38]), ischemic heart disease (aHR 1.55 [1.12–2.14]) and hypertension (aHR 1.54 [1.21–1.95]) [42].

Another study in the older adult population of the city of Bogota, Colombia, who participated in the Salud, Bienestar y Envejecimiento (SABE- Health, Wellness and Aging) study, conducted in 2012, included a significant sample of 2,000 people aged 60 years and older. It described the association between cognitive impairment assessed by the score obtained in the modified Mini-Mental State Examination (3MSE) validated in Spanish as a dependent variable and the consumption and duration of PPI use as independent variables. Based on the ROC curve, a duration of PPI use of 24 months or more was selected, and a multivariate logistic regression model was performed. An interaction variable between age and duration of drug use was employed. The average age of participants was 71.17 ± 8.05 years, and the prevalence of PPI use was 20.7 %, with an average duration of PPI use of 74.8 ± 93.7 months. The 3MSE showed alterations in 12.6 % of the respondents. In multivariate analysis, the use of PPIs for 24 or more months, adjusted for age, sex, educational level and marital status variables, showed a 1.90-fold increase in the risk of association (*OR*: 1.90; CI: 1.11-3.24; $p = 0.018$) [43].

Evidence from meta-analysis and systematic reviews

According to a 2017 systematic review in four European observational studies investigating the association between use of PPIs and dementia, three of them found a positive association between dementia and the use of OPZ, esomeprazole, LPZ and pantropazole, with an approximately 1.4-fold increased risk for any dementia in cohorts using PPIs (95 % CI: 1.36-1.52; $p < 0.001$) [44].

In 2019, one meta-analysis and two systematic reviews and meta-analyses were published to determine the association between the use of PPIs and the risk of dementia. Two of them found no association, while one did find an association.

In the first of these studies, Li et al. included cohort studies, published as of February 2018, reporting the risk of dementia or AD among PPI users compared with nonusers. From six cohort studies, they found a relative risk (RR) of 1.23 (95 % CI: 0.90 to 1.67) for dementia and 1.01 (95 % CI: 0.78 to 1.32) for AD, compared with those who did not use PPIs. This systematic review and meta-analysis did not show a statistically significant association between the use of PPIs and the risk of dementia or AD ($p > 0.05$) [45].

In a meta-analysis published in 2019 from 10 independent studies involving 642,305 participants, Song et al. found that PPI users did not exhibit a significant association with dementia (pooled hazard ratio [HR] = 1.04, 95 % CI: 0.92-1.15; I2 heterogeneity index = 95.6 %, $p < 0.001$) and AD (HR = 0.96, 95 % CI: 0.83-1.09; I2 = 80.7 %, $p < 0.001$). Sensitivity analyses showed no significant differences in the estimates of effects. However, they highlighted remarkable heterogeneity among the analyzed studies [46]. In another meta-analysis published at the end of 2019 based on six cohort studies—two from Germany and one each from the United States, Romania, China and Korea—Zhang et al. calculated pooled hazard ratios (HRs). In a total of 166,146 participants, the overall result showed a significant increase in the risk of dementia with the use of PPIs (HR = 1.29, 95 % CI: 1.12-1.49). Subgroups analyses showed a significant association between the use of PPIs and the risk of dementia in Europe (HR = 1.46, 95 % CI: 1.23-1.73) and among participants aged 65 years or more (HR = 1.39, 95 % CI: 1.17-1.65). For follow-up time ≥ 5 years, the pooled HR was 1.28 (95 % CI: 1.12-1.46), i.e., there was a 1.28-fold increased risk of developing dementia among PPI users. In terms of regional impact, participants from Europe showed an overall pooled HR estimate of 1.46 (95 % CI: 1.23-1.73). There was no evidence of publication bias. The results of this meta-analysis support that the use of PPIs increases the risk of dementia [47].

Finally, two recently published meta-analyses and systematic reviews, one of which included only prospective studies, once again cast doubt on the negative effect of PPIs on the development of dementia.

Hussain et al. conducted another meta-analysis and systematic review to assess the association between the use of PPIs and the risk of dementia. They included cohort and case-control studies published through March 31, 2019, that evaluated such an association. The primary outcome was the pooled risk of dementia among PPI users compared to nonusers. Secondary outcomes included the risk of dementia according to subgroups. From 12 studies (8 cohort and 4 case-control studies), a pooled RR of 1.05 was recorded (95 % CI: 0.96-1.15), $p = 0.31$. Subgroup analysis was based on study design (cohort: $p = 0.14$; cases and controls: $p = 0.14$), sex (RR 1.25 [95 % CI: 0.97-1.60], $p = 0.08$), use of histamine 2 receptor antagonists ($p = 0.93$), and AD (RR 1.00 [95 % CI: 0.91-1.09], $p = 0.93$). These results indicate that no significant association was found between the use of PPIs and the risk of dementia or AD [48].

Desay et al. conducted a meta-analysis and systematic review of only prospective studies examining the risk of cognitive impairment and dementia among PPI users versus nonusers. The primary outcome was the HR of any dementia among PPI users compared to nonusers. The secondary outcomes were the pooled HR for AD from long-term follow-up studies on PPIs (more than 5 years). The analysis included a total of six studies (one randomized and five prospective clinical trials) with 308,249 individuals whose mean age was 75.8 ± 5.2 years, with a follow-up period of 5 (range 1.5-11) years. The pooled HR for any dementia was 1.16 ($n = 6$, 95 % CI: 0.86-1.47). The results

remained unchanged when only studies with long-term PPI use were analyzed (for more than 5 years) (*n* = 4, pooled HR 1.10, 95 % CI: 0.66-1.53). The pooled HR for AD was 1.06 (*n* = 3, 95 % CI: 0.70-1.41). Notable heterogeneity was found among the inclusion studies (I2 = 93 %). The meta-regression did not demonstrate a significant role of age at study initiation (*p* = 0.1) or duration of PPI use on the incidence of dementia [49].

Thus, these consolidated results, along with others, do not show a significant relationship between the use of PPIs and dementia in prospective studies with at least five years of follow-up [50].

CONCLUSIONS

PPIs are the most prescribed medications, especially for older adults. Although their usefulness in the prevention and management of different forms of acid peptic disease is clear, they are not free of adverse events associated with their chronic use. In the context of the frequent presence of comorbidities in this population group, some of these have been postulated as causal effects and others as association effects, as in the case of cognitive impairment.

The evidence in this regard is limited and conflicting: on one hand, most studies do not specify either the spectrum or the type of cognitive impairment assessed; on the other hand, there is methodological disparity between the different studies. For example, the reversibility of the findings was not assessed since, in most cases, data were obtained retrospectively from a history of chronic exposure to PPIs or prospectively during chronic exposure to PPIs for a certain period of time, but subsequent neurocognitive evaluations without exposure to PPIs were not described in these cases.

Based on the foregoing, the overall results of the described effects of PPIs on cognitive function are outlined. Thus, to date, according to the consolidated evidence available in the most recent meta-analyses and systematic reviews of the literature, no significant association has been found between the use of PPIs and the risk of dementia or cognitive impairment, though the quality of the evidence is not robust.

Cognitive effects of PPIs are likely to be due also to drug interactions, especially in polymedicated elderly patients. Such interactions might have not been considered confounding factors. Additionally, factors such as hypertension, family history of dementia, diabetes mellitus, level of physical activity and air pollution have recently been identified as risk factors for cognitive impairment and dementia.

Therefore, to clarify the effects of chronic use of PPIs on brain functioning and to be able to take a clear stance for the use of PPIs in various clinical settings in older adults, well-designed cohort studies are needed. Such studies should have established parameters for assessing various mental domains and spectra of cognitive impairment, including representative sample sizes and long follow-up periods. Moreover, a reliable method of analysis should be used to adjust for confounding factors such as comorbidities, drug interactions and adverse reactions, and polypharmacy, which are very frequent in this population group.

On the other hand, it is important to clarify that the available evidence on the anti-inflammatory and neuroprotective effects of PPIs comes only from a few experimental studies in microglia and astrocyte cell cultures. These results generate hypothesis maybe for future research in concrete clinical scenarios but cannot be extrapolated as proven pleiotropic clinical effects.

In conclusion, in older adults, PPI therapy should be constantly re-evaluated and limited to appropriate clinical scenarios for a defined period of time. It should not be used for long periods of time as part of treatment of these patients, most of whom have various chronic pathologies, provided that it is determined that the benefits outweigh the potential risks.

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