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REVIEW ARTICLE

The Janus-like Association between Proton Pump Inhibitors and Dementia

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Abstract: Early pharmacoepidemiological studies suggested that Proton Pump Inhibitors (PPIs) might increase the risk of Alzheimer's Disease (AD) and non-AD related dementias. These findings were supported by preclinical studies, specifically stressing the proamyloidogenic and indirect anticholinergic effects of PPIs. However, further large-scale pharmacoepidemiological studies showed inconsistent results on the association between PPIs and dementia. Pharmacodynamically, these findings might be related to the LXR/RXR-mediated amyloid clearance effect and anti-inflammatory action of PPIs. Further aspects that influence PPI effects on AD are related to patient-specific pharmacokinetic and pharmacogenomic characteristics. In conclusion, a personalized (individualized) medicinal approach is necessary to model and predict the potential harmful or beneficial effects of PPIs in AD and non-AD-related dementias in the future.

Keywords: Alzheimer's disease, dementia, LXR, pharmacodynamics, pharmacoepidemiology, pharmacogenomics, pharmacokinetics, PPARγ, proton pump inhibitor, RXR.

1. INTRODUCTION

1.1. Proton Pump Inhibitors - Indications, Pharmacoepidemiology, Pharmacodynamics and Adverse Reactions

Proton Pump Inhibitors (PPIs) are widely used for the prevention and treatment of acid-related conditions such as dyspepsia, esophageal, duodenal and stomach peptic ulcers, including after endoscopic treatment for bleeding, NSAID-associated ulcers, gastroesophageal reflux disease (GERD) including endoscopy-negative reflux disease, laryngopharyngeal reflux causing laryngitis and chronic cough, Barrett's esophagus, eosinophilic esophagitis, gastrinomas and related complex conditions, *e.g.* Zollinger-Ellison syndrome [1-7].

PPIs are among the top 10 prescribed medications in the world [8], and the class of PPI medications is on the World Health Organization's (WHO) List of Essential Medicines [9]. Omeprazole was the first PPI in clinical use, followed by, i.a., lansoprazole, pantoprazole, rabeprazole, esomeprazole and dexlansoprazole [10-12]. Based on the National Health and Nutrition Examination Survey (1999 to 2012), the prescription rate of PPIs nearly doubled from 4.9% to 8.3% in adults aged 40-60 years in the USA [13, 14]. Importantly, 50-70% of the patients did not meet the proper indication for PPI use, particularly hospitalized elderly individuals [15-17]. Another survey in the USA (2002-2017 Medical Expenditure Panel Survey) revealed that the overall percentage of PPI users increased from 5.70% in 2002-2003 to 6.73% in 2016-2017, also, in most patient subgroups [18]. In Germany, PPI prescriptions are also increasing. While the annual national report on drug prescription of 2018 and 2019 reveals a decrease in omeprazole prescription (quantified as Defined Daily Dose (DDD)) by 5.1%, other PPIs exhibit strong increases in prescription, *e.g.*, pantoprazole (1.2%), lansoprazole (20.0%), esomeprazole (5.1%) and rabeprazole (1.6%) [19].

Structurally, PPIs belong to the benzimidazole family, and the activated forms covalently and irreversibly inhibit the H^+/K^+-ATPase by interaction with cysteine residues on the luminal surface of the parietal cells, therefore suppressing gastric acid secretion [2, 10]. The primary active H^+/K^+-ATPase belongs to the PII subfamily of P-type ATPases such as the Ca^{2+}-ATPase or the Na^+/K^+-ATPase [20]. In humans, one of the genes encoding the H^+/K^+-ATPase (ATP12A/ATP1AL1) is also expressed in the brain, whereas the gene ATP4A is expressed specifically in gastric epithelial cells [21]. There is clear evidence that H^+/K^+-ATPase activity is present in the Central Nervous System (CNS) [22] and that the related antiporter affects acid/base and K^+ homeosta-

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sis [21]. Vesicular proton pumps (H^+-ATPases or V-type ATPases) are of central relevance in neurotransmitters storage in synaptic vesicles. Besides these H^+-ATPases, vesicular H^+/K^+-ATPases also seem to play an essential role in exo- and endocytosis in nerve endings [23, 24].

A central pharmacokinetic aspect regarding PPIs is their ability to penetrate the blood-brain barrier (BBB). For instance, 15% of a single i.v. administered dose of omeprazole was reported to enter the CNS [25]. Similarly, lansoprazole was also described to penetrate the BBB [26]. Overall, PPIs such as lansoprazole, esomeprazole and pantoprazole, seem to penetrate the BBB which is in line with the occurrence of adverse neurological effects, *e.g*., headache, dizziness/vertigo, depression, diplopia, sleep alterations, drowsiness, insomnia, tremor, nervousness, hallucinations and delirium [27-32]. Apart from these direct adverse reactions, further neurological side effects of PPIs can originate from indirect systemic alterations, *e.g*., *via* magnesium or vitamin B12 deficiency.

Originally, PPIs were judged to have an excellent safety profile and became one of the most prescribed drugs in recent years [13, 18, 19]. With globally increasing prescription rates, the number of previously underrecognized/underestimated, potentially detrimental effects significantly increased. The latter included - dose-dependently -, stroke, myocardial infarction, nausea, vomiting, abdominal pain and constipation, increased risk of infections with clostridium difficile, non-typhoid salmonella, Campylobacter spp., Clostridium difficile and spontaneous bacterial peritonitis, vitamin B12 deficiency, iron and calcium deficiency, hypomagnesemia, musculoskeletal impairment (hip fracture, osteoporosis/osteoporotic fracture and myopathy/rhabdomyolysis), increased risk of cirrhosis-related complications such as hepatic encephalopathy, and hepatocellular carcinoma, kidney diseases (acute interstitial nephritis, acute kidney injury and chronic kidney disease), anemia, thrombocytopenia and increased risk for pneumonia [33-38]. Recently, it has also been suggested that PPI users might be more vulnerable to high COVID-19 viral loads, although the interdependence between PPI intake and COVID-19 infection/SARS-Cov2 is still under investigation [39-41]. Based on these observations, the safety profile of PPIs, particularly related to cognitive functions and dementia, has received increasing attention.

2. ALZHEIMER'S DISEASE AND NON-ALZHEIMER'S DISEASE RELATED DEMENTIAS - EPIDEMIOLOGY AND RISK FACTORS

Based on the epidemiological World Alzheimer Report, the prevalence of dementia worldwide was rated over 46.8 million people in 2015, with an anticipated prevalence of 74.7 million by 2030 and 131.5 million by 2050. About 63% and 68% of patients suffering from dementia will be located in low- and middle-income countries by 2030 and 2050, respectively [42]. Clearly, this development will impose tremendous challenges on health care systems and therefore, dementia was designated a public health priority due to the WHO [43]. Although AD accounts for 50-70% of all cases of dementia, other non-AD related dementias also need to be considered [44]. In general, the prevalence of AD increase with age from 3.5% in patients with 75 years of age up to 46.3% in patients >95 years [45]. For the USA, the Alzheimer's Association Report "2021 Alzheimer's Disease Facts and Figures" provides a detailed statistical resource for AD data and future perspectives. As in other countries, the prevalence and incidence of AD and non-AD related dementias are increasing and likely to escalate in the upcoming decades due to the ageing society. In the USA, prevalence of AD exhibit the following increase with age: 5.3% of people aged 65-74 years, 13.8% of people aged 75-84 years, and 34.6% of people aged >85 years suffer from AD [46]. Notably, the number of individuals >65 years is expected to increase from 58 million in 2021 to 88 million by 2050 [47]. Recent calculations suggest that in the USA, approximately 6.2 million inhabitants aged >65 years suffer from AD in 2021 [47]. Similar results were observed for incidence parameters. According to evaluations in the USA in 2011, the annual incidence in people aged 65-74 years was 0.4%; in people aged 75-84 years, the incidence turned out to be 3.2% and for individuals aged >85 years an incidence of 7.6% was detected [48, 49]. Overall, it is estimated that the incidence of AD and non-AD related dementias is about to double by 2050 [50]. Thus, one predominant risk factor for late-onset AD is older age, *i.e*., the incidence of AD strongly increases with age [51, 52]. Data from the Framingham Heart Study were used to calculate lifetime risks of AD dementia by age and sex [53]. The estimated lifetime risk for AD at age 45 was approximately 20% for women and 10% for men. The risks for both sexes were slightly higher at an age of 65 years [53]. Importantly, gender specific differences in prevalence, incidence and lifetime risk were consistently detected for AD and non-AD related dementias with increased parameters in females compared to males [46]. Furthermore, racial and ethnic differences in the prevalence of AD and other dementias were observed. In the USA for example, older Hispanic and Black Americans have a higher probability than older White Americans to develop AD and other dementias [48]. In general, AD is supposed to depend on multiple factors rather than a single cause. The latter holds true, *e.g*., for genetic alterations that can dramatically increase the risk of AD. Such genetic factors include, for example, the APOE-ε4 status [54, 55]. The APOE-ε4 gene exerts a tremendous impact on late-onset AD and is engaged in intravascular cholesterol transport. Three different alleles of the APOE gene have been characterized, *i.e*., ε2, ε3 and ε4, which can be arranged in six potential allelic settings: ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4. Both racial and ethnic background affect the APOE allelic distribution [56-58]. The APOE-ε4 form poses a higher specific risk of developing AD on its owner compared to those carrying the ε3 allele. Importantly, the APOE-ε2 form is supposed to decrease the AD risk compared to APOE-ε3 carriers. Inheritance of one ε4 copy goes together with a 3-fold higher risk of developing AD compared to a ε3/ε3 carrier. Moreover, the ε4/ε4 genotype goes together with an 8-12-fold risk of AD development [59-61]. Also, ε4 inheritance increases the level of amyloid beta (Aβ) accumulation [62] and triggers AD at an earlier age compared to ε2 or ε3 carriers [63]. In the USA,

56-65% of patients diagnosed with AD turned out to be monoallelic APOE-ε4 gene carriers, whereas 11% of AD patients carried two APOE-ε4 copies [64, 65]. Importantly, long-lasting strong mental activity and challenges, complex social networking and interactions can beneficially counteract the development of AD in APOE-ε4 risk patients [66].

Genetic mutations, in general, account for a rather small percentage (< 1%) of AD cases [67]. Some are relevant in early-onset familial Alzheimer Disease (AD) and include mutations in the amyloid precursor protein (APP), presenilin 1 and presenilin 2 [68]. Complex genetic syndromes such as trisomy 21 (Down's syndrome) represent rather uncommon genetic conditions that, however, greatly influence Alzheimer's risk [69]. Large population-based studies revealed that - although a family history of AD is not a prerequisite for developing AD - individuals with first-degree relatives with AD are more likely to develop AD than those without a first-degree relative with AD [59, 70, 71].

Numerous other risk/susceptibility factors were identified to contribute to the etiopathogenesis and clinical progression of AD (see AD continuum, *i.e*., preclinical AD, Mild Cognitive Impairment (MCI), mild, moderate and severe AD) and multiple more are likely to be discovered in the future [72]. Besides intrafamilial factors including heredity (genetic factors), other non-genetic, modifiable factors are also of special relevance. Modifiable risk factors associated with an increased risk of dementia include cardiovascular diseases [73], smoking [74-78], diabetes [79-82], midlife obesity [83-87], prehypertension [87], hypertension [83, 87-91], high cholesterol [92, 93], diet/nutrition, inadequate sleep or poor sleep quality [94], excessive alcohol use [95], depression [96] and hearing impairment [97]. Notably, the functional interdependence between risk factors and AD is complex, *e.g*., late-onset of obesity and hypertension actually seems to reduce the risk of dementia [98, 99]. It should be noted that Traumatic Brain Injury (TBI), even mild TBI, and chronic traumatic encephalopathy (*e.g*. in contact sports) also increase the risk of dementia [100, 101].

Further important risks factors are related to the exposure to environmental factors, *e.g*. substances toxic to the nervous system such as air pollution, lead and pesticides [102-104]. There is emerging evidence that exposure to air pollution, *e.g*., fine particulate matter air pollution, which consists of tiny solid particles and liquid droplets generated by fuel combustion, fires, and processes that produce dust, may increase the risk of dementia [105-107].

Another important risk factor is education. Individuals with formal education, a mentally stimulating environment with complex social and cultural interactions, physical activity and high socioeconomic status have a lower risk for AD and non-AD related dementias [57, 108-113]. In contrast, less years of education are accompanied by more cardiovascular risk factors, less physical activity, higher risk of diabetes [114-116], hypertension [117] and smoking [118], all of which increasing the risk of developing dementia.

It has been suggested that positive interference with modifiable risk factors is capable of preventing up to 40% of dementia cases [47]. It is important to point out that risk factors can differentially affect various types of dementia.

In summary, genetic, environmental and modifiable, non-genetic factors characterize the individual health settings, including comorbidity, multimorbidity, (poly)medication and health care factors. All these parameters contribute to the individual risk of developing AD or non-AD related dementias. The importance of a positive modification of these risk factors is also underlined by the lack of effective therapy options in AD and related dementias.

3. PPI MEDICATION AND DEMENTIA - CLINICAL TRIALS AND PHARMACO EPIDEMIOLOGICAL STUDIES

In the beginning of this century, some studies first raised concerns of a potential impairment of cognitive function and increased risk of conversion to MCI, dementia in general, and specifically AD among PPI users. Subsequently, these findings triggered a number of further studies and investigations (Table **1**).

In 2015, Haenisch *et al*. reported results from a longitudinal, multicenter cohort study in elderly primary care patients (German Study on Aging, Cognition and Dementia in Primary Care Patients, AgeCoDe). Patients receiving PPI medication had a significantly increased risk of any dementia and AD in specific compared with non-users [119]. Later, the same group presented additional results from a prospective cohort study using observational data from 2004 to 2011, derived from the largest German statutory health insurer in elderly patients. Those receiving regular PPI medication were reported to have a significantly increased risk of incident dementia compared with patients not receiving PPI medication [14]. Both studies considered covariates as potential confounding factors, *i.e*., age, sex, comorbidities/multimorbidity and polypharmacy. In addition, Haenisch *et al*. (2015) took into account the APOE-ε4 allele carrier status and the educational level.

Many authors raised concerns regarding interference with further confounders, such as alcohol use/abuse, hypertension, but also prion infection susceptibility [120-129]. Nguyen and Hur (2016) specifically questioned the proposed underlying mechanism of action linking dementia and PPI use. The latter suggested that the modulation of enzymatic activity may result in increased Aβ levels. Thus, open questions also remained concerning the potential mechanism(s) related to other forms of dementia [127]. Keller (2016) specifically raised the confounding factor of dietary aluminium ingestion which is speculated to play a pathophysiological role in the onset and progression of dementia [128, 130]. Meta-analysis revealed that individuals exposed to aluminum were 71% more likely to develop AD [131]. It is also likely that patients with indication for PPI use have used strong antacids containing aluminum hydroxide which might have interfered with the observed association reported by Gomm *et al*. (2016).

Table 1. Studies / publications investigating a potential association between PPI uptake and the incidence and progression of dementia (in chronological order).

Studies / Publications	Study Design / Data Origin	Country	Study Group Sizes / Characteristics	Types of Dementia / Parameters Investigated	Potential Confounders Considered / Limitations	Conclusions
Haenisch *et al.* (2015)	Longitudinal, multicenter cohort study in elderly primary care patients (German Study on Aging, Cognition and Dementia in Primary Care Patients, AgeCoDe).	Germany	3,327 community-dwelling persons aged ≥ 75 years.	AD and non-AD related dementias.	Age, sex, education, ApoE4 allele status, polypharmacy, comorbidities, i.a. depression, diabetes, ischemic heart disease, and stroke.	Patients receiving PPI medication had a significantly increased risk of any dementia.
Akter *et al.* (2015)	Computerized neuropsychological testing using the Cambridge Neuropsychological Test Automated Battery.	Bangladesh	Sixty volunteers of either gender (age range 20-26 years).	Visual memory, executive functions, working memory, planning and strategy development, speed of response, and sustained attention.	Short-term PPI adminstration, limited sample size.	Significant impairment in visual memory, attention, executive function, and working and planning function upon PPI uptake.
Gomm *et al.* (2016)	Prospective cohort study using observational data from 2004 to 2011, derived from the largest German statutory health insurer (Allgemeine Ortskrankenkassen, AOK).	Germany	73,679 participants, aged ≥ 75 years, free of dementia at baseline.	AD and non-AD related dementias.	Analysis was adjusted for potential confounding factors, including age, sex, comorbidities, and polypharmacy.	Patients receiving regular PPI medication had a significantly increased risk of incident dementia compared with the patients not receiving PPI medication.
Wijarnpreecha *et al.* (2016)	Literature search performed in the MEDLINE and EMBASE database from inception to April 2016.	See related original studies / databases	See related original studies / databases.	See related original studies / databases.	See related original studies / databases.	Increased risk of dementia among PPI users.
Booker *et al.* (2016)	Case-control study including German primary care patients with first diagnosis of dementia (all-cause) during the index period (01/2010-12/2014).	Germany	11,956 cases (initial diagnosis of dementia, all causes) and the 11,956 controls (without dementia), aged 70-90 years. Participants were matched on the basis of age, sex, type of health insurance, and physician.	AD (Alzheimer's disease (G30)) and related dementias (vascular dementia (F01) and unspecified dementia (F03)).	Diabetes, lipid metabolism, stroke incl. Transient Ischemic Attack (TIA), Parkinson's Disease (PD), intracranial injury, coronary heart disease, Mild Cognitive Impairment (MCI), mental and behavioral disorders due to alcohol use. Related medication was also assessed.	PPIs were associated with a decreased risk of developing dementia.
Goldstein *et al.* (2017)	Observational, longitudinal study, data from National Alzheimer's Coordinating Center (NACC) database from 33 Alzheimer's Disease Centers from September 2005 through September 2015 (NIH-NIA supported).	USA	10486 persons aged ≥ 50 years (all had baseline normal cognition (n = 7,404) or MCI (n = 3,082)).	AD	Demographic characteristics, vascular comorbidities, metabolic disorders, mood, polypharmacy, i.a., use of anticholinergics and antihistamines, reliance on self-reported PPI use and lack of dispensing data.	PPIs were not associated with greater risk of dementia or of AD. Continuous or intermittent PPI use was associated with lower risk of decline in cognitive function and lower risk of conversion to MCI or AD. This lower risk was found for persons with normal cognition or MCI.

(Table 1) contd….

Studies / Publications	Study Design / Data Origin	Country	Study Group Sizes / Characteristics	Types of Dementia / Parameters Investigated	Potential Confounders Considered / Limitations	Conclusions
Taipale *et al.* (2017)	A Finnish nationwide nested case-control study (MEDALZ). Data were derived from a Finnish nationwide health-care register, including Special Reimbursement Register, Prescription Register, Hospital Discharge Register.	Finland	Community-dwelling individuals with newly diagnosed AD during 2005-2011 (n = 70,718), and up to four age-, sex-, and region of residence-matched comparison individuals for each case (n = 282,858)	AD	Cardiovascular diseases (hypertension, coronary artery disease, chronic heart failure, chronic arrhythmias), diabetes, stroke, depression, polypharmacy.	PPI use was not associated with risk of AD with 3-year lag window applied between exposure and outcome. Longer duration of use was not associated with risk of AD. Higher dose use was not associated with an increased risk. In conclusion, no clinically meaningful association between PPI use and risk of AD was detected. The results for longer duration of cumulative use or use with higher doses did not indicate dose-response relationship.
Lochhead *et al.* (2017)	Prospectively collected data on medication use and other potential risk factors from the Nurses' Health Study II (NHS II, based on self-administered computerized neuropsychological test battery).	USA	13,864 female participants (aged 50–70 years).	Assessment of cognitive function.	Education level, comorbidities (smoking status, alcohol consumption, cardiovascular diseases, metabolic disorders, BMI, *etc.*), polypharmacy.	The study results do not support the suggestion that PPI use increases dementia risk.
Batchelor *et al.* (2017)	Systematic review (meta-analysis) according to the PRISMA statement (registered on PROSPERO).	See related original studies / databases	Relevant studies were identified in Medline, EMBase, Cochrane Central Register of Controlled Trials (CENTRAL), PSYCinfo, Scopus, Web of Science and ClinicalTrials.gov. Eleven studies were included (with four studies investigating PPI use and dementia and seven studies exploring PPI use and acute cognitive impairment).	AD, non-AD dementias and acute cognitive impairment (see also related original studies / databases).	Familiy history of dementia, hypertension, diabetes, physical exercise, air pollution, intestinal microbiota, aluminium containing medications and medication in general (see also related original studies / databases).	The interpretation of the reported association between PPI treatment and dementia is hampered by methodological aspects and potential bias. The latter require future longitudinal studies.
Tai *et al.* (2017)	Population-based retrospective cohort study using the Taiwan National Health Insurance (NHI) claims database-National Health Insurance Research Database (NHIRD).	Taiwan	Patients initiating PPI therapy between January 2000 and December 2003 without a prior history of dementia. Analysis of data of 15726 participants aged >40 years. PPI users (n = 7,863), non-PPI users (n = 7,863).	AD and non-AD dementias.	Comorbidities included, *i.e.*, diabetes mellitus, hypertension, hyperlipidemia, peripheral vascular disease, ischemic heart disease, depression, and ischemic stroke. Potential confounding drugs included anticoagulants, NSAIDs, antiplatelet agents, antidiabetic agents, antihypertensives, and statins.	An increased risk for dementia was identified among the Asian PPI users. Cumulative PPI use was significantly associated with dementia.

(Table 1) contd….

Studies / Publications	Study Design / Data Origin	Country	Study Group Sizes / Characteristics	Types of Dementia / Parameters Investigated	Potential Confounders Considered / Limitations	Conclusions
Gray *et al*. (2018)	Prospective population-based cohort study (Kaiser Permanente Washington, an integrated healthcare delivery system in Seattle, Washington).	USA	Individuals aged ≥ 65 years without dementia at study entry (n = 3,484).	AD and non-AD dementias.	Demographic characteristics (age at study entry, sex, years of education), medical history (cardiovascular disorders, metabolic diseases), health behaviors (BMI, smoking behavior, exercise, mood disorders), functional measures and medications.	PPI use was not associated with dementia risk, even for people with high cumulative exposure.
Imfeld *et al*. (2018)	A case-control analysis on the UK-based Clinical Practice Research Datalink (CPRD) through a license from the UK Medicines and Healthcare products Regulatory Agency (MHRA).	UK	41,029 patients aged ≥ 65 years with newly diagnosed AD, vascular dementia or unspecified dementia between 1998 and 2015.	AD, vascular dementia and unspecified dementia.	Age, sex, calendar time, general practice, and number of years of recorded history were matched between groups. Comorbidities and co-medications at or within the year prior to the index date were considered. Covariates include arterial hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, stroke, depression, and polypharmacy (i.a., of platelet aggregation inhibitors, anticoagulants, NSAIDs, SSRIs, SNRIs).	Long-term PPI use was not associated with an increased risk of developing AD or VaD.
Hwang *et al*. (2018)	A population-based longitudinal study using the Korean National Health Insurance Corporation claims database merged with national health examination data for 2002-2013.	Republic of Korea	The study cohort included 70,529 individuals who were free of dementia in 2007. Incident dementia was assessed throughout follow-up until 2013. 1,297 participants developed dementia during the study period.	AD and non-AD dementias.	Covariates included pulmonary diseases, renal diseases, liver diseases, metabolic disorders.	PPI use was not associated with an increased risk of dementia. PPI use was not associated with increased risk.
Li *et al*. (2019)	Meta-analysis to determine potential association of PPI use and risk of dementia among older people.	See related original studies / databases	Studies were identified in PubMed, EMBASE, and Cochrane Library databases from inception to February 2018. Cohort studies that had identified a risk of dementia or AD among PPI users compared with non-PPI users were considered. Quality of studies was catagorized *via* the Newcastle-Ottawa Scale (NOS). Six cohort studies were selected.	See related original studies / databases.	See related original studies / databases.	No significant association between PPI intake and risk of dementia or AD could be detected.
Song *et al*. (2019)	Meta-analysis to investigate the risk of dementia and AD among PPI users.	See related original studies / databases	Relevant studies were identified in PubMed, Web of Science, EMBase and ScienceDirect. Ten independent studies with 642,305 participants were included.	See related original studies / databases.	See related original studies / databases.	PPI intake does not increase the risk of dementia and AD.

(Table 1) contd….

Studies / Publications	Study Design / Data Origin	Country	Study Group Sizes / Characteristics	Types of Dementia / Parameters Investigated	Potential Confounders Considered / Limitations	Conclusions
Torres-Bondia *et al*. (2020)	A community-based retrospective cohort study based on data available from 1st January 2002 to 31st December 2015 in the Catalan health service (CatSalut) system.	Catalonia / Spain	PPI users (n = 36,360) and non-users (n = 99,362) aged ≥ 45 years. A lag window of 5 years was considered between the beginning of the PPI treatment and the diagnosis of dementia.	AD and non-AD dementias.	Age, sex, hypertension, diabetes and dyslipidaemia were considered as confounding variables.	PPI use was not associated with the risk of AD. A weakly but significantly increased risk of non-AD dementias was observed among PPI users. A higher dose of PPIs was not associated with an increased risk of either AD or non-AD dementias. An increased risk of AD and non-AD dementias was detected in users of two types of PPIs compared with one type PPI users.
Cooksey *et al*. (2020)	Large-scale, multi-centre, population-based study using electronic health-data from the Secure Anonymised Information Linkage (SAIL) Databank, Wales (UK) from 1999 to 2015.	UK	183,968 persons who had ever been prescribed PPIs, aged ≥ 55 year, compared to 131,110 non-PPI exposed individuals.	AD and non-AD dementias.	Personal characteristics (*e.g*., age, sex, smoking status, obesity, alcohol consumption), confounding comorbidities (diabetes, cardiovascular disease, depression, anxiety, head injury, hypertension, high cholesterol, vitamin-B12 deficiency), concomitant medications (anxiolytics, anti-depressants, anticoagulants, antiplatelets, statins, hormone replacement therapy (HRT), vitamin-B12 supplements, iron and antihypertensives).	No association between PPI use and increased dementia risk was detected.
Desai *et al*. (2020)	Meta-analysis to investigate a potential association between PPI use and the risk of dementia.	See related original studies / databases	Literature search in PubMed, Embase, Google Scholar, and Cochrane for studies investigating the risk of cognitive decline and dementia among PPI users versus non-PPI users in prospective studies.	See related original studies / databases.	Retrospective database linkage studies, case reports, case series, editorials, uncontrolled cohort studies, cross-sectional studies, and review articles were excluded.	No significant relationship between PPI use and dementia in prospective studies with at least a 5-year follow-up.
Khan *et al*. (2020)	Meta-analysis to investigate a potential association between PPI intake and the risk of dementia.	See related original studies / databases	Literature / study search in MEDLINE, EMBASE, ISI Web of Science, and Cochrane databases, up to February 2019. Quality categorisation of observational studies was assessed using the Newcastle-Ottawa scale and the GRADE approach. Eleven studies were included comprising 642,949 individuals.	See related original studies / databases.	See related original studies / databases.	No evidence for an association between PPI use and increased risk of dementia.

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Studies / Publications	Study Design / Data Origin	Country	Study Group Sizes / Characteristics	Types of Dementia / Parameters Investigated	Potential Confounders Considered / Limitations	Conclusions
Zhang *et al.* (2020)	Meta-analysis to investigate a potential association between PPI intake and the risk of dementia.	See related original studies / databases	Literature search in English and Chinese databases from origination to December 2018. Six studies were considered, including a total of 166,146 participants.	See related original studies / databases.	See related original studies / databases. Exclusion criteria included animal experimental models, systematic review articles, letters, meta-analyses, comments, case reports; duplicated studies, studies without possibility to retrieve or calculate data of interest.	Result show a significant increase in dementia risk with PPI use. Subgroup analyses revealed a significant association between PPI use and the risk of dementia in Europe and among participants aged ≥ 65 years.
Chen *et al.* (2020)	Population-based retrospective cohort study using the Taiwan National Health Insurance (NHI) claims database-National Health Insurance Research Database (NHIRD).	Taiwan	Patients aged ≥ 65 years with cumulative PPI use between January 2000 and December 2005 (PPI user cohort n = 6,584; PPI non-user cohort, n = 6,584).	AD and non-AD dementias.	Covariates included sex, age, comorbidities (*e.g.* diabetes mellitus, hyperlipidemia, coronary artery disease, stroke, depression) and comedication (*e.g.* NSAIDs, anti-hypertensives, anti-diabetic agents, statins, aspirin, and anti-depressants).	PPI users exhibited a significantly elevated risk of dementia compared to PPI non-users.
Wu *et al.* (2020)	Population-based propensity score matched retrospective cohort study using Taiwan's National Health Insurance (NHI) Research Database.	Taiwan	Patients aged ≥ 40 years with PPIs use between 2000 and 2010 (PPI user cohort compared to PPI non-user cohort, n = 2,583 each).	AD and non-AD dementias.	Covariates considered: age, sex, hypertension, diabetes mellitus, coronary artery disease, hyperlipidaemia, stroke, asthma, chronic renal failure, depression.	No association between PPI uptake and a risk of developing dementia was detected.
Collin *et al.* (2021)	Wisconsin Registry for Alzheimer's Prevention study.	USA	Questionnaires on medical history, blood samples and neuropsychological assessments from n = 1,573 individuals over a 10–15 year period.	AD and non-AD dementias.	Covariates included gender, antihypertensive drug use, physical activity, cigarette use, APO ε4 carrier status, H2RA use, heart disease, diabetes, depression, anxiety, lung disease.	PPI use was not associated with memory decline in a sample of subjects with familial risk factors for dementia.
Ahn *et al.* (2020)	Population-based cohort Study of Health in Pomerania (SHIP).	Germany	Participants aged 21 - 89 years, n = 2653 (baseline examinations 1997-2001, follow-up examination 2002-2006 and 2008-2012).	Brain volume (MRI), estimated brain age and cognitive function (Verbal Learning and Memory Test, VLMT; Nuremberg Age Inventory, NAI).	Multiple regression used to adjust confounding factors, *e.g.* age, sex, BMI, cognitive function-altering medications and further medication, socio-demographic variables, income, educational level, smoking experience, alcohol consumption, diabetes and cerebrovascular pathologies.	No relationship between PPI use and brain aging was detected.
Thunell *et al.* (2021)	Meta-analysis / scoping review to identify drug classes (including PPIs) associated with increasing or decreasing risk for AD or related dementias	See related original studies / databases	Systematic search using PubMed, SCOPUS, and Cochrane Central Register of Controlled Trials (CENTRAL) databases for all published studies on humans from January 2008 till August 2018.	See related original studies / databases.	See related original studies / databases.	Twelve observational and four review studies examining PPIs were considered and exhibited mixed findings. Five of the 12 studies described increased risk of dementia or cognitive decline, two reported neuroprotective benefits, and five were inconclusive.

Note: Relevant publications are listed including information about study design/data origin, country, study group characteristics (number of participants), types of dementia investigated, consideration of potential confounding factors and conclusions. Publications suggesting an association of PPI use and increased risk of dementias are highlighted in red. Those studies or meta-analyses reporting no increased risk of dementias upon PPI use or a neuroprotective effect are highlighted in blue. Neutral publications are listed in black.

Most important, both studies by Haenisch *et al*. (2015) and Gomm *et al*. (2016) initiated a number of subsequent investigations to gain further insight and clarification regarding the functional interdependence between PPIs and AD or non-AD related dementias (Table **1**).

A literature search by Wijarnpreecha *et al*. (2016) including four observational studies and another small interventional study carried out by Akter *et al*. (2015) seemed to support the hypothesis of an increased risk of dementia among PPI users [17, 132]. Apparently, these findings were also backed up by preclinical data that suggested that PPIs can enhance Aβ (Aβ37, Aβ40 and Aβ42) production. Aβ is derived from the sequential cleavage of the Amyloid Precursor Protein (APP) by β- and γ-secretases and was found to be increased in both cellular and animal models upon PPI exposure [133]. Recently, Kumar *et al*. (2020) reported that PPIs also act as inhibitors of the choline acetyltransferase (ChAT) and that this mechanism might serve as an ultimate biochemical explanation for the potentially increased incidence of dementia upon PPI use [134]. Various other pathobiochemical and pathophysiological implications of PPIs related to AD and non-AD related dementias have been reported including the interaction with tau protein and effects on the neuronal microenvironment [135].

Notably, both early preclinical and clinical findings have now triggered a number of large-scale clinical trials worldwide to get further insight into the potential association between the use of PPIs and the risk of dementia. Importantly, most of these subsequent trials and meta-analyses could not confirm the initial alerting results: A case-control study including primary care patients (aged 70-90 years with 11,956 cases and 11,956 controls) with first diagnosis of dementia showed that the use of PPIs correlated with a decreased risk of developing dementia [136]. An observational, longitudinal study by Goldstein *et al*. (2017) revealed that PPI intake was not accompanied with a greater risk of dementia or of AD [7]. A Finnish nationwide nested case-control study also did not find a clinically meaningful association between PPI use and risk of AD [137]. The analysis of prospectively collected data of the Nurses' Health Study II did not reveal a convincing association between PPI use and cognitive function or any evidence for an increased risk of dementia [138]. A prospective population-based cohort study by Gray *et al*. (2018) demonstrated that PPI use did not increase the risk of dementia, even in individuals with high cumulative PPI exposure [139]. Studies by Moayyedi *et al*. (2017) using health care registry data could also not reveal a correlation between PPI use and AD, even with long-term or high-dosage use [140]. At that time, a meta-analysis and systematic review on information available so far on dementia, cognitive impairment and PPI treatment pointed out the inconsistent results and methodological limitations and requested for further studies [141].

Next, a case-control analysis on the UK-based Clinical Practice Research Datalink (CPRD) found no evidence of increased risk of AD-related dementias to PPIs [142]. Hwang *et al*. (2018) reported from a population-based longitudinal study that was based on the Korean National Health Insurance Corporation claims database merged with national health examination data for the period 2002-2013. The study revealed no increased risk of dementia upon PPI use [143]. A large-scale, multi-center, population-based study using electronic health data from the SAIL (Secure Anonymised Information Linkage) Databank in Wales (UK) revealed no association between PPI use and increased risk of dementia [144]. Another large community-based retrospective cohort including data from 2002 to 2015 in the Catalan health service (CatSalut) system revealed no higher incidence of AD among PPI users. However, a minor increase in the risk of non-AD related dementias among PPI users was detected [145]. A recent study testing neuropsychological functioning in healthy adults with familial risk factors for dementia (APOE-ε4 carrier status) could not detect any association with memory decline [146]. A population based cohort study from West Pomerania (Germany) investigated the effects of PPI treatment on brain volume, estimated brain age and cognitive function. No relationship between PPI use and brain aging was detected [147]. In addition, several meta-analyses were recently published using, i.a., PubMed, Web of Science, Embase, Google Scholar, and Cochrane library databases to examine a potential association between PPIs and AD [148-151]. None of these studies provided evidence that PPI intake increases dementia and AD risk. Zhang *et al*. (2020), however, performed a meta-analysis which is in support of an association between PPIs and dementia [152, 153]. Potential reasons are different inclusion/exclusion criteria for the different studies. The authors, for example, included only cohort studies, as case-control studies could introduce selection and recall biases. Furthermore, in cohort studies, the demonstration of causality was judged to be stronger. Finally, quality criteria also play an important role. The results are also affected by stratification, *e.g*., of age of the participants, the follow-up time, the location of the study and most importantly, the adjustment of potential confounding factors. Also, the primary outcome of interest differs, focusing on AD, non-AD related dementias, or all dementias.

A recent scoping review by Thunell *et al*. (2021) analyzed reports about drug classes and associated increasing or decreasing AD or related dementia risk. Besides tetracyclic antidepressants, antispasmodics and antihistaminics, a hypothesized increased risk for dementia was also attributed to PPIs [154]. The authors also confessed that there is a mixed picture of PPI effects on dementia.

The general drawbacks of retrospective studies are nicely pinpointed by reports of Tai *et al*. (2017), Chen *et al*. (2020) and Wu *et al*. (2020). All three studies rely on population-based retrospective cohort studies using the same Taiwan National Health Insurance Research Database (NHIRD). The data coverage and the pharmacoepidemiological analytical details differ in some points. Whereas Tai *et al*. (2017) and Chen *et al*. (2020) suggest that PPI users exhibited a significantly elevated risk of dementia compared to PPI non-users, Wu *et al*. (2020) clearly indicated that no association between PPI uptake and risk of developing dementia was detected [155-157].

It should be noted that there are further studies on PPIs and dementia/cognitive decline that were published in national journals only [158] or as case reports [31, 159-161]. Some studies have focused on PPI use and delirium [162, 163]. All these studies are not further discussed in this summary.

Importantly, none of the studies carried out so far met Randomized Controlled Trials (RCT) criteria that reflect the gold standard of clinical trials [154]. Thus, to evaluate and establish direct cause and effect relationships between PPI use and incident dementia in the elderly, randomized, prospective clinical trials are needed.

4. PPIs AND DEMENTIA - RELEVANCE OF PHARMACODYNAMICS, PHARMACOKINETICS AND PHARMACOGENOMICS

Obviously, early and recent pharmacoepidemiological results on PPIs and dementia are diverse which is likely to be related to the characteristics of specific study designs, different patient populations, and potential limitations of data sources, including unknown/masked confounding factors [1].

Often used data sources for pharmacoepidemiological analyses such as claims data have several advantages, *e.g*. analyses can be performed in a real-life setting in an unselected patient population. Health claims data cover the total population, including people who live in institutions such as nursing homes or assisted living. Furthermore, recall bias or selection bias is avoided because of the use of routine health care records. Limitations include residual confounding despite adjusting for several potential confounding factors. In particular, claims data mostly lack detailed socioeconomic, laboratory, or genetic parameters.

An additional aspect that might shed new and clarifying light on the potential controversy about PPI effects on AD and non-AD related dementias is associated with the biochemical and physiological, *i.e*. the pharmacodynamic effects of PPIs. Many, if not most, drugs are indeed multi-target in character and the same holds true for PPIs [164]. It is beyond the scope of this review to elaborate the etiopathogenesis of the various types of dementia described so far. To illustrate the complex functional interdependence between PPIs and dementive processes, we will therefore focus on AD and how PPIs might interfere with the related etiology and pathogenesis. As outlined above, the central histopathological hallmarks of AD comprise the deposition of extracellular Aβ plaques (Aβ dyshomeostasis, amyloid hypothesis) and intracellular neurofibrillary tangles (NFTs) originating from hyperphosphorylated tau protein. Both processes result in neurodegeneration and progressive neuronal cell loss [94, 165].

Whereas early pharmacoepidemiological studies - in favor of an association between PPIs and AD - referred to the potential increase of Aβ and alterations in vitamin B12 homeostasis upon PPI intake as potential pathophysiological mechanisms [135], it is mandatory to point out that PPIs were also reported to exert anti-amyloidogenic and anti-inflammatory biochemical effects and might thus be beneficial in AD. PPIs for example are known to exert anti-inflammatory actions. Inflammatory processes such as astrocytic activation are involved in the pathogenesis of different neurodegenerative diseases. Hashioka *et al*. (2011) demonstrated that PPIs attenuate interferon gamma (IFN-γ)-induced neurotoxicity of human astrocytes via suppression of the signal transducer and activator of transcription 3 (STAT3) signaling pathway. PPIs with antineurotoxic properties were thus speculated to serve as a potential treatment option in AD and other neuroinflammatory disorders associated with activated astrocytes [166-168]. A striking biochemical mechanism that seems largely underestimated, is the interference of PPIs with Liver X Receptors (LXRs) [169]. LXRα and LXRβ serve as transcription factors that control gene expression primarily related to cholesterol metabolism. Within the CNS, cholesterol metabolism is relevant for APP proteolytic cleavage, secretase activities, Aβ aggregation and clearance [169]. Importantly, LXR mediates the transcriptional control of APOE which plays a crucial role in AD [170]. Cronican *et al*. (2010) demonstrated that PPIs, such as lansoprazole act as LXR agonists and enhance the expression of LXR modulated target genes [171, 172]. Whereas lansoprazole increased APOE levels in primary wild-type astrocytes, this effect was abolished in LXRα/β double KO mice. Notably, other PPIs also exhibit agonistic effects on LXR with different efficiencies [171]. In 2015, these results were further supported by studies of Skerrett *et al*., who demonstrated that LXRs- and peroxisome-proliferator receptor γ (PPARγ)- agonists reduce Aβ levels as both soluble and deposited forms of Aβ. They further improve cognitive deficits in AD mouse models by inducing transcription and lipidation of APOE and by suppression of microglial proinflammatory genes [173]. These beneficial effects were also confirmed on the behavioral level in an AD mouse model [174].

The LXR/PPARγ pathway is likely to play an essential role in the interpretation of recent pharmacoepidemiologic results and the planning of future studies. The clearance of Aβ from the CNS is known to be dependent on the APOE gene related polymorphism being facilitated by APOE-ε2 [170]. The latter is transcriptionally regulated by PPARγ and LXR, in combination with the Retinoid X Receptor (RXR) [175]. Compelling results demonstrated that the RXR agonist bexarotene, originally approved for the treatment of cutaneous T cell lymphoma, dramatically enhances APOE mediated clearance of soluble and deposited Aβ and restores cognitive deficits in various AD mouse models [176-180]. Similar results were observed for PPARγ agonists such as pioglitazone. The latter stimulates Aβ degradation by both microglia and astrocytes via LXR and APOE activation in AD mouse models, *e.g*., APP/PS1. Amyloid deposits were removed, microglia and astrocytes were massively recruited for clearance, and memory deficits were restored in PPARγ agonist treated mice [181, 182].

Another PPI interdependence with AD was suggested to be based on prion infections. In mice, the acidic gastric juice was shown to protect against prion infection [183]. Prions

are known to trigger/induce neurodegenerative processes. Notably, this phenomenon seems to be underestimated in general [183].

It is obvious that pathophysiologically, either a decrease of Aβ production or an increase of Aβ clearance is beneficial in AD treatment. As outlined above, the armamentarium of pharmacodynamic properties of PPIs covers various biochemical, cellular actions such as enhanced Aβ production, ChAT-inhibition, LXR-receptor and APOE activation with potentially enhanced Aβ clearance, disturbance of vitamin B12 homeostasis, attenuated IFN-γ-induced neurotoxicity and suppression of the STAT3 signaling pathway, V-ATPase inhibition of lysosomes with reduced clearance of Aβ, or other yet discovered and still unknown mechanisms [135, 164]. Pharmacodynamically, PPIs can clearly trigger opposing mechanisms, *i.e*., an increase in Aβ production and proinflammation on the one hand, and increased clearance of soluble Aβ and amyloid plaques from the CNS facilitated by APOE with anti-inflammatory action on the other hand. At a first glance, the Janus-like discrepancies in pharmacoepidemiologic results (Table **1**) might solely originate from differences in study designs and multiple inherent known and unknown confounding factors. However, given their multi-target character, PPIs might exert a net pharmacodynamic effect in Aβ homeostasis which either aggravates or reduces Aβ production, Aβ clearance, inflammatory processes and the cognitive/behavioral phenotype. However, this net effect itself might be dependent on the various pharmacokinetic parameters of the different PPI members, such as BBB permeability or cytochrome P450 (CYP) dependent metabolization. Other patient related (risk) factors such as the individual APOE gene related polymorphism might be of central importance here as well [170, 184].

CONCLUSION

Currently, PPIs are important and practically irreplaceable drugs in the prevention and treatment of specific medical conditions for defined periods of time [185]. However, numerous adverse reactions became obvious, particularly following excessive and prolonged treatment with PPIs. Clearly, as regards the controversial implications of PPIs in AD and non-AD related dementias, further studies, particularly RCT need to be conducted. It might be hypothesized that a future solution will originate from a personalized medicinal approach, in which individualized pharmacokinetic and pharmacogenomic data of patients are modelled to predict the potential harm or benefit of short and long-term use of PPIs on AD and non-AD related dementias.

LIST OF ABBREVIATIONS

AD = Alzheimer's Disease

APP = Amyloid Precursor Protein

BBB = Blood Brain Barrier

ChAT = Choline Acetyltransferase

CNS = Central Nervous System

GERD = Gastroesophageal Reflux Disease

INF = Interferone

LXR = Liver X Receptor

MCI = Mild Cognitive Impairment

PPARγ = Peroxisome-Proliferator Receptor γ

PPI = Proton Pump Inhibitor

RXR = Retinoid X Receptor

STAT3 = Signal Transducer And Activator of Transcription 3

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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