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Proton Pump Inhibitors Do Not Cause Dementia: Refuting Sensationalized Claims in a Post-Modern Epidemiologic Era

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This summary reviews Mehta R, Kochra B, Zhou Z, et al. Association of Proton Pump Inhibitor Use with Incident Dementia and Cognitive Decline in Older Adults: A Prospective Cohort Study. Gastroenterology 2023; 165: 564-72.

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STRUCTURED ABSTRACT

Question: Is proton pump inhibitor (PPI) use associated with an increased risk of dementia or cognitive decline?

Design: Prospective cohort study based on post hoc analysis of randomized controlled trial (RCT).

Setting: ASPirin in Reducing Events in the Elderly (ASPREE) trial.

Patients: Patient population consisted of 18,934 older (≥ 65 years old) Australian and US adults with no cardiovascular disease, dementia, cognitive impairment, or physical disability and at least 5 years of life expectancy at enrollment between 2010-2014. All patients were randomized to receive low-dose (100 mg) aspirin vs placebo. No difference in mortality, dementia, or physical disability was identified, although aspirin-treated patients were more likely to have major hemorrhage events (hazard ratio [HR] = 1.38; 95% confidence interval [CI]: 1.18-1.62) during median 4.7 years of follow-up.

Interventions/Exposure: At baseline, 4667 study patients were using PPIs (24.6%), 368 used H2 receptor antagonists (1.9%) and remainder did not receive medications for gastric acid suppression.

Outcome: Since dementia and cognitive impairment were secondary outcomes of the ASPREE RCT, study patients underwent 4 cognitive tests at baseline and again at years 1, 3, 5 and final visit. Individuals with suspected dementia based on these tests were referred for definitive cognitive and functional assessments. Adjudication of dementia diagnosis was determined by a panel of neurologists, neuropsychiatrists and geriatricians using DSM-4 criteria and required presence of memory impairment plus either aphasia, apraxia, agnosia, or executive dysfunction. Panel was blinded to study patient characteristics and medication use.

Patients also had annual study visits where they were asked to bring all of their current medications as part of annual assessment. Additional potential confounders were assessed at baseline visit and annual visits, including demographic data, smoking status, alcohol consumption, body mass index, chronic kidney disease, hypertension, and diabetes.

Data Analysis: Intention-to-treat analysis. Hazard ratios (HR) calculated using Cox proportional hazards model after adjusting for baseline covariates. A "time-varying" repeated exposures analysis was performed to assess the association between new use of PPIs after age 65 with incident dementia. Finally, a network analysis was constructed using a co-occurrence matrix to determine which medications were most often used concomitantly in PPI users.

Funding: National Institute of Health. ASPREE RCT supported by National Institute on Aging, National Cancer Institute, and Medical Research Council of Australia.

Results: Among 18,934 study patients, 14,267 patients were PPI nonusers and 4667 patients were PPI users with mean age: 75.2, female: 55%-59%, White: 83%-92%, mean body mass index (BMI): 28-29, former/current smoker: 44%-46%. PPI users were more likely to be White, have lower education level, higher depression score, have chronic kidney disease, and were more likely to be using anti-hypertensive medications, statins, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants and benzodiazepines.

During total of 84,995 person-years of follow-up (median 4.5 years per person), 572 incident cases of dementia were diagnosed with 449 in PPI nonusers and 123 in PPI users. After adjusting for age, sex, years of education, race/

ethnicity, smoking status, alcohol consumption, body mass index, family history of dementia, chronic kidney disease, type 2 diabetes, hypertension, depression scores, baseline cognition and receiving aspirin or placebo at baseline, there was no difference between PPI nonusers, PPI users, and H2RA users for dementia or cognitive impairment (**Table 1**). Using additional data from the ASPREE-XT, 120,194 person-years of follow-up (median 6.3 years per person) also did not show any association: HR = 0.91; 95% CI: 0.78-1.07. Finally, using time-varying analyses to assess associations between sustained PPI use use (increasing duration of PPI use) and incident dementia, no association was identified: multivariate HR = 0.96; 95% CI: 0.91-1.00.

Medication	Dementia	Cognitive Impairment
PPI (n = 4667)	aHR = 0.88 (95% CI: 0.72-1.08)	aHR = 1.00 (95% CI: 0.92-1.09)
H2RA (n = 368)	aHR = 1.00 (95% CI: 0.59-1.74)	aHR = 1.02 (95% CI: 0.79-1.31)

Table 1. Multivariate Hazard Ratio for Dementia and Cognitive Decline for PPI Users and H2RA Users Compared to Non-Users.
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; PPI, proton pump inhibitor.

COMMENTARY

Why Is This Important?

In August 2023, Northius et al published their retrospective analyses of the Atherosclerosis Risk in Communities (ARIC) Study in Neurology and reported that PPI use "for > 4.4 years by individuals ages 45 years and older is associated with a higher incidence of newly diagnosed dementia".[1] Unfortunately, this led to a multitude of headlines in the lay media similar to this from Bloomberg: "Could Medicines for Heartburn Be Causing Dementia?"[2] Of course, as has happened with many similar reports from epidemiologic studies, this was followed by many phone calls and visits from concerned PPI users. Understandably, even primary care providers and specialists who lack epidemiologic training may be misled by these reports. Fortunately, this excellent study from the Clinical and Translational Epidemiology Unit at Massachusetts General Hospital, helps reassure patients and clinicians that PPI use does not cause dementia.

Some additional "bottom lines" may be helpful. Although observational studies linked PPIs with multiple adverse events like pneumonia, diabetes, and all-cause mortality, RCTs and prospective cohort studies[3-4] have not demonstrated any association, much less a causal relationship. This is unsurprising. Retrospective observational studies are inherently susceptible to multiple potential flaws such as misclassification of diagnosis (e.g., using post-hospitalization *International*

Classification of Diseases- 9th edition codes to identify dementia) or failure to adjust for confounders (e.g., alcohol use, chronic kidney disease, family history of dementia), which were both present in the study by Northius et al. Interestingly, earlier observational studies linked multiple medications, including antihypertensives, NSAIDs, aspirin and PDE5 inhibitors (e.g., sildenafil) with dementia, but subsequent RCTs and prospective cohort studies failed to confirm those findings.

As eloquently expressed by George Davey Smith[5], there is an "epidemic of epidemiologic reports of 'risk factors' for disease from studies that cannot realistically contribute to causal understanding," although, these studies utilize graphs, tables, and language inferring causation. Ultimately, in a post-modern epidemiologic world, there should be a greater reliance on the classic Bradford-Hill criteria[6] before any suggestion of a causal relationship is made.

Key Study Findings

After appropriate adjustment for potential confounders, there was no association between PPI use and dementia: HR = 0.88 (95% CI: 0.72-1.08).

Using additional data from the ASPREE -XT, 120,194 person-years of follow-up (median 6.3 years per person) also did not show any association: HR = 0.91; 95% CI: 0.78-1.07. Finally, using time-varying analyses to assess associations between sustained PPI use (increasing duration of PPI use) and incident dementia, no association was identified: multivariate HR = 0.96; 95% CI: 0.91-1.00.

Caution

Observational studies always have a risk of confounding, which means that there may be unmeasured variables associated with PPI use and dementia which could impact the analysis. Although adjusting for multiple confounders was performed, only an appropriately-sized RCT can (usually) overcome this problem. Data on duration or dose of PPIs used prior to onset of study was not quantified. Also, it's essentially impossible to "prove" a negative outcome, although this well-designed study should be very reassuring to PPI users worried that PPI use may increase the risk of dementia.

My Practice

When my patients and primary care colleagues express concern about the safety of PPIs, I emphasize that properly designed studies have NOT demonstrated associations between PPI use and most publicized adverse events or diseases, including dementia, hip fractures, b12 deficiency, pneumonia, etc.[2-3] PPI use is probably associated with an increased risk of enteric infections[2], including recurrent *Clostridioides difficile* colitis, and there is contradictory data about whether PPI use could be associated with renal insufficiency, possibly due to rare episodes of acute

interstitial nephritis.

Unfortunately, since PPIs are over-prescribed in individuals with any digestive symptoms, I educate my patients that PPI use in poorly, but sensationalized, epidemiologic studies are essentially identifying patients with multiple co-morbidities and polypharmacy. Therefore, I encourage patients with erosive esophagitis, recurrent or complicated peptic ulcer disease, Barrett's esophagus, or chronic and frequent GERD symptoms that are only responsive to PPIs, to continue their medications (albeit at the lowest effective dose) and not be scared by media reports. Having said that, PPIs are overprescribed and should be de-prescribed if there isn't an appropriate indication.

For Future Research

In this post-modern epidemiologic era, authors of retrospective analyses of large databases should emphasize that these are hypothesis-generating studies, as opposed to hypothesis-answering, while applying Bradford-Hill criteria before making any suggestions of causality between an exposure and an adverse outcome.

Conflict of Interest

Dr. Schoenfeld has no relevant conflicts of interest.

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