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Proton-pump inhibitor use is associated with a broad spectrum of neurological adverse events including impaired hearing, vision, and memory

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Proton-pump inhibitors, PPIs, are considered effective therapy for stomach acid suppression due to their irreversible inhibition of the hydrogen/potassium pump in the gastric parietal cells. They are widely prescribed and are considered safe for over-the-counter use. Recent studies have shown an association between PPI use and Alzheimer dementia, while others have disputed that connection. We analyzed over ten million United States Food and Drug Administration Adverse Event Reporting System reports, including over forty thousand reports containing PPIs, and provided evidence of increased propensity for memory impairment among PPI reports when compared to histamine-2 receptor antagonist control group. Furthermore, we found significant associations of PPI use with a wide range of neurological adverse reactions including, migraine, several peripheral neuropathies, and visual and auditory neurosensory abnormalities.

Proton pump inhibitors (PPIs) are drugs commonly used in treatment of acid-related disorders including gastroesophageal reflux disease, *Helicobacter Pylori* induced gastric ulcers, duodenal ulcer, erosive esophagitis, and Zollinger-Ellison syndrome[1,2]. Treatment of acid-related disorders includes antacids, PPIs, and histamine-2 receptor antagonists (H2RAs)[3]. The PPIs are preferred over the H2RAs because of their superior efficacy due to their irreversible inhibition of the H+/K+ ATPase[4,5]. National Health and Nutrition Examination Survey (NHANES) revealed a rise in the number of PPI prescriptions (2.9–7.8%) among 40–64 year old individuals from 1999 to 2012[6]. NHANES did not account for over-the-counter (OTC) PPI intake. The class of PPI drugs includes six Food and Drug Administration (FDA) approved medications such as rabeprazole, lansoprazole, pantoprazole, esomeprazole, omeprazole, and dexlansoprazole. The high number of the PPI prescriptions, their OTC availability, and the increased likelihood of long-term use have raised concerns over unexpected adverse reactions (ADRs). It was demonstrated that the PPI pharmacology may not be limited to local inhibition of H-K-ATPase pump in parietal cells in the stomach[7,8].

Common ADRs of PPIs, observed in clinical trials, include diarrhea, nausea, vomiting, flatulence, and headache[9–12]. Serious ADRs include breathing difficulty, rash, facial swelling, and throat tightness[9–12]. Recent studies revealed growing evidence of association with electrolyte abnormalities[13,14] kidney injury[15,16], bone fractures[17], Clostridium difficile-associated diarrhea[18], Alzheimer disease (AD)[19], and non-AD type dementia[19,20]. However, other studies were not able to confirm the association between PPI use and a greater risk of dementia of both AD or non-AD type[21,22].

Dementia associated with AD has a substantial impact on the quality of life of the patients and their caregivers[23,24] and on the healthcare costs[25,26]. AD is considered the third most costly disease in the United States, with the costs being primarily associated with long-term care in nursing facilities[27].

The current lack of consensus on PPI association with AD and non-AD type dementia warranted further investigation and analysis of other neurological outcomes. In our study, we performed an analysis of the FDA Adverse Event Reporting System database (FAERS/AERS) and identified significant increases of AD and non-AD

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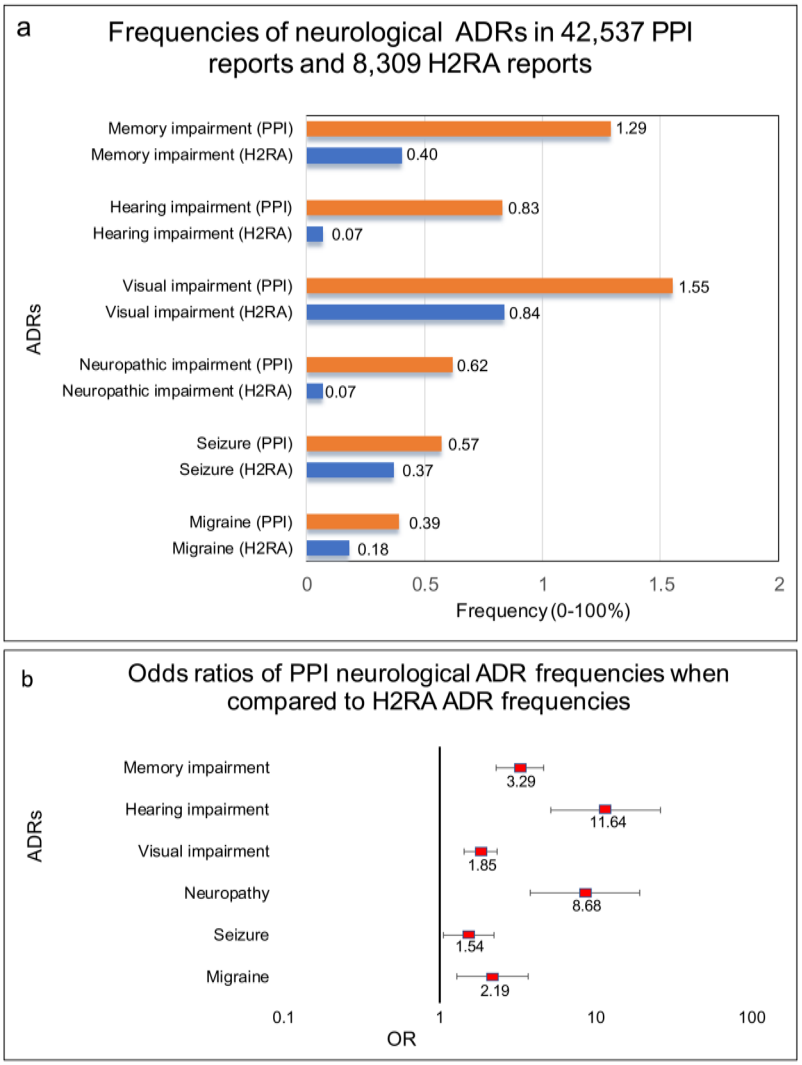

Figure 1. FAERS-reported frequencies and odds ratios of neurological/neurosensory adverse drug reactions. (**a**) Frequencies of neurological/neurosensory adverse events for patients in FAERS/AERS who took PPIs (n = 42,537) and H2RAs (n = 8,309). (**b**) Odds ratios were calculated comparing adverse event frequencies of PPI and H2RA patients. Ranges represent 95% confidence intervals (95% CI) (see Methods). A logarithmic X-axis shows odds ratios and their confidence intervals.

dementia reports along with increased association with other types of memory impairment in PPI patients. Additionally, we found a significant increase in wide variety of peripheral neurological and neuropathic adverse events, as well as visual and auditory impairment ADRs.

Results

PPI "monotherapy" - neurological and neurosensory ADRs. Reports in which PPIs were administered with no reported concurrent medications had a significant increase in memory impairment ADRs in comparison with H2RAs reports (OR 3.28, 95% CI [2.31, 4.67]) (Fig. 1b, Table 1). The outcomes included memory impairment, amnesia, dementia of the AD type, and non-AD dementia. Surprisingly, the H2RA cohort (n = 8,309) had three out of four ADRs listed above, but had no single report of dementia of the AD type (Table 1) while the PPI cohort (n = 42,537) had as many as 80 reports of the AD dementia. Interestingly, the auditory and visual ADRs followed a similar trend, with ORs being (11.64 [5.20, 26.11]) and (1.85 [1.44, 2.37]) respectively (Fig. 1b Tables 2 and 3). Neuropathic/neurological impairment ADR frequencies were also increased in the described above PPI cohort (8.68 [3.86, 19.49]) (Fig. 1b, Table 4). These included cranial and peripheral neuropathies, sciatica, and nerve injury as well as other neuropathic ADRs (Table 4). There was a small but significant increase in reported seizures (1.54 [1.06, 2.24]) (Fig. 1b and Table 5) and a significant increase in migraine reports in the PPI cohort (2.19 [1.29, 3.72]) (Fig. 1b and Table 6).