pharmacoepidemiology

MDPI

Article

Depression Events Associated with Proton-Pump Inhibitors in Postmarketing Drug Surveillance Data

Tigran Makunts *, Haroutyun Joulfayan, Kenneth Ta and Ruben Abagyan *

Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, CA 92093, USA; hajoulfayan@ucsd.edu (H.J.)

* Correspondence: tmakunts@health.ucsd.edu (T.M.); rabagyan@health.ucsd.edu (R.A.)

Abstract: Proton-pump inhibitors, PPIs, are widely prescribed and are available over the counter for prolonged reduction of stomach acid production and related disorders. PPIs irreversibly inhibit the hydrogen/potassium ATPase in gastric parietal cells. Recent retrospective studies have described an association between PPI use and depression. However, there is conflicting evidence that PPI therapy improves depressive symptoms. Considering the widespread use and over-the-counter availability of these drugs, further investigation into depression adverse event was warranted with a larger-scale postmarketing set of reports. Here we analyzed over 125,923 reports from the FDA Adverse Event Reporting System consisting of PPI and histamine-2 receptor antagonist monotherapy records and found a statistically significant association between use of PPIs and depression. Additionally, we analyzed each of the six currently marketed PPIs individually and observed the association with the depression adverse reaction for all of them.

Keywords: proton-pump inhibitors; PPIs; FAERS; depression; drug safety; adverse events

Citation: Makunts, T.; Joulfayan, H.; Ta, K.; Abagyan, R. Depression Events Associated with Proton-Pump Inhibitors in Postmarketing Drug Surveillance Data. *Pharmacoepidemiology* **2023**, *2*, 272–282. https://doi.org/10.3390/pharma2030023

Academic Editors: Li-Ting Kao, Yu-Tien Chang, Ke-Ting Pan and Matteo Franchi

Received: 19 June 2023
Revised: 24 July 2023
Accepted: 25 August 2023
Published: 30 August 2023

1. Introduction

Proton-pump inhibitors (PPIs) are commonly used to treat acid-related disorders such as Helicobacter Pylori-induced gastric ulcers, gastroesophageal reflux disease (GERD), erosive esophagitis, and Zollinger–Ellison syndrome [1–5]. PPIs have therapeutic superiority to histamine-2 receptor antagonists (H2RAs) [6] due to their irreversible inhibition of the H+/K+ ATPase in gastric parietal cells [4,5,7,8]. However, PPI pharmacology may not be limited to localized parietal cell action [9,10]. Despite efforts to minimize over-prescription of these medications, PPI use has been steadily increasing [11]. According to National Health and Nutrition Examination Survey, the number of PPI prescriptions among 40–64-year-old individuals had increased from 1999 to 2012 [12], even though these studies did not account for over-the-counter (OTC) use of PPIs.

Currently, there are six drugs of the PPI class approved by the US Food and Drug Administration: rabeprazole (Aciphex), pantoprazole (Protonix), dexlansoprazole (Dexilant), lansoprazole (Prevacid, Prevacid OTC), esomeprazole (Nexium, Nexium 24 h), and omeprazole (Prilosec, Prilosec OTC). The latter three are available OTC without any restrictions.

Common adverse drug reactions (ADRs) associated with PPIs observed in controlled trials include nausea, diarrhea, flatulence, vomiting, and headache. Serious ADRs include throat tightness, rash, and difficulty breathing [13–18]. Post-approval studies have found additional association of PPI use with the following ADRs: *Clostridium difficile*-associated diarrhea, calcium deficiency, bone fractures, and hypomagnesemia, which are now listed as precautions in the FDA package inserts.

PPI drug use has been associated with neurological disorders such as Alzheimer's and non-Alzheimer's dementia [19–21]. Additionally, recent studies analyzing the FDA Adverse Event Reporting System (FAERS) data have observed multiple electrolyte abnormalities and a broad spectrum of neurological disorders disproportionally reported after PPI use when compared to H2RAs [22,23].

The physiology behind neurological and psychiatric conditions often shares common molecular mechanisms [24,25], resulting in depression's comorbidity with neurological disorders and vice versa [26]. There are multiple hypothesized mechanisms behind the psychiatric/neurologic adverse reactions of PPIs [27–29]. In an epidemiological study by Laudisio et al., PPI use was associated with depression in a geriatric population, while the association was not observed in the H2RA cohort [30]. In another study conducted in Sweden by Wang et al. [31], PPI use was associated with increased risk of anxiety and depression in children. Furthermore, a Taiwanese nationwide population-based study by Huang et al. [32] confirmed this association. There is conflicting evidence suggesting improvement of depressive symptoms following PPI therapy [33].

Depression was declared by the World Health Organization (WHO) to be the third greatest cause of burden for disease worldwide [34], and considering the common use of PPIs, this association needed to be further investigated. In this study, we performed an analysis of millions of FAERS reports and identified a rare but statistically significant increase in depression reports in patients taking PPIs as monotherapy when compared to H2RA-related reports.

2. Methods

2.1. FDA Adverse Event Reporting System

The FDA Adverse Event Reporting System (FAERS) and its older version AERS contain the FDA's postmarketing drug and biologic product safety data. Reports are submitted by product vendors, and, on a voluntary basis, by legal representatives, healthcare professionals, and consumers to the FDA through MedWatch [35,36], the FDA Safety Information and Adverse Event Reporting Program. Pharmaceutical industry/manufacturers are legally required to forward the information to the FDA.

Over 19.1 million FAERS/AERS reports, collected from January 2004 to March 2023, were used for the analysis. Datasets are available online at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm (accessed on 16 May 2023).

2.2. Data Preparation

Quarterly FAERS/AERS ASCII reports were downloaded in their original format. The data from different years were unified into a consistent format. Additionally, since the ADR reports were collected from around the world, it was necessary to translate drug brand names into generic ones using online drug databases. A total of 19,190,582 combined FAERS/AERS reports were used for the analysis [37,38]. The reports were further narrowed down to exclude reports submitted by consumers and legal representatives to avoid potential bias. All the reports submitted by physicians, pharmacists, nurses, and other healthcare professionals were included in the analysis datasets.

2.3. Analysis and Control Cohort Selection

FAERS/AERS reports where PPIs and H2RAs were used as monotherapy were selected into the respective cohorts. The term "monotherapy" pertains to records where only a single treatment is listed in the report. The query included US approved brand and generic names of PPIs and H2RAs. The dictionary for brand vs. generic names was compiled from resources such as USAN and WHO Drug Global, which were employed for a non-US brand name report recognition. Additionally, frequent misspellings of both generic and brand names were manually added to the translation dictionary. PPI monotherapy cohorts collectively included 8488 reports, and H2RA monotherapy cohorts included 117,435 reports.

Reporting odds ratio (ROR) analysis was performed by comparing the reported PPI ADRs in relation to H2RA report numbers with and without an ADR of interest. The PPI monotherapy cohort was further split into individual PPI cohorts, which included omeprazole (n = 2651), esomeprazole (n = 1993), pantoprazole (n = 1846), lansoprazole

(n = 1170), dexlansoprazole (n = 405), and rabeprazole (n = 423). Individual PPI-reported depression ADRs were calculated and compared to the H2RA cohort to screen for potential ADR variability within individual PPIs in the cohort. Demographic analysis was performed (Tables 1–3). Additionally, co-occurring adverse events were analyzed for presence of any additional events that may be related psychiatric disorders (Tables 4 and 5)

Table 1. Report numbers by sex.

	PPI Monotherapy	H2RA Monotherapy	PPI Depression	H2RA Depression
Total reports	100% (8488)	100% (117,435)	0.73% (62)	0.01% (17)
Male	36.92% (3134)	54% (63,411)	0.54% (17)	0.01% (7)
Female	49.61% (4211)	42.35% (49,732)	0.95% (40)	0.02% (9)
Unspecified sex	13.47% (1143)	3.65% (4292)	0.44% (5)	0.02% (1)

Table 2. Report numbers by age.

	PPI Monotherapy	H2RA Monotherapy	PPI Depression	H2RA Depression
Total reports	100% (8488)	100% (117,435)	0.61% (52)	0.01% (17)
Invalid ages (<1 y.o.)	1.43% (121)	0.08% (97)	0% (0)	1.03% (1)
Unspecified ages (empty)	32.93% (2795)	1.08% (1267)	0.25% (7)	0.08% (1)
1–9 y.o.	1.35% (115)	0.06% (76)	0% (0)	0% (0)
10–19 y.o.	1.93% (164)	0.16% (185)	1.22% (2)	0.54% (1)
20–29 y.o.	3.13% (266)	1.44% (1691)	0.75% (2)	0% (0)
30–39 y.o.	5.9% (501)	5.54% (6508)	1.4% (7)	0.02% (1)
40–49 y.o.	8.14% (691)	15.95% (18,729)	1.01% (7)	0.02% (3)
50–59 y.o.	12.13% (1030)	32.08% (37,669)	1.55% (16)	0.02% (6)
60–69 y.o.	12.45% (1057)	29.94% (35,165)	1.23% (13)	0% (1)
≥70 y.o.	20.59% (1748)	13.67% (16,048)	0.46% (8)	0.02% (4)

Table 3. Report numbers by country.

	PPI Monotherapy	H2RA Monotherapy	PPI Depression	H2RA Depression
Total reports	100% (8488)	100% (117,435)	0.61% (52)	0.01% (17)
United States	48.94% (4154)	99.36% (116,683)	0.7% (29)	0.01% (16)
France	9.57% (812)	0.02% (18)	1.63% (11)	0% (0)
United Kingdom	7.95% (675)	0.06% (73)	1.19% (8)	0% (0)
Japan	5.6% (475)	0.24% (286)	0.21% (1)	0% (0)
Italy	4.38% (372)	0.06% (66)	0.81% (3)	0% (0)
Canada	3.05% (259)	0.04% (52)	0.77% (2)	0% (0)
Germany	2.69% (228)	0.02% (21)	0.88% (2)	0% (0)
Spain	2.52% (214)	0.02% (25)	0% (0)	0% (0)
Turkey	1.73% (147)	0% (1)	0% (0)	0% (0)
Brazil	1.72% (146)	0.01% (10)	0.68% (1)	0% (0)
Other countries	11.31% (960)	0.16% (192)	0.1% (5)	0.52% (1)

Table 4. B12 abnormality reports.

Adverse Event	n (%)
Vitamin B12 increased	1 (0.01)
Vitamin B12 abnormal	2 (0.02)
Anemia vitamin B12 deficiency	13 (0.15)
Vitamin B12 decreased	8 (0.09)
Vitamin B12 deficiency	35 (0.41)

Table 5. Magnesium abnormality reports.

Adverse Event	n (%)
Blood magnesium increased	1 (0.01)
Magnesium deficiency	2 (0.02)
Blood magnesium decreased	33 (0.39)

2.4. Statistical Analysis

Descriptive statistics: Frequency for depression ADR was calculated by the following equation:

$$\text{Frequency} = (\text{nReports with depression in a cohort})/\text{nReports in a cohort} \times 100 \quad (1)$$

Comparative statistics: Depression report rates were compared via the Reporting Odds Ratio (ROR) analysis:

$$\text{ROR} = (a/b)/(c/d) \quad (2)$$

where

a = Number of cases in PPI group with depression;
b = Number of cases in PPI group with no depression;
c = Number of cases in H2RA group with depression;
d = Number of cases in H2RA group with no depression.

$$\text{LnROR} = \text{Ln}(\text{ROR}) \quad (3)$$

Standard Error of Log Reporting Odds Ratio:

$$\text{SE\_LnROR} = \sqrt{(1/a + 1/b + 1/c + 1/d)} \quad (4)$$

95% Confidence Interval:

$$95\%\text{CI} = [\exp(\text{LnROR} - 1.96 \times \text{SE\_LnROR}), \exp(\text{LnROR} + 1.96 \times \text{SE\_LnROR})] \quad (5)$$

Haldane–Anscombe correction was not applied to cohorts with zero depression reports [39].

3. Results

Combined PPI monotherapy reports had a significantly higher number of depression ADRs in comparison with H2RA monotherapy reports. The reported frequency of depression AE reports in the PPI cohorts ranged from 0.25% for dexlansoprazole to 1.42% for rabeprazole, and 0.73% for the combined cohort (Figure 1), with ROR being 50.82 (95% CI [29.70, 86.96]). When studied individually, all of the six PPI monotherapy cohorts had a significant increase in the number of reported depression ADRs in comparison with the H2RA control cohort. The ROR values were as follows: omeprazole (ROR 73.73, 95% CI [40.31, 134.87]), pantoprazole (ROR 45.19, 95% CI [21.55, 94.76]), rabeprazole (ROR 99.38, 95%

CI [38.99, 253.31]), esomeprazole (ROR 34.83, 95% CI [15.93, 76.16]), and dexlansoprazole (ROR 17.10, 95% CI [2.27, 128.77]) (Figures 1 and 2).

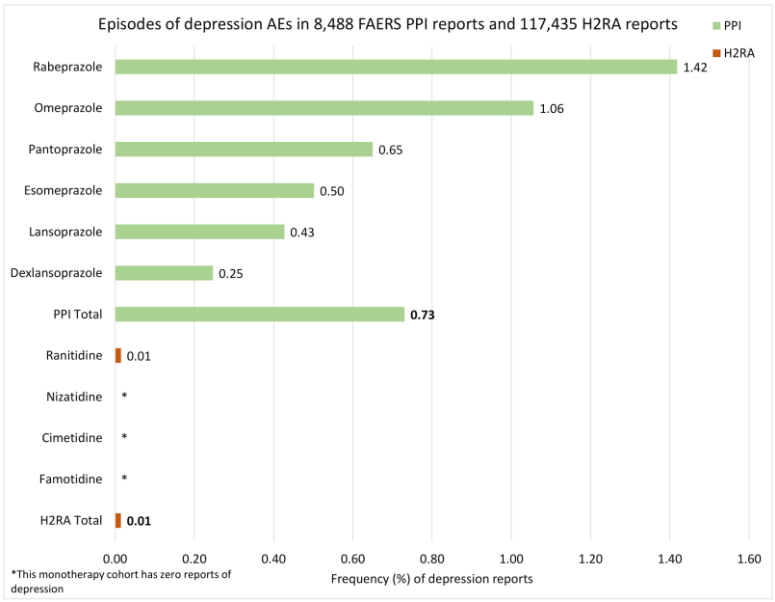

Figure 1. Reported frequencies of depression ADRs for patients in FAERS/AERS who took PPIs (n = 8488) and H2RAs (117,435) as monotherapy. The bolded numbers show the totals.

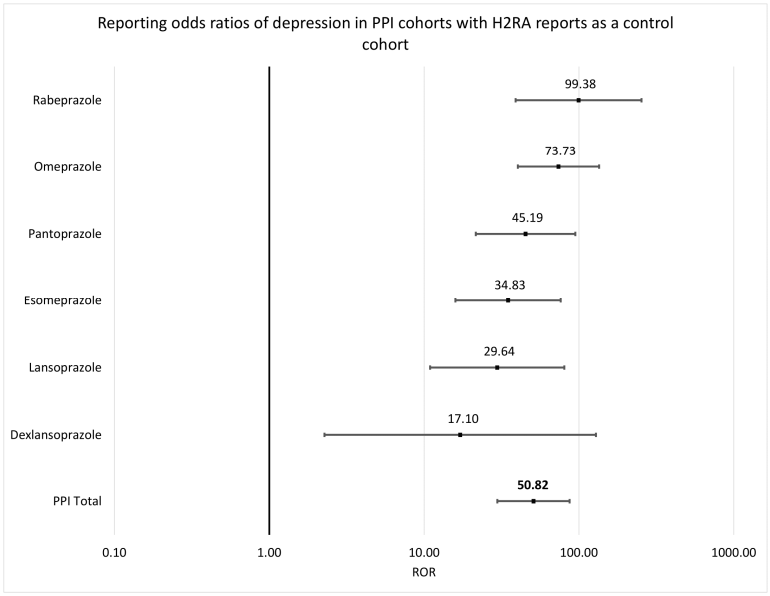

Figure 2. Reporting odds ratios (RORs) for patients in FAERS/AERS who took PPIs (n = 8488) and H2RAs (117,435) as monotherapy. PPI monotherapy cohort was further split into individual PPI cohorts which included omeprazole (n = 2651), esomeprazole (n = 1993), pantoprazole (n = 1846), lansoprazole (n = 1170), dexlansoprazole (n = 405), and rabeprazole (n = 423) for individual ROR analysis. X-axis is presented in log scale.

3.1. Depression Reports in Males

There was a significant increase in the number of reported depression ADRs in the combined PPI monotherapy cohort when compared to the H2RA monotherapy cohort (ROR39.40, 95% CI [20.47, 119.21]) when only male patients taking PPIs were analyzed. Each of the individual PPI treatments analyzed had a significant increase in the number of depression ADRs in comparison with the H2RA control, with the exception of dexlan-

soprazole, which had zero depression ADR reports. The ROR values were as follows: omeprazole (ROR 47.26, 95% CI [15.86, 140.84]), pantoprazole (ROR 82.59, 95% CI [27.68, 246.43]), rabeprazole (ROR 55.23, 95% CI [6.76, 451.43]), esomeprazole (ROR 39.84, 95% CI [10.28, 154.41]), and lansoprazole (ROR 25.51, 95% CI [3.13, 207.93]) (Figures 3 and 4).

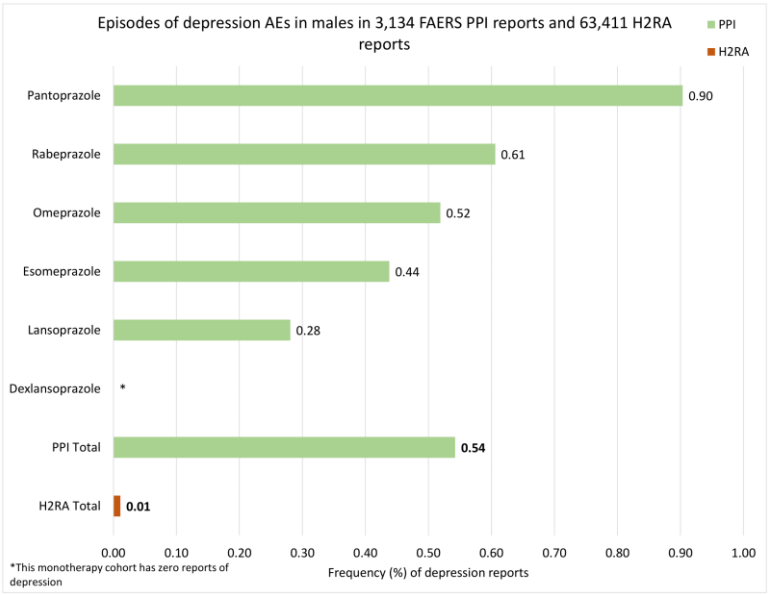

Figure 3. Reported frequencies of depression ADRs for male patients in FAERS/AERS who took PPIs (n = 3134) and H2RAs (n = 63,411) as monotherapy.

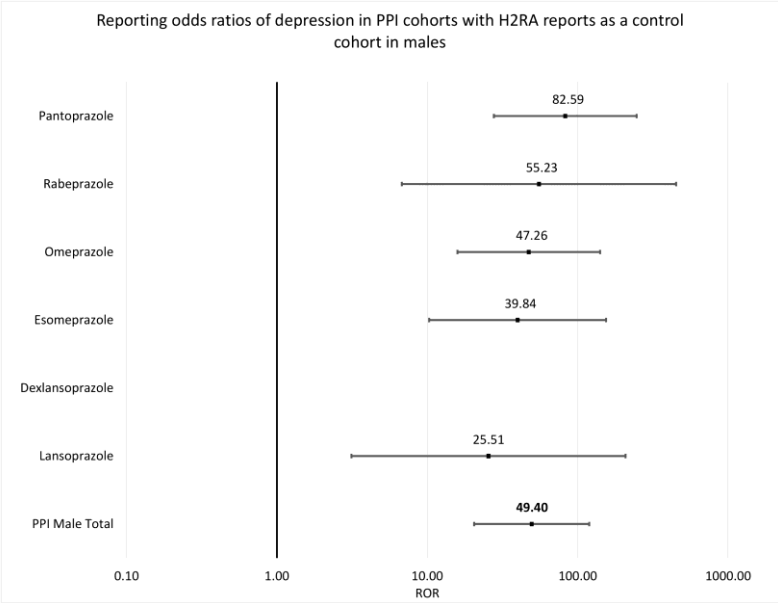

Figure 4. Reporting odds ratios (RORs) for male patients in FAERS/AERS who took PPIs (n = 3134) and H2RAs (n = 63,411) as monotherapy. PPI monotherapy male cohort was further split into individual PPI cohorts which included omeprazole (n = 1156), esomeprazole (n = 685), pantoprazole (n = 664), lansoprazole (n = 356), dexlansoprazole (n = 108), and rabeprazole (n = 165) for individual ROR analysis. X-axis is presented in log scale. Dexlansoprazole cohort had no depression ADR reports.

3.2. Depression Reports in Females

There was a significantly higher number of depression ADR reports in the combined PPI monotherapy female-only cohort when compared to the H2RA monotherapy cohort (OR 27.54, 95% CI [13.35, 56.80]). All individual PPI cohorts had a significant increase in

the number of depression ADR reports when compared to the H2RA control, as follows: omeprazole (ROR 51.24, 95% CI [23.54, 111.51]), pantoprazole (ROR 12.30, 95% CI [3.78, 40.01]), rabeprazole (ROR 50.83, 95% CI [15.54, 166.25]), esomeprazole (ROR 18.12, 95% CI [6.44, 51.01]), dexlansoprazole (ROR 11.26, 95% CI [1.42, 89.22]), and lansoprazole (ROR 15.06, 95% CI [4.07, 55.78]) (Figures 5 and 6).

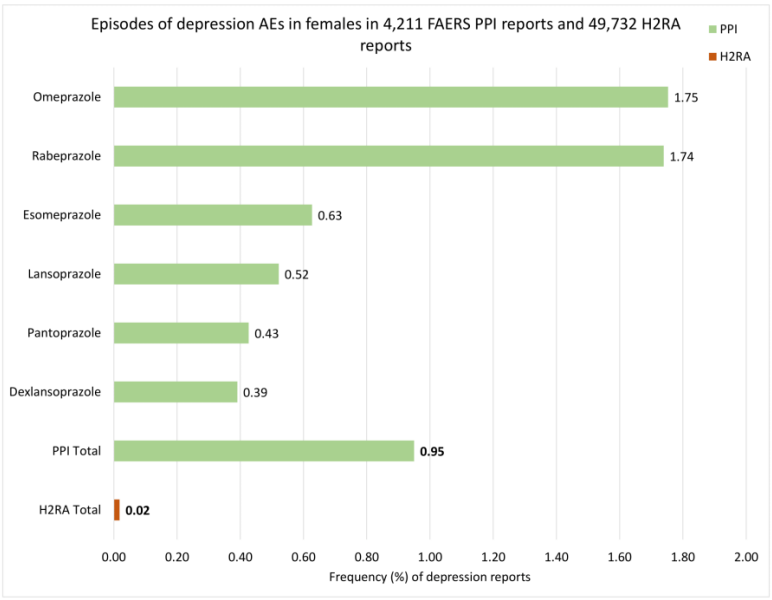

Figure 5. Reported frequencies of depression ADRs for female patients in FAERS/AERS who took PPIs (n = 4211) and H2RAs (n = 49,732) as monotherapy.

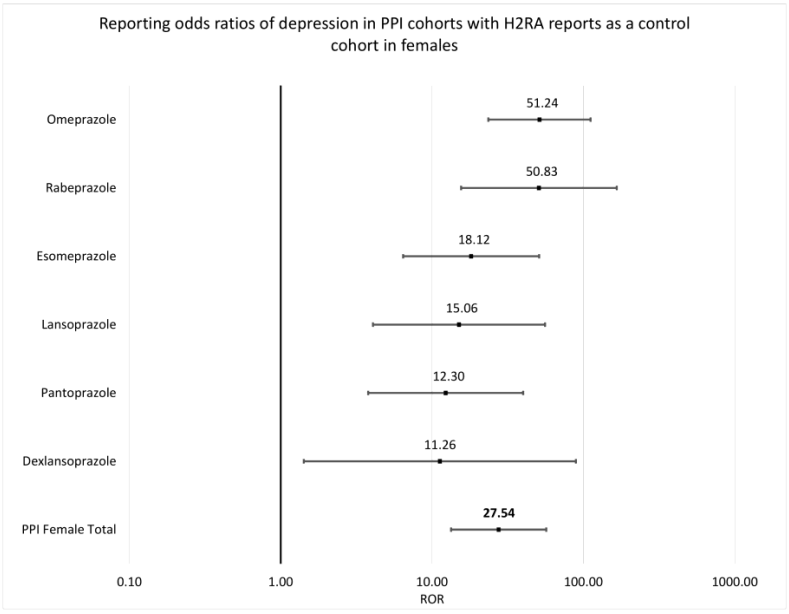

Figure 6. Reporting odds ratios (RORs) for female patients in FAERS/AERS who took PPIs (n = 4211) and H2RAs (n = 49,732) as monotherapy. PPI monotherapy female cohort was further split into individual PPI cohorts which included omeprazole (n = 1255), esomeprazole (n = 957), pantoprazole (n = 938), lansoprazole (n = 575), dexlansoprazole (n = 256), and rabeprazole (n = 230) for individual ROR analysis. X-axis is presented in log scale.

4. Discussion

In this study, we quantified and confirmed a statistically significant association between PPI exposure and depression ADRs using 125,923 PPI and H2RA ADR reports from

the FAERS/AERS database. To our knowledge, it is the first study investigating the relationship of PPI use with depression utilizing the most recent population-scale postmarketing surveillance data.

Although the fraction of depression reports was relatively low, ranging from 0.25% to 1.42% of PPI monotherapy ADR reports, the depression ADR ROR numbers were statistically significant when compared to the H2RA control cohort. This study expanded on the previous epidemiological evidence provided in the geriatric study by Laudisio et al. [30] and the pediatric study by Wang et al. [31]. Additionally, in our study, depression ADRs were analyzed across age groups. The depression ADR signal prevailed in all groups above 20–29 to ≥70-year-old cohorts (Table 2).

The molecular mechanisms of the observed association may originate from several pathways and are beyond the scope of this study. Due to complex pharmacology of PPIs, it is difficult to pinpoint a single physiological mechanism involved in the etiology of depression ADRs. In a previously published mini-review, we discussed some of the mechanisms by which PPIs might be causing neurological adverse events [27], including hypomagnesemia and impaired vitamin B absorption.

A systematic review published by Derom et al. [40] found an association between higher dietary magnesium intake and lower depression symptoms. In another publication by Cheungpasitporn et al. [41], the investigators evaluated the effect of high magnesium and found a similar association. Magnesium is known to play multiple important roles in the central nervous system (CNS) [42], and inadequate levels affecting psychiatric symptoms seem intuitive.

In a four-year longitudinal study by Laird et al. [43] in adults 50 years and older, vitamin B12 deficiency was found to be associated with increased depressive symptoms. In another study by Syed et al. [44], when supplemented along with antidepressants, vitamin B12 significantly decreased depressive symptoms. A systematic review by Almeida et al. [45] has found that the severity of depression symptoms in not decreased over a short period. However, there are long-term benefits in vitamin B12 supplementation for depression management.

Coincidentally, the PPI users reported both hypomagnesemia and vitamin B12 deficiency. The report counts were as follows: 35 reports of decreased vs. 1 report of increased magnesium levels, and 43 reports of decreased vs. 1 report of increased vitamin B12 levels (Tables 4 and 5). This associations of PPIs with vitamin B12 and magnesium absorption abnormalities [46,47] are plausible mechanisms that could explain the elevated reporting numbers of depression ADRs. Moreover, regardless of specific molecular mechanisms related to depression ADRs, it is not surprising to see psychiatric ADRs, given the previous evidence of a wide range of neurological damage associated with PPI use [21,23,48–50].

The observed increased risk of depression with use of PPIs calls for more careful consideration in using PPIs for people at high risk of depression. PPIs should be used for the shortest time necessary as recommended by the FDA and other regulatory authorities. Prescribers should be aware of this potential risk and educate the patients to avoid deviations on recommended dose, frequency, and use duration. Further studies are needed to evaluate the neurologic and psychiatric adverse events of PPIs in a controlled setting, identify at-risk populations, and identify the molecular mechanisms associated with the PPIs' neuropsychiatric adverse events.

Study Limitations

Only a fraction of population incidences is represented in FAERS/AERS due to the mostly voluntary nature of the reporting. FAERS/AERS reporting can be biased based on multiple factors such as legal challenges or news events influencing submissions [51]. Additionally, significant underreporting of AEs has been observed depending of drug, type of ADR, and seriousness [52]. Causality of depression cannot be inferred from the association found in this study since the cases were not individually adjudicated by a clinician. However, the study provides a statistically significant signal that needs to be

further investigated in a controlled setting. Drug brand names from some countries may not have been translated if they did not pass the FDA AE submission application. Only reports where the brand name has been registered with WHO Drug were included in the dictionary.

Author Contributions: H.J. performed the experiments, R.A. and T.M. designed the study, K.T., H.J., R.A. and T.M. drafted the manuscript and reviewed the final version. R.A. processed the dataset. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by in part the National Institutes of Health (NIH R35GM131881).

Institutional Review Board Statement: Institutional Review Board requirements do not apply under 45 CFR 46.102. There was no direct human participation in the study. All experiments were performed in accordance with relevant guidelines and regulations.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets available online to the public are de-identified. Institutional Review Board requirements do not apply under 45 CFR 46.102. https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files (accessed on 15 May 2023). Both FAERS and AERS datasets are de-identified and are made available online at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm (accessed on 15 May 2023).

Acknowledgments: We thank Rabia Atayee and Isaac V. Cohen for helpful discussions.

Conflicts of Interest: The authors declare no competing interests.

References

1. Song, H.; Zhu, J.; Lu, D. Long-term proton pump inhibitor (PPI) use and the development of gastric pre-malignant lesions. *Cochrane Database Syst. Rev.* **2014**, *12*, CD010623. [CrossRef]
2. Katz, P.O.; Dunbar, K.B.; Schnoll-Sussman, F.H.; Greer, K.B.; Yadlapati, R.; Spechler, S.J. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. *Am. J. Gastroenterol.* **2022**, *117*, 27–56. [CrossRef]
3. Londong, W.; Barth, H.; Dammann, H.G.; Hengels, K.J.; Kleinert, R.; Müller, P.; Rohde, H.; Simon, B. Dose-related healing of duodenal ulcer with the proton pump inhibitor lansoprazole. *Aliment. Pharmacol. Ther.* **1991**, *5*, 245–254. [CrossRef]
4. Wu, J.C.Y.; Sheu, B.S.; Wu, M.S.; Lee, Y.C.; Choi, M.G. Phase 4 Study in Patients From Asia With Gastroesophageal Reflux Disease Treated With Dexlansoprazole. *J. Neurogastroenterol. Motil.* **2020**, *26*, 85–95. [CrossRef]
5. Kinoshita, Y.; Miwa, H.; Kasugai, K. Efficacy and safety of esomeprazole, compared with omeprazole, in maintenance therapy for reflux esophagitis -a phase III, multicenter, randomized, double-blind trial-. *Nihon Shokakibyo Gakkai Zasshi* **2013**, *110*, 1428–1438.
6. Zhao, F.; Wang, S.; Liu, L.; Wang, Y. Comparative effectiveness of histamine-2 receptor antagonists as short-term therapy for gastro-esophageal reflux disease: A network meta-analysis. *Int. J. Clin. Pharmacol. Ther.* **2016**, *54*, 761–770. [CrossRef]
7. Walan, A.; Bader, J.P.; Classen, M.; Lamers, C.B.; Piper, D.W.; Rutgersson, K.; Eriksson, S. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. *N. Engl. J. Med.* **1989**, *320*, 69–75. [CrossRef]
8. Clissold, S.P.; Campoli-Richards, D.M. Omeprazole. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peptic ulcer disease and Zollinger-Ellison syndrome. *Drugs* **1986**, *32*, 15–47. [CrossRef]
9. Shin, J.M.; Sachs, G. Pharmacology of proton pump inhibitors. *Curr. Gastroenterol. Rep.* **2008**, *10*, 528–534. [CrossRef]
10. Shin, J.M.; Munson, K.; Vagin, O.; Sachs, G. The gastric HK-ATPase: Structure, function, and inhibition. *Pflugers Arch.* **2009**, *457*, 609–622. [CrossRef]
11. Abrahami, D.; McDonald, E.G.; Schnitzer, M.; Azoulay, L. Trends in prescribing patterns of proton pump inhibitors surrounding new guidelines. *Ann. Epidemiol.* **2021**, *55*, 24–26. [CrossRef]
12. Kantor, E.D.; Rehm, C.D.; Haas, J.S.; Chan, A.T.; Giovannucci, E.L. Trends in Prescription Drug Use Among Adults in the United States From 1999–2012. *JAMA* **2015**, *314*, 1818–1831. [CrossRef]
13. FDA Label-Omeprazole. United States Food and Drug Administration. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019810s096lbl.pdf (accessed on 1 October 2022).
14. FDA Label-Esomeprazole. United States Food and Drug Administration. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022101s014021957s017021153s050lbl.pdf (accessed on 1 October 2022).
15. FDA Label-Rabeprazole. United States Food and Drug Administration. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020973s035204736s005lbl.pdf (accessed on 1 October 2022).
16. FDA Label-Pantoprazole. United States Food and Drug Administration. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020987s045lbl.pdf (accessed on 1 October 2022).

17. FDA Label-Lansoprazole. United States Food and Drug Administration. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020406s078-021428s025lbl.pdf (accessed on 1 October 2022).
18. FDA Label-Dexlansoprazole. United States Food and Drug Administration. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020406s078-021428s025lbl.pdf (accessed on 1 October 2022).
19. Haenisch, B.; von Holt, K.; Wiese, B.; Prokein, J.; Lange, C.; Ernst, A.; Brettschneider, C.; König, H.H.; Werle, J.; Weyerer, S.; et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. *Eur. Arch. Psychiatry Clin. Neurosci.* **2015**, *265*, 419–428. [CrossRef]
20. Gomm, W.; von Holt, K.; Thomé, F.; Broich, K.; Maier, W.; Fink, A.; Doblhammer, G.; Haenisch, B. Association of Proton Pump Inhibitors With Risk of Dementia: A Pharmacoepidemiological Claims Data Analysis. *JAMA Neurol.* **2016**, *73*, 410–416. [CrossRef]
21. Goldstein, F.C.; Steenland, K.; Zhao, L.; Wharton, W.; Levey, A.I.; Hajjar, I. Proton Pump Inhibitors and Risk of Mild Cognitive Impairment and Dementia. *J. Am. Geriatr. Soc.* **2017**, *65*, 1969–1974. [CrossRef]
22. Makunts, T.; Cohen, I.V.; Awdishu, L.; Abagyan, R. Analysis of postmarketing safety data for proton-pump inhibitors reveals increased propensity for renal injury, electrolyte abnormalities, and nephrolithiasis. *Sci. Rep.* **2019**, *9*, 2282. [CrossRef]
23. Makunts, T.; Alpatty, S.; Lee, K.C.; Atayee, R.S.; Abagyan, R. Proton-pump inhibitor use is associated with a broad spectrum of neurological adverse events including impaired hearing, vision, and memory. *Sci. Rep.* **2019**, *9*, 17280. [CrossRef]
24. Melero, I.; Grimaldi, A.M.; Perez-Gracia, J.L.; Ascierto, P.A. Clinical development of immunostimulatory monoclonal antibodies and opportunities for combination. *Clin. Cancer Res.* **2013**, *19*, 997–1008. [CrossRef]
25. Verghese, A. The integration of psychiatry and neurology. *Indian J. Psychiatry* **2016**, *58*, 104–105. [CrossRef]
26. Rickards, H. Depression in neurological disorders: An update. *Curr. Opin. Psychiatry* **2006**, *19*, 294–298. [CrossRef]
27. Makunts, T.; Abagyan, R. How can proton pump inhibitors damage central and peripheral nervous systems? *Neural Regen. Res.* **2020**, *15*, 2041–2042. [CrossRef]
28. Song, T.; Jeon, H.K.; Hong, J.E.; Choi, J.J.; Kim, T.J.; Choi, C.H.; Bae, D.S.; Kim, B.G.; Lee, J.W. Proton Pump Inhibition Enhances the Cytotoxicity of Paclitaxel in Cervical Cancer. *Cancer Res. Treat.* **2017**, *49*, 595–606. [CrossRef]
29. Yepuri, G.; Sukhovershin, R.; Nazari-Shafti, T.Z.; Petrascheck, M.; Ghebre, Y.T.; Cooke, J.P. Proton Pump Inhibitors Accelerate Endothelial Senescence. *Circ. Res.* **2016**, *118*, e36–e42. [CrossRef]
30. Laudisio, A.; Antonelli Incalzi, R.; Gemma, A.; Giovannini, S.; Lo Monaco, M.R.; Vetrano, D.L.; Padua, L.; Bernabei, R.; Zuccalà, G. Use of proton-pump inhibitors is associated with depression: A population-based study. *Int. Psychogeriatr.* **2018**, *30*, 153–159. [CrossRef]
31. Wang, Y.H.; Wintzell, V.; Ludvigsson, J.F.; Svanström, H.; Pasternak, B. Proton pump inhibitor use and risk of depression and anxiety in children: Nationwide cohort study. *Clin. Transl. Sci.* **2022**, *15*, 1112–1122. [CrossRef] [PubMed]
32. Huang, W.S.; Bai, Y.M.; Hsu, J.W.; Huang, K.L.; Tsai, C.F.; Su, T.P.; Li, C.T.; Lin, W.C.; Tsai, S.J.; Pan, T.L.; et al. Use of Proton Pump Inhibitors and Risk of Major Depressive Disorder: A Nationwide Population-Based Study. *Psychother. Psychosom.* **2018**, *87*, 62–64. [CrossRef] [PubMed]
33. Wu, C.L.; Chen, C.L.; Wen, S.H. Profile of the Change in Depression during Proton-Pump Inhibitor Therapy in Patients with Gastroesophageal Reflux Disease: Influence of the Mucosal Break. *Int. J. Environ. Res. Public. Health* **2021**, *18*, 5964. [CrossRef] [PubMed]
34. WHO-Global Burden of Disease. World Health Organization. Available online: https://apps.who.int/iris/bitstream/handle/10665/43942/9789241563710_eng.pdf (accessed on 1 October 2022).
35. Craigle, V. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. *J. Med. Libr. Assoc.* **2007**, *95*, 224–225. [CrossRef]
36. Kessler, D.A. Introducing MEDWatch. A new approach to reporting medication and device adverse effects and product problems. *JAMA* **1993**, *269*, 2765–2768. [CrossRef] [PubMed]
37. Wollmer, M.A.; Makunts, T.; Krüger, T.H.C.; Abagyan, R. Postmarketing safety surveillance data reveals protective effects of botulinum toxin injections against incident anxiety. *Sci. Rep.* **2021**, *11*, 24173. [CrossRef]
38. Keshishi, D.; Makunts, T.; Abagyan, R. Common osteoporosis drug associated with increased rates of depression and anxiety. *Sci. Rep.* **2021**, *11*, 23956. [CrossRef]
39. Weber, F.; Knapp, G.; Ickstadt, K.; Kundt, G.; Glass, Ä. Zero-cell corrections in random-effects meta-analyses. *Res. Synth. Methods* **2020**, *11*, 913–919. [CrossRef]
40. Derom, M.L.; Sayón-Orea, C.; Martínez-Ortega, J.M.; Martínez-González, M.A. Magnesium and depression: A systematic review. *Nutr. Neurosci.* **2013**, *16*, 191–206. [CrossRef] [PubMed]
41. Cheungpasitporn, W.; Thongprayoon, C.; Mao, M.A.; Srivali, N.; Ungprasert, P.; Varothai, N.; Sanguankeo, A.; Kittanamongkolchai, W.; Erickson, S.B. Hypomagnesaemia linked to depression: A systematic review and meta-analysis. *Intern. Med. J.* **2015**, *45*, 436–440. [CrossRef]
42. Vink, R.; Nechifor, M. *Magnesium in the Central Nervous System*; University of Adelaide Press: Adelaide, Australia, 2011.
43. Laird, E.; O'Halloran, A.M.; Molloy, A.M.; Healy, M.; Hernandez, B.; O'Connor, D.; Kenny, R.A.; Briggs, R. Low vitamin B. *Br. J. Nutr.* **2021**, *130*, 268–275. [CrossRef] [PubMed]
44. Syed, E.U.; Wasay, M.; Awan, S. Vitamin B12 supplementation in treating major depressive disorder: A randomized controlled trial. *Open Neurol. J.* **2013**, *7*, 44–48. [CrossRef] [PubMed]

45. Almeida, O.P.; Ford, A.H.; Flicker, L. Systematic review and meta-analysis of randomized placebo-controlled trials of folate and vitamin B12 for depression. *Int. Psychogeriatr.* **2015**, *27*, 727–737. [CrossRef] [PubMed]
46. Heidelbaugh, J.J. Proton pump inhibitors and risk of vitamin and mineral deficiency: Evidence and clinical implications. *Ther. Adv. Drug Saf.* **2013**, *4*, 125–133. [CrossRef]
47. Lam, J.R.; Schneider, J.L.; Zhao, W.; Corley, D.A. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. *JAMA* **2013**, *310*, 2435–2442. [CrossRef]
48. Rajabally, Y.A.; Jacob, S. Neuropathy associated with lansoprazole treatment. *Muscle Nerve* **2005**, *31*, 124–125. [CrossRef]
49. García Rodríguez, L.A.; Mannino, S.; Wallander, M.A. Ocular safety of antiulcer drugs. *Lancet* **1995**, *345*, 1059–1060. [CrossRef] [PubMed]
50. Sáez, M.E.; González-Pérez, A.; Gaist, D.; Johansson, S.; Nagy, P.; García Rodríguez, L.A. Risk of seizure associated with use of acid-suppressive drugs: An observational cohort study. *Epilepsy Behav.* **2016**, *62*, 72–80. [CrossRef] [PubMed]
51. Maciejewski, M.; Lounkine, E.; Whitebread, S.; Farmer, P.; DuMouchel, W.; Shoichet, B.K.; Urban, L. Reverse translation of adverse event reports paves the way for de-risking preclinical off-targets. *eLife* **2017**, *6*, e25818. [CrossRef] [PubMed]
52. Alatawi, Y.M.; Hansen, R.A. Empirical estimation of under-reporting in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). *Expert. Opin. Drug Saf.* **2017**, *16*, 761–767. [CrossRef] [PubMed]