Education Article

HOSPITAL PHARMACOLOGY
International Multidisciplinary Journal

ISSN 2334-9492 (Online)

Hospital Pharmacology. 2024; 11(2):1396-1402

UDC: 615.243.4.033

doi:10.5937/hpimj2402396H

# Exploring and Understanding Adverse Effect of Proton Pump Inhibitors

Majedul M. Hoque

Department of Pharmacy, Jahangirnagar University, Savar, Dhaka-1342, Bangladesh

## SUMMARY

**Introduction:** Over the past few decades, proton pump inhibitors (PPIs) have been used more often; nonetheless, there are concern regarding misuse and the severe adverse effects that have been described.
**Methods:** This paper will present information from relevant professional/scientific sources including Scopus, EBSCO, PubMed regarding unwanted adverse events of PPIs.
**Topic:** The causality of correlations between PPI usage and possible adverse effects is unknown. Increased risk of kidney, liver, and cardiovascular disease; dementia; gastrointestinal tract enteroendocrine tumors; susceptibility to respiratory and gastrointestinal infections; and reduced nutritional absorption are just a few of the long-term adverse effects of widespread use of PPI that have come to light. Thus, given growing concerns regarding PPI overuse in the general population, the purpose of this investigation is to review the relationship between PPI usage and the risk of major side consequences.
**Conclusion:** Due to the numerous known side effects of PPIs on the system, further study is necessary, including changing the drug's molecular structure and creating a new medication from its parent. By administering these drugs effectively for the relevant diagnosis, reevaluating patients' symptoms on a regular basis to determine the least amount and duration of therapy, and closely monitoring any potential side effects, it is feasible to minimize expenditures with health risk and maximize beneficial outcomes.

**Keywords:** Proton Pump Inhibitors, PPI, Ulcer, Adverse Effect, Liver Diseases, Respiratory, Malabsorption

## INTRODUCTION

Acid secretion is decreased by proton pump inhibitors (PPIs), which are irreversible inhibitors of the stomach $H^+K^+$ATPase in parietal cells. Although PPIs have a brief plasma half-life, they bind to proton pumps irreversibly, necessitating the synthesis of new proton pumps before acid secretion may be resumed. Repeated PPI dose causes stomach hypoacidity to a degree and duration significantly greater than that of competitive histamine 2 receptor antagonists (H2RA) [1,2], almost completely eliminating a biological function that has been phylogenetically well-preserved [3]. PPIs have long been used for the treatment of gastrointestinal disorders linked to acid production, including GERD and peptic ulcers. Nonetheless, throughout the past several decades, a rise in the usage of PPIs has been extensively documented in numerous nations [4,5]. This increase is perceived to be caused by the widespread use of PPIs in treatment of dyspepsia and prevention of gastrointestinal bleeding

Corresponding author:
Majedul M. Hoque, PharmD, MS
Department of Pharmacy, Jahangirnagar University, Savar, Dhaka-1342, Bangladesh
E-mail: majed.pharmju44@gmail.com

in patients prescribed antiplatelet therapy or non-steroid anti-inflammatory drugs (NSAIDs), coupled with the belief that PPIs have few adverse effects. Furthermore, even though the indications for PPI use have expanded, numerous studies have documented prevalent inappropriate PPI prescription [6,7]. PPI side effects appear to be mostly brought on by the medication's intended purpose [8], which is to promote stomach hypoacidity, which may be harmful either directly or indirectly. PPIs' short-term effects have been well researched, but long-term profound acid inhibition's effects are less well understood since epidemiological studies sometimes have short observation periods insufficientto uncover disorders. The (Figure 1) represents how PPIs reduce acid production in the stomach.

## METHODS

A computerized literature search was performed using the SCOPUS, PubMed and EBSCO database from 2023 November to 2024 March. Components that were each tied to a distinct causal relationship in a formal problem structure were used to conduct the literature search. Proton pump inhibitor, GERD, overutilization, risk(s), renal disorders, cardiovascular diseases, bone/hip/osteoporotic fracture, vitamin/mineral malabsorption, dementia, and liver disease were among the terms used in the search to find all papers. Following their evaluation of the publications' abstracts found by the search, the authors evaluated the whole manuscripts that satisfied the inclusion requirements on their own. A critical assessment was conducted on the study's design, methods, and appropriate and relevant outcomes that are pertinent to the present practice of medication and gastroenterology, hepatology, and nephrology. The side effects connected to PPIs were identified in extensively.

## TOPIC

### Renal disease

Acute interstitial nephritis, or AIN, was originally linked to PPI usage in 1992. Over ten years later, AIN caused by PPIs was acknowledged as a distinct clinical condition [9]. Due to their widespread use, PPIs are now considered to be among the most common causes of drug-induced AIN worldwide [10]. There is no clear explanation for the reported elevated risk of CKD among PPI users. When the renal tubular proton pump ($H^+$-ATPase) in an in vitro rat tubule solution appeared to be impacted by high doses of omeprazole, it was first wondered if medications intended to block the stomach proton pump also inhibited other proton pumps [11]. At first, doctors thought that proton pumps in the renal tubule and other organs in addition to the stomach may be inhibited by PPIs, but there isn't enough solid proof to support this in a clinical context.

### Gastrointestinal malignancies

The relationship between PPIs and the development of neuroendocrine tumors and gastrointestinal tract carcinomas can be explained by the fact that PPIs reduce stomach acid production, thus compensatory elevation of gastrin levels in patients has a proliferative effect on the formation of enterochromaffin-like cells [12,13]. PPIs also contribute to the gastric pan-colonization of Helicobacter pylori by reducing the usual acidic environment

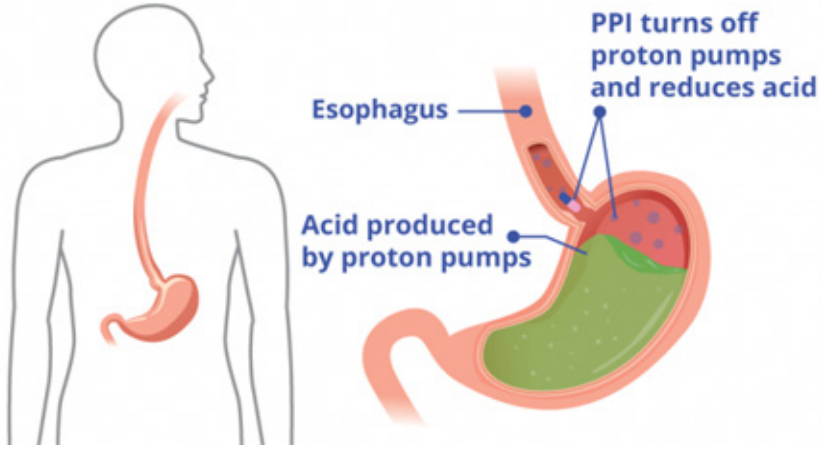


**Figure 1.** How PPIs work inside stomach

of the stomach. Epidemiological investigations corroborated the mechanistic studies' findings that hypoacidity and hypergastrinemia raise the incidence of stomach cancer in the corpus/fundus.

**Liver diseases**

Using PPIs has been associated with a higher incidence of complications from cirrhosis, including spontaneous bacterial peritonitis, liver cancer, and hepatic encephalopathy [14]. These effects appear to be related to chronic PPI use, as patients who underwent more than one year of follow-up after initiating treatment with PPIs had twice the risk of hepatocellular carcinoma than did those with no more than one year of follow-up [15]. Patients with liver illness may be more susceptible to enhanced hepatotoxicity from PPIs, which might result in hypergastrinemia-induced carcinogenic consequences, particularly on liver cells [16,17]. PPIs are metabolized in the liver. Lastly, the scientists revealed that following PPI exposure, the gene expression in cultured human liver cells resembled those of established liver carcinogens.

**Micronutrient deficiency**

Increased risk of vitamin B12 deficiency has been a concern since absorption of protein-bound, but not unbound, vitamin B12 was found to be reduced during PPI use [18]. However, a considerable number of other studies has not reproduced these findings and there seems to be insufficient evidence for routine measurements of B12 concentration in blood.

Patients with stomach hypoacidity may have decreased iron absorption; this is seen in those using omeprazole and oral ferrous sulphate supplements [19]. It's interesting to note that individuals with hereditary hemochromatosis absorb less non-heme iron from their diets, and using PPIs also appears to lessen the need for phlebotomies [20]. PPI usage has been linked, in a large case-control study, to an increased risk of iron shortage; however, the clinical significance of this association has been questioned, and the extent of impaired iron absorption is probably minor in most persons [21].

The absorption of calcium may be hampered by profound acid inhibition [22]. However, prolonged PPI does not appear to decrease the absorption of dietary calcium or water-soluble calcium salts, which has further undermined the theory that abnormal calcium metabolism raises the risk of fracture.

**Cardiovascular disease**

PPI usage has been linked to increased cardiovascular morbidity and death within the last ten years [23,43]. Long-term or heavy PPI use has been linked to an increased risk of significant acute cardiovascular events, such as acute myocardial infarction and stroke [24]. By inhibiting the enzymatic activity of dimethylarginine dimethyl-aminohydrolase, which is in charge of clearing asymmetric dimethylarginine and thus lowering nitrous oxide synthase activity, PPI usage may result in a decrease in endothelial nitrous oxide levels [25]. PPIs likely to raise blood levels of chromogranin A, a significant neuroendocrine tumor marker that may possibly be a biomarker for cardiovascular disease, according to research [26,44].

**Fracture risk**

Retrospective studies have suggested the existence of a dose-dependent relationship between PPIs and decreased bone mineral density, leading to an increase in fracture risk, especially hip fractures. The risk appears to be higher in patients with a risk factor for osteoporosis, such as renal dysfunction. Routine prophylaxis for osteoporosis is suggested for PPI users to prevent osteoporotic fractures [27]. Hypochlorhydria-associated malabsorption of calcium (absorption of which is indispensable to maintaining bone microstructure), gastrin-induced parathyroid hyperplasia, and inhibition of bone resorption by blocking local H+/K+ ATPase are some of the proposed mechanisms that link long-term PPI-based therapy with decreased bone mineral density [28,29].

**Dementia**

Headaches and vertigo/dizziness have been connected to neurological adverse effects of various PPIs, including pantoprazole, lansoprazole, and esomeprazole. The central nervous system is associated with less often reported adverse effects, such as depression, diplopia, sleep disturbance, sleepiness, insomnia, tremor, anxiety, and anomalies of the

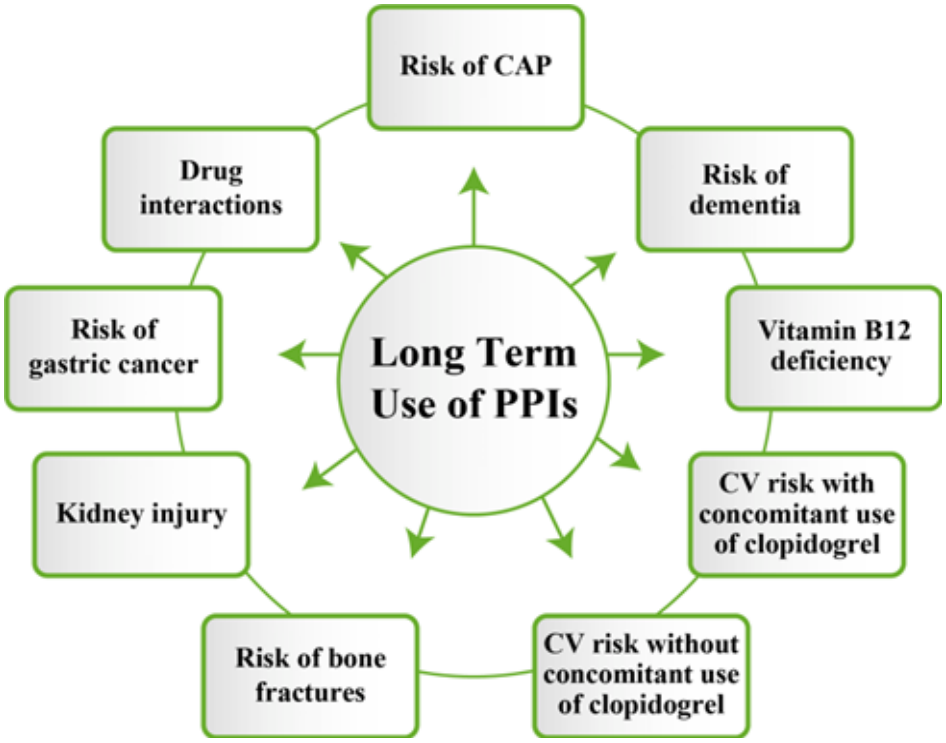


**Figure 2.** Possible risk of long term use of proton pump inhibitor

senses and perception, such as hallucinations and delirium [30, 41]. The impact of PPIs on ionic pumps that regulate neuronal membrane potential appears to account for the neurological effects of the drugs, despite the fact that the exact mechanisms behind these effects remain unclear [31]. The lysosomes of patients taking PPIs seem to be less acidic than those of patients not taking them, which may make cells less able to degrade amyloid-beta protein, the principal substance that accumulates in the brain in patients with Alzheimer's disease. Other hypotheses include that PPI and H2 receptor antagonist use have indirect effects related to systemic abnormalities (i.e., magnesium and vitamin B12 deficiency) [32,33,42].

**Uncommon adverse effect**

Fundic gastric polyps seem to be the result of the stomach mucosa's cystic reaction to long-term, significant acid inhibition-induced physiological changes [35]. Long-term PPI use was linked to a four-fold rise in the prevalence of fundic gastric polyps, although the risk of dysplasia was minimal, according to a study involving 599 patients undergoing gastroscopy [36]. During physiological reflux, the suppression of gastric acid results in an increase in the colonization of bacteria in the upper gastrointestinal tract and aspiration of the gut flora. Three sizable case control studies with up to 360 000 participants and seven years of follow-up showed that PPI users had a 16–50% higher risk of pneumonia [37,38]. Acute interstitial pneumonia caused by proton pump inhibitors is rare, although a rising number of cases are being documented [39]. Vitamin B12 absorption is decreased by proton pump inhibitor medication, most likely due to inhibition of intragastric proteolysis and subsequent release from food, which is necessary for the vitamin to bind to R-proteins and gastric intrinsic factor and then be released from the terminal ileum [40].

## CONCLUSION

It is trending with new technology [34], to combat with diseases smartly going on ahead. When prescribing PPIs, physicians should take into account the known and probably undiscovered negative effects of long-term stomach acid inhibition, according to the findings of mechanistic research, which includes trials on animals. Generally, PPI usage has advantages and disadvantages that should be carefully assessed, particularly for young patients whose treatment with these medications may persist for many years. PPIs have a number of documented system-related adverse effects; as a result more research including modification of drug's molecular structure and design-

ing new drug from parent drug is demanding. Minimizing costs and maximizing positive outcomes can be achieved by using these medications appropriately for the right diagnoses, periodically reevaluating patient symptoms to find the least amount and length of therapy, and closely monitoring any possible side effects.

## CONFLICTS OF INTEREST

The author declares no conflict of interest.

## REFERENCES


1. Wilder-Smith, C.; Halter, F.; Ernst, T.; Gennoni, M.; Zeyen, B.; Varga, L.; Roehmel, J.J.; Merki, H.S. Loss of acid suppression during dosing with H2-receptor antagonists. Aliment. Pharmacol. Ther. 1990, 4 (Suppl. 1), 15–27.

2. Cederberg, C.; Rohss, K.; Lundborg, P.; Olbe, L. Effect of once daily intravenous and oral omeprazole on 24-hour intragastric acidity in healthy subjects. Scand. J. Gastroenterol. 1993, 28, 179–184.

3. Chen, Y. et al. Will proton pump inhibitors increase the risk of diabetes mellitus? A systemic review and meta-analysis. Turk. J. Gastroenterol. 2022; 33, 497–504.

4. De laCobaOrtiz,C.; ArguellesArias, F.;Martin deArgila de Prados,C.; JudezGutierrez, J.; Linares Rodriguez,A.; Ortega Alonso, A.; Rodriguez de Santiago, E.; Rodriguez-Tellez,M.; VeraMendoza,M.I.; Aguilera Castro, L.; et al. Proton-pump inhibitors adverse effects: A review of the evidence and position statement by the Sociedad Espanola de Patologia Digestiva. Rev. Esp. Enferm. Dig. 2016, 108, 207–224.

5. Pottegard, A.; Broe, A.; Hallas, J.; de Muckadell, O.B.; Lassen, A.T.; Lodrup, A.B. Use of proton-pump inhibitors among adults: A Danish nationwide drug utilization study. Ther. Adv. Gastroenterol. 2016, 9, 671–678.

6. Lai, S. W., Liao, K. F., Lin, C. L. & Lin, C. H. Association between Parkinson's disease and proton pump inhibitors therapy in older people. Biomedicine, 2020; 10, 1–4.

7. Ahrens, D.; Behrens, G.; Himmel, W.; Kochen, M.M.; Chenot, J.F. Appropriateness of proton pump inhibitor recommendations at hospital discharge and continuation in primary care. Int. J. Clin. Pract. 2012, 66, 767–773

8. Hoque, M., Rafi, I.K., Ripon, A.I. How hospital patients use antiulcer drugs: An observational study in a general hospital in Bangladesh. GSC Biological and Pharmaceutical Sciences, 2023, 25(02), 387–393. DOI: https://doi.org/10.30574/gscbps.2023.25.2.0508

9. Geevasinga, N.; Coleman, P.L.; Webster, A.C.; Roger, S.D. Proton pump inhibitors and acute interstitial nephritis. Clin. Gastroenterol. Hepatol. 2006, 4, 597–604

10. Moledina, D.G.; Perazella, M.A. PPIs and kidney disease: From AIN to CKD. J. Nephrol. 2016, 29, 611–616

11. Froissart, M.; Borensztein, P.; Houillier, P.; Leviel, F.; Poggioli, J.; Marty, E.; Bichara, M.; Paillard, M. Plasma membrane Na(+)-H+ antiporter and H(+)-ATPase in the medullary thick ascending limb of rat kidney. Am. J. Physiol. 1992, 262, C963–C970.

12. Cavalcoli F, Zilli A, Conte D, Ciafardini C, Massironi S: Gastric neuroendocrine neoplasms and proton pump inhibitors: fact or coincidence?. Scand J Gastroenterol. 2015, 50:1397-1403. 10.3109/00365521.2015.1054426

13. Waldum HL, Sørdal ØF, Mjønes PG: The enterochromaffin-like [ECL] cell—central in Gastric physiology and pathology. Int J Mol Sci. 2019, 20:2444. 10.3390/ijms20102444

14. Tran KT, McMenamin C, Hicks B, et al.: Proton pump inhibitor and histamine-2 receptor antagonist use and risk of liver cancer in two population-based studies. Aliment Pharmacol Ther. 2018, 48:55-64. 10.1111/apt.14796

15. Song HJ, Jiang X, Henry L, Nguyen MH, Park H: Proton pump inhibitors and risk of liver cancer and mortality in patients with chronic liver disease: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2020, 76:851-866. 10.1007/s00228-020-02854-8

16. Fossmark R, Sagatun L, Nordrum IS, Sandvik AK, Waldum HL: Hypergastrinemia is associated with adenocarcinomas in the gastric corpus and shorter patient survival. APMIS. 2015, 123:509-514. 10.1111/apm.12380

17. Hoque M (2023) Prevalence of renal disease in Bangladesh. International Journal of Research (IJR) 10: 09. doi: 10.5281/zenodo.8338909

18. Schenk, B.E.; Festen, H.P.; Kuipers, E.J.; Klinkenberg-Knol, E.C.; Meuwissen, S.G. E
ect of short- and long-term treatment with omeprazole on the absorption and serum levels of cobalamin. Aliment. Pharmacol. Ther. 1996, 10, 541–545

19. Ajmera, A.V.; Shastri, G.S.; Gajera, M.J.; Judge, T.A. Suboptimal response to ferrous sulfate in iron-deficient patients taking omeprazole. Am. J. Ther. 2012, 19, 185–189

20. Hutchinson, C.; Geissler, C.A.; Powell, J.J.; Bomford, A. Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary haemochromatosis. Gut 2007, 56, 1291–1295.

21. Lam, J.R.; Schneider, J.L.; Quesenberry, C.P.; Corley, D.A. Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use and Iron Deficiency. Gastroenterology 2017, 152, 821–829.

22. O'Connell, M.B.; Madden, D.M.; Murray, A.M.; Heaney, R.P.; Kerzner, L.J. E
ects of proton pump inhibitors on calcium carbonate absorption in women: A randomized crossover trial. Am. J. Med. 2005, 118, 778–781

23. Manolis AA, Manolis TA, Melita H, Katsiki N, Manolis AS: Proton pump inhibitors and cardiovascular adverse effects: real or surreal worries?. Eur J Intern Med. 2020, 72:15-26. 10.1016/j.ejim.2019.11.017

24. Casula M, Scotti L, Galimberti F, Mozzanica F, Tragni E, Corrao G, Catapano AL: Use of proton pump inhibitors and risk of ischemic events in the general population. Atherosclerosis. 2018, 277:123-129. 10.1016/j.atherosclerosis.2018.08.035

25. Dhaun N, Webb DJ: Endothelins in cardiovascular biology and therapeutics . Nat Rev Cardiol. 2019, 16:491-502. 10.1038/s41569-019-0176-3

26. Goetze JP, Alehagen U, Flyvbjerg A, Rehfeld JF: Chromogranin A as a biomarker in cardiovascular disease . Biomark Med. 2014, 8:133-140. 10.2217/bmm.13.102

27. Poly TN, Islam MM, Yang HC, Wu CC, Li YC: Proton pump inhibitors and risk of hip fracture: a metaanalysis of observational studies. Osteoporos Int. 2019, 30:103-114. 10.1007/s00198-018-4788-y

28. Moayyedi P, Eikelboom JW, Bosch J, et al.: Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. Gastroenterology. 2019, 157:682-691.E2. 10.1053/j.gastro.2019.05.056

29. Targownik LE, Goertzen AL, Luo Y, Leslie WD: Long-term proton pump inhibitor use is not associated with changes in bone strength and structure. Am J Gastroenterol. 2017, 112:95-101. 10.1038/ajg.2016.481

30. Ortiz-Guerrero G, Amador-Muñoz D, Calderón-Ospina CA, López-Fuentes D, Mesa MON: Proton pump inhibitors and dementia: physiopathological mechanisms and clinical consequences. Neural Plast. 2018, 10.1155/2018/5257285

31. Sebastián DJJ: Omeprazole-induced hallucinations. Not as rare as you might think . Gastroenterol Hepatol. 2018, 41:266-267. 10.1016/j.gastre.2018.04.013

32. Badiola N, Alcalde V, Pujol A, et al.: The proton-pump inhibitor lansoprazole enhances amyloid beta production. PLoS One. 2013, 8:1-8. 10.1371/journal.pone.0058837

33. Bloom GS: Amyloid-ß and tau: the trigger and bullet in Alzheimer disease pathogenesis . JAMA Neurol. 2014, 71:505-508. 10.1001/jamaneurol.2013.5847

34. Hoque, M et al., Advancing healthcare: Exploring recent innovations in drug delivery systems, International Journal of Multidisciplinary Research and Growth Evaluation, 2023, 4(5), 50-55, https://doi.org/10.54660/.IJMRGE.2023.4.5.50-55.

35. Yeomans ND, Dent J. Personal review: alarmism or legitimate concerns about long-term suppression of gastric acid suppression? Aliment Pharmacol Ther 2000;14:267–71.

36. Jalving M, Koornstra JJ, Wesseling J, Boezen HM, DE Jong S, Kleibeuker JH. Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. Aliment Pharmacol Ther 2006;24:1341–8.

37. Laheij RJ, Miriam C, Sturkenboom JM, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA 2004;292:1955–60.

38. Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. Arch Intern Med 2007;167:950–5.

39. Ray S, Delaney M, Muller AF. Proton pump inhibitors and acute interstitial nephritis. BMJ 2010;341:4412.

40. Allen RH, Seetharam B, Podell E, Alpers DH. Effect of proteolytic enzymes on the binding of cobalamin to R protein and intrinsic factor. In vitro evidence that a failure to partially degrade R protein is responsible for cobalamin malabsorption in pancreatic insufficiency. J Clin Invest 1978;61:47–54.

41. Fong, P. et al. Association of suicidal ideation and depression with the use of proton pump inhibitors in adults: a cross-sectional study. Sci. Rep. 2022; 12, 19539.

42. Laudisio, A. et al. Use of proton-pump inhibitors is associated with depression: a population-based study. Int. Psychogeriatr. 2018; 30, 153–159.

43. D'Silva, K. M. et al. Proton pump inhibitor use and risk for recurrent Clostridioides difficile infection: a systematic review and metaanalysis. Clin. Microbiol. Infect. 2021; 27, 697–703.

44. Nolde, M. et al. Proton pump inhibitors and the risk of cardiovascular events and cardiovascular mortality: a systematic review and meta-analysis of observational studies. Eur. J. Intern. Med. 2022; 106, 80–89.

# Pretraživanje i razumevanje neželjnih dejstava inhibitora protonske pumpe

Majedul M. Hoque

Department of Pharmacy, Jahangirnagar University, Savar, Dhaka-1342, Bangladesh

## KRATAK SADRŽAJ

**Uvod:** Tokom poslednjih nekoliko decenija, inhibitori protonske pumpe (PPI) se sve češće koriste; ipak, postoji zabrinutost u vezi sa zloupotrebom i ozbiljnim štetnim efektima koji su opisani.
**Metode:** Ovaj rad će predstaviti informacije iz relevantnih stručnih/naučnih izvora uključujući Scopus, EBSCO, PubMed u vezi sa neželjenim neželjenim događajima IPP.
**Tema:** Uzročnost korelacije između upotrebe PPI i mogućih štetnih efekata nije poznata. Povećan rizik od bolesti bubrega, jetre i kardiovaskularnog sistema; demencija; enteroendokrini tumori gastrointestinalnog trakta; osetljivost na respiratorne i gastrointestinalne infekcije; i smanjena nutritivna apsorpcija su samo neki od dugoročnih štetnih efekata široke upotrebe PPI koji su izašli na videlo. Stoga, imajući u vidu rastuću zabrinutost u vezi sa prekomernom upotrebom IPP u opštoj populaciji, svrha ovog istraživanja je da se preispita odnos između upotrebe PPI i rizika od velikih nuspojava.
**Zaključak:** Zbog brojnih poznatih neželjenih efekata IPP-a na sistem, neophodno je dalje proučavanje, uključujući promenu molekularne strukture leka i stvaranje novog leka od njegovog roditelja. Efikasnim davanjem ovih lekova za relevantnu dijagnozu, redovnom procenom simptoma pacijenata kako bi se odredila najmanja količina i trajanje terapije i pomnim praćenjem svih potencijalnih neželjenih efekata, moguće je minimizirati troškove sa zdravstvenim rizikom i maksimizirati korisne ishode.

**Ključne reči:** PPI, čir, ulcus, neželjeno dejstvo, bolesti jetre, respiratorna infekcija, malapsorpcija

**Received:** June 17, 2024
**Accepted:** July 9, 2024