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editorial-office@sciformat.ca

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LONG-TERM PROTON PUMP INHIBITOR THERAPY: IS IT REALLY SAFE? A NARRATIVE REVIEW

Alicja Smolińska *(Corresponding Author, Email: alicja.julia2000@gmail.com)*
Polish Red Cross Maritime Hospital, Gdynia, Pomerania, Poland
ORCID ID: 0009-0004-1800-8825

Maria Bołoz
Śniadeckiego Voivodeship Hospital in Bialystok, Białystok, Poland
ORCID ID: 0009-0009-9200-0342

Izabela Grzyb
Polish Red Cross Maritime Hospital, Gdynia, Pomerania, Poland
ORCID ID: 0009-0001-7861-4585

Jan Szewczyk
Polish Red Cross Maritime Hospital, Gdynia, Pomerania, Poland
ORCID ID: 0009-0003-6214-5192

Sylwia Haba
University Clinical Hospital of Bialystok, Białystok, Podlasie, Poland
ORCID ID: 0000-0001-8396-5948

Ewa Dapkiewicz
Samodzielny Publiczny Zakład Opieki Zdrowotnej MSWiA w Białymstoku, Białystok, Podlasie, Poland
ORCID ID: 0009-0000-2148-3484

Dawid Gąsowski
Samodzielny Publiczny Zakład Opieki Zdrowotnej w Łapach, Podlasie, Poland
ORCID ID: 0009-0006-9574-584X

Katarzyna Łysynkiewicz
Wojewódzki Szpital Zespolony im. Jędrzeja Śniadeckiego, Bialystok, Podlasie, Poland
ORCID ID: 0009-0004-2097-722X

Zuzanna Wątek
Wojewódzki Szpital Zespolony im. Jędrzeja Śniadeckiego, Bialystok, Podlasie, Poland
ORCID ID: 0009-0001-3486-9113

Patrycja Krawczyk
Wojewódzki Szpital Zespolony, Kielce, Świętokrzyskie, Poland
ORCID ID: 0009-0001-0536-4570

ABSTRACT

Background: Proton pump inhibitors (PPIs) are among the most commonly prescribed medications worldwide and remain the cornerstone of treatment for acid-related gastrointestinal disorders. Despite their effectiveness and good safety profile, concerns have arisen regarding overuse and potential long-term adverse effects.
Aim: This review assessed the safety of long-term PPI therapy, summarized current evidence on adverse effects and addressed common misconceptions.
Material and methods: A narrative review of PubMed/MEDLINE and Google Scholar literature (2020–2026) was conducted, including key earlier studies. Priority was given to systematic reviews, meta-analyses, randomized trials and guidelines from ACG, AGA, NICE, FDA, and EMA.
Results: Long-term PPI use has been linked to vitamin B12 and iron deficiency, fractures, chronic kidney disease, Clostridioides difficile infection and possible cognitive impairment. However, most data are observational, and causality is unproven. Higher risk occurs in older adults, patients with comorbidities and those on prolonged high-dose therapy. Inappropriate prescribing and prolonged treatment without clear indications remain significant clinical concerns.
Conclusions: PPIs are effective and generally safe when used appropriately. Potential risks should not limit their use when indicated. Therapy should be individualized, regularly reassessed and use the lowest effective dose for the shortest duration.

KEYWORDS

Proton Pump Inhibitors, PPI, Long-Term Therapy, Adverse Effects, Safety, Gastroesophageal Reflux Disease

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1. Introduction

Since their introduction in 1989, proton pump inhibitors (PPIs) have revolutionised the management of acid peptic diseases due to their efficacy, accessibility and safety profile.

They decrease gastric acid production by inhibiting the enzyme H+/K+ ATPase in the parietal cells of gastric mucosa. [1] Currently, there are six PPIs available: omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole and dexlansoprazole; the first three are available over-the-counter in Poland [2; current data as of May 2026].

PPIs remain one of the most common drugs prescribed worldwide. In the United States of America, it was estimated that more than 7% of adults take prescription PPIs, and many more use PPIs acquired over the counter. In England, omeprazole prescriptions tripled between 2006 and 2016, and more than 35 million omeprazole prescriptions were issued in 2022-2023, making it the second most prescribed drug in the country. [3] In Germany, approximately 2.87 billion PPI tablets were sold during 2020-2021. [4]

The indications for PPI treatment include GORD (gastro-oesophageal reflux disease), including oesophagitis and Barrett's esophagus, gastric and duodenal ulcer disease, gastritis, Zollinger-Ellison syndrome, and *Helicobacter pylori* eradication; proton pump inhibitors are also frequently prescribed prophylactically to patients treated with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. [5, 6]

PPIs are considered to be exceptionally safe, with benefits outweighing the risk of their use. Almost all PPIs are tolerated well with a rate of 1-3% of side effects. [1] Typical side effects of PPIs are minor and easily managed; these include headache, diarrhoea, constipation and abdominal discomfort. [7] The acknowledged safety of PPIs treatment applies to their use within recommended doses and time periods. According to European and American guidelines, a 4 to 8-week treatment is recommended for dyspepsia or GORD; the administered dose should be minimal. [3, 8, 9] In rare cases in which prolonged PPI treatment is necessary, an annual review to determine the ongoing need is necessary. [10]

However, there is an increasing concern about the overuse of the PPIs. Studies have documented a high prevalence of off-label PPI use worldwide, including both inappropriate administration without valid indications and prolonged maintenance therapy without dose reduction despite established indications. [11] Moreover, in a recent meta-analysis and systematic review, it was estimated that up to 60-70% of PPI prescriptions lack a valid indication. [12] In a large UK primary care cohort, approximately 25% of patients continued PPI therapy beyond one year without necessity. [13] This potential overuse has drawn attention from scientific and regulatory bodies due to the increasing amount of data correlating prolonged PPI use with potential disadvantages. Several long-term observational and population-based cohort studies have highlighted the association between long-term use of PPIs and increased risk of bone fractures, vitamin B12 deficiency, kidney injury, infections (particularly Clostridioides difficile), dementia and others. [1, 14, 15] Consequently, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued several safety warnings and concerns associated with long-term use of PPIs. [4, 14, 16]

In this review, we aimed to assess the safety of long-term PPI treatment. We focused on providing current data on the mechanism of action and potential risks associated with prolonged PPI use, as well as addressing the most common myths regarding the aforementioned therapy and providing practical insight into PPI administration.

2. Methods

Literature for the review was identified through PubMed/MEDLINE and Google Scholar searches for articles published preferably between 2020-2026, although older references were used when appropriate after careful assessment of their credibility and reliability. Priority was allocated to national and international clinical guidelines and databases, such as the National Institute for Health and Care Excellence (NICE), the American College of Gastroenterology (ACG), the Food and Drug Administration (FDA), the European Medicines Agency (EMA), Polish and Union Register of medicinal products for human use, as well as systematic reviews, meta-analyses and randomised controlled trials. We used the search terms „PPIs", „proton pump inhibitors" in combination with the terms „long-term", „safety", „myths", „therapy", „side effects",„osteoporosis",„vitamin B12". 102 publications were analysed, including meta-analyses, epidemiological studies and experimental studies.

3. Mechanism of action

The efficacy of PPIs is linked to their structure, which must undergo acid activation in parietal cells to allow for the ionization of the PPI and the formation of covalent disulfide bonds with the cysteines of H^+-K^+-adenosine triphosphatase (H^+-K^+-ATPase). Binding of the PPI to the proton pump results in its inactivation.

Cytochrome P450 CYP2C19 and, to a lesser extent, CYP3A4 metabolize PPIs. These enzymes are immature at birth and reach adult activity levels within 5–6 months after birth. [17] There is substantial evidence describing the impact of CYP2C19 variability on PPIs and its potential role in tailoring PPI therapy; however, CYP2C19 pharmacogenetics has not yet been widely implemented in clinical practice [18]. PPIs are generally prescribed for four to eight weeks. However, healthcare providers also prescribe PPIs for patients with comorbidities and multiple medications for a longer period of time [15]. While this remains true in terms of effectiveness, there has been a growing concern over the potential safety issues associated with the long-term use of PPIs

4. Selected potential consequences of long-term use

4.1 Anemia

Vitamin B12 requires the low pH of stomach acid and pepsin to be released from its protein-bound form and then bind to intrinsic factor (IF) so that it can be absorbed in the terminal ileum. Inhibition of acid secretion can impair vitamin B12 absorption, resulting in megaloblastic anemia [19]. The study compared over 25,000 patients with vitamin B12 deficiency to nearly 200,000 patients without vitamin B12 deficiency to assess the association with acid-suppressing therapy. In individuals who received proton pump inhibitor therapy for over 2 years, the risk of vitamin B12 deficiency was 65% higher compared to those who did not receive such treatment [19]. Some observational studies suggest an increased risk in individuals using both PPIs (OR 1.65) and H2 receptor blockers (OR 1.25). However, other studies have not confirmed these findings, and the evidence appears insufficient to recommend routine vitamin B12 supplementation for these individuals [20].

Additionally, a large case-control study found that PPI use is associated with an increased risk of iron deficiency, although the extent of reduced iron absorption is likely small in most people. Therefore, researchers question its clinical significance [21].

4.2 Bone fractures

Long-term use of proton pump inhibitors is associated with reduced intestinal calcium absorption [15]. It has been suggested that the use of PPIs is associated with an increased risk of osteoporotic fractures due to bone fragility, mainly of the spine and hips. The strength of this association is weak, and studies have shown that it is slightly more pronounced with continuous use or with the use of higher than recommended daily doses of PPIs [22].

However, the dose-response or duration-response relationship is not well documented, likely due to the presence of confounding factors [23]. A recent meta-analysis comprising nearly 20 observational studies found that the use of proton pump inhibitors was associated with a slight increase in the risk of fracture at any site (RR, 1.33; 95% CI, 1.15–1.54) and the risk of vertebral fractures (RR, 1.58; 95% CI, 1.38–1.82) [22].

A prospective cohort study by van der Hoorn et al. showed that rabeprazole and esomeprazole were associated with an increased risk of fractures and osteoporosis in older women; therefore, when prescribing these drugs, a proper assessment of the benefit-risk ratio should be carried out [24].

In summary, the greatest risk of osteoporotic fractures associated with PPI use may arise when a higher than recommended daily dose of the drug is taken for an indefinite period. Particular caution should be exercised when prescribing preparations containing rabeprazole and esomeprazole, especially to those in high-risk groups (older women).

4.3 CKD

The mechanism underlying the development of chronic kidney disease (CKD) associated with the use of proton pump inhibitors stems from acute, subclinical interstitial nephritis, which, if left untreated, can lead to nephron damage [25].

A large-scale study involving over 10,000 participants was conducted. Renal function was monitored throughout the study period (nearly 14 years) in patients treated with PPIs and individuals who did not take PPIs during the study. After adjusting the analysis, the results showed that people using PPIs had a 50% higher risk of developing CKD than those not using them, with the absolute risk increasing by 3.3% [25].

These results were replicated in a cohort of nearly 250,000 patients followed for an average of 6 years. During this period, the risk of chronic kidney disease in those taking PPIs increased by nearly 20%, and the risk was higher when PPIs were administered twice daily compared with a single dose [26].

In another population-based study involving 290,592 participants aged over 65, a 2.5-fold higher risk of acute kidney injury and a three-fold higher risk of acute interstitial nephritis in elderly patients who had recently started treatment with proton pump inhibitors was reported [26].

In summary, PPIs, which are a cause of interstitial nephritis, may contribute to the development of CKD. The highest risk is borne by elderly patients who have been taking these medicines for a long time.

4.4 Infections

PPI-induced hypochlorhydria adversely affects one of the body's natural defence mechanisms against bacterial absorption, thereby facilitating bacterial colonisation, changes in the gut microbiome and increased susceptibility to intestinal infections [27].

The association between PPI use and the potential risk of developing Clostridioides difficile infection was investigated. A meta-analysis of 42 observational studies revealed an increased risk of Clostridioides difficile infection and recurrence in patients treated with PPIs (OR, 1.74; 95% CI, 1.47–2.85 and OR 2.51; 95% CI, 1.16–5.44.) [28]. In their meta-analysis, Trifan et al. observed a significant association between PPI use and infection with this pathogen (pooled OR, 1.99; 95% CI, 1.73–2.30; $P < 0.001$) [29]. However, these results should be interpreted with caution, as they are derived from observational, retrospective and heterogeneous studies. Further prospective studies involving larger patient cohorts are therefore needed to definitively confirm the validity of these findings.

A potential association has also been sought between the use of PPIs and the development of small intestinal bacterial overgrowth (SIBO) and spontaneous peritonitis (SBP). However, the presented study results are contradictory and are considered controversial [30,31].

4.5 Dementia

Proton pump inhibitors may, in theory, increase amyloid synthesis and reduce its degradation. Beta-amyloid protein is broken down in lysosomes acidified by proton pumps. PPIs inhibit this acidification, reducing the lysosomes' ability to break down proteins and contributing to the accumulation of this protein in the brain [32].

Haenisch et al. studied a cohort of over 3,000 patients aged 75 and older with no prior history of dementia. After adjusting for confounding variables, they found that those using PPIs had a 38% higher risk of developing dementia and a 44% higher risk of Alzheimer's disease [33].

On the other hand, the largest study on pantoprazole (>17,000 patients from 33 countries randomly assigned to pantoprazole or placebo, followed up for a median of approximately three years), conducted by Moayyedi et al., found no significant difference between pantoprazole and placebo in terms of dementia (0.6% versus 0.5%; p=0.36) [34]. A second study, analysing 70,000 new cases of Alzheimer's disease obtained from Finnish national medical records, also found no association between PPI use and an increased risk of developing the disease [35]. Recently, a new meta-analysis found no significant association between PPI use and the development of Alzheimer's disease, and Li et al. also reported no statistical association with an increased risk of dementia or Alzheimer's disease using the same methodology [36].

The effect of PPIs on the development of Alzheimer's disease and dementia remains unclear. Further prospective and larger-scale studies are needed to draw a definitive conclusion regarding the impact of proton pump inhibitors on human cognitive function.

5. Facts and Myths

Extensive clinical application of PPIs has generated considerable debate regarding their long-term safety profile. Among the most common, but contradictory at the same time, claims are that PPIs inevitably lead to osteoporosis or cancer, whereas others argue that prolonged therapy is entirely harmless. Many of these claims are based on observational studies with conflicting results and limited ability to establish causality [37].

5.1 Facts: PPIs are generally safe in short-term therapy

Short-term PPI use is considered both safe and highly effective in the treatment of acid-related gastrointestinal disorders. Nonetheless, prolonged administration has been associated with several potential adverse effects that warrant clinical consideration [37]. Almost all PPIs are tolerated well with a rate of 1-3% of side effects. [1]

5.2 Myths

„PPI use inevitably leads to osteoporosis"

Long-term PPI therapy has been associated with impaired calcium absorption secondary to gastric acid suppression. This has led to concerns regarding an increased risk of osteoporotic fractures, particularly involving the hip and vertebrae. Although several observational studies and meta-analyses suggest a modest increase in fracture risk, the overall strength of this association remains weak and may be influenced by confounding variables such as advanced age, comorbidities, and concomitant medication use [38].

Importantly, available evidence does not consistently demonstrate a direct relationship between PPI use and significant bone mineral density (BMD) loss. The risk of fractures appears most pronounced in patients receiving high-dose or prolonged therapy, especially older individuals.

Another mechanism potentially contributing to impaired bone health involves PPI-induced hypomagnesemia [39], which may interfere with vitamin D metabolism and negatively affect skeletal integrity. Nevertheless, current evidence remains insufficient to conclude that PPIs directly cause osteoporosis.

„Long-term use does not cause side effects"

Vitamin and mineral deficiencies

PPIs have been associated with hypomagnesemia [39], particularly in predisposed individuals such as patients with low dietary magnesium intake or impaired gastrointestinal absorption.

Chronic kidney disease

Although the evidence is limited due to its observational nature and causality has not been definitively established, these findings suggest that renal function monitoring may be warranted in long-term users [25].

Infections and alterations of the gut microbiome

Long-term therapy has been associated with an increased risk of Clostridioides difficile infection and recurrence [40]. Emerging evidence also suggests alterations in gut microbiota composition, including increased colonization by pathogenic bacteria [40].

„Long-term PPI use causes cancer"

At present, no conclusive evidence supports a direct causal relationship between PPI therapy and gastric cancer. Observed associations are likely confounded by underlying disease such as GERD [41].

5.3 Conclusion

Current evidence indicates that PPIs remain highly effective and generally safe medications when prescribed appropriately. Although prolonged therapy has been associated with several potential adverse outcomes, including micronutrient deficiencies, kidney disease, infections, and possible skeletal complications, most available evidence derives from observational studies with substantial limitations.

Consequently, the potential risks of long-term PPI therapy should not discourage their use when clinically indicated. Instead, treatment should be individualized, employing the lowest effective dose for the shortest necessary duration while considering patient-specific risk factors. At the same time, the persistent issue of PPI overprescription highlights the need for regular reassessment of therapy and further high-quality research aimed at clarifying the true long-term clinical impact of these medications.

6. Discussion

Proton pump inhibitors (PPIs) are effective therapeutic agents that enable the management of symptoms associated with a wide range of gastrointestinal disorders. However, their use should be accompanied by an awareness of potential adverse effects, particularly in the context of long-term therapy. The likelihood of adverse effects associated with PPI use is increased in patients of advanced age, those with multiple comorbidities, and individuals receiving concomitant medications. Older adults may be at increased risk of adverse events associated with long-term PPI therapy due to multimorbidity and polypharmacy. Therefore, regular monitoring of older adults using PPIs is recommended to reassess the ongoing necessity of this treatment. [42] Moreover certain concomitant medications, such as metformin and diuretics, may potentiate adverse effects associated with PPI therapy. The combined use of PPIs and metformin can impair vitamin B12 absorption, thereby increasing the risk of vitamin B12 deficiency. Similarly, the concomitant administration of PPIs and diuretics has been associated with a higher incidence of hypomagnesemia. [43]

One of the major clinical concerns is the persistent overprescription of PPIs, particularly in patients without clear indications for long-term therapy. Inappropriate prescribing most commonly involves prolonged therapy without reassessment of the indication. [44] Previous studies have shown that up to 60-70% of PPI prescriptions are issued without a clear indication. In a prospective observational study conducted in an emergency department, nearly one-third of prescriptions were considered inappropriate, while another study of hospitalized patients reported inappropriate PPI use in almost half of cases. [45]

Therefore, PPIs should be prescribed wisely and only when clinically indicated. When their use is necessary, particular attention should be paid to potential interactions with other drugs and the risk of adverse effects. Careful monitoring is especially important in elderly patients, who are more susceptible to complications associated with long-term PPI therapy.

7. Clinical implications

For most indications, including GERD, Helicobacter pylori eradication and peptic ulcer disease, PPI therapy is recommended for a limited duration, usually between 4 and 12 weeks depending on the indication. In contrast, long-term or indefinite treatment may be warranted in patients with Barrett's esophagus or severe erosive esophagitis. [46]

The American Gastroenterological Association provides several evidence-based recommendations for the management of GERD. These include considering histamine-2 receptor antagonists as alternatives to PPIs when appropriate, administering PPIs 30–60 minutes before meals rather than at bedtime and maintaining long-term PPI therapy in patients with Los Angeles grade C or D esophagitis. Lifestyle modifications, including weight reduction and avoidance of late meals, may additionally improve symptom control. Current recommendations emphasize regular reassessment of the indication for long-term PPI therapy and the use of the lowest effective maintenance dose whenever clinically feasible. [9]

Regular reassessment of the indication for long-term PPI therapy is recommended. Dose reduction or discontinuation should be considered in patients without persistent indications; however, long-term treatment remains necessary in selected high-risk groups, including patients with severe erosive esophagitis or Barrett's esophagus. Patients should also be informed about the possibility of transient rebound acid hypersecretion following treatment withdrawal. [47]

Clinical decision-making should therefore be individualized and based on a careful evaluation of the benefits and potential risks of long-term therapy.

Author's contribution:
Conceptualisation: Alicja Smolińska, Maria Bołoz
Methodology: Izabela Grzyb, Jan Szewczyk
Software: Katarzyna Łysynkiewicz, Patrycja Krawczyk
Check: Dawid Gąsowski, Maria Bołoz
Formal analysis: Zuzanna Wątek, Ewa Dapkiewicz
Investigation: Sylwia Haba, Alicja Smolińska
Resources: Ewa Dapkiewicz
Data curation: Patrycja Krawczyk, Jan Szewczyk
Writing-rough preparation: Izabela Grzyb, Zuzanna Wątek, Katarzyna Łysynkiewicz
Writing review and editing: Alicja Smolińska, Maria Bołoz, Izabela Grzyb, Jan Szewczyk, Katarzyna Łysynkiewicz, Sylwia Haba, Dawid Gąsowski, Zuzanna Wątek, Patrycja Krawczyk, Ewa Dapkiewicz
Visualisation: Sylwia Haba, Dawid Gąsowski
Project administration: Alicja Smolińska

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REFERENCES

1. Koyyada, A. (2021). Long-term use of proton pump inhibitors as a risk factor for various adverse manifestations. *Therapie, 76*(1), 13–21. https://doi.org/10.1016/j.therap.2020.06.019
2. Polish Register of Medicinal Products. (n.d.). Retrieved May 3, 2026, from https://rejestry.ezdrowie.gov.pl/rpl/search/public
3. Plehhova, K., Wray, J., Aluko, P., Sutton, S., McArdle, J., Dawson, A., Coyle, C., & Stevens, R. M. (2025). Prescribing practices for proton pump inhibitors among primary care physicians in England: An evaluation. *BJGP Open, 9*(2), BJGPO.2024.0059. https://doi.org/10.3399/BJGPO.2024.0059
4. Andrawes, M., Andrawes, W., Das, A., & Siau, K. (2025). Proton pump inhibitors (PPIs)—An evidence-based review of indications, efficacy, harms, and deprescribing. *Medicina, 61*(9), 1569. https://doi.org/10.3390/medicina61091569
5. Al-Aly, Z., Maddukuri, G., & Xie, Y. (2020). Proton pump inhibitors and the kidney: Implications of current evidence for clinical practice and when and how to deprescribe. *American Journal of Kidney Diseases, 75*(4), 497–507. https://doi.org/10.1053/j.ajkd.2019.07.012
6. Sandhu, D. S., & Fass, R. (2018). Current trends in the management of gastroesophageal reflux disease. *Gut and Liver, 12*(1), 7–16. https://doi.org/10.5009/gnl16615
7. Spechler, S. J. (2019). Proton pump inhibitors: What the internist needs to know. *The Medical Clinics of North America, 103*(1), 1–14. https://doi.org/10.1016/j.mcna.2018.08.001
8. Kahrilas, P., Anastasiou, F., Bredenoord, A. J., El Serag, H. B., Labenz, J., Mendive, J., Savarino, E. V., Sifrim, D., Udrescu, M., Yadlapati, R., & Hungin, A. P. (2024). Proton pump inhibitors: Rational use and use-reduction—The Windsor Workshop. *Digestive Diseases, 42*(3), 211–220. https://doi.org/10.1159/000538399
9. Katz, P. O., Dunbar, K. B., Schnoll-Sussman, F. H., Greer, K. B., Yadlapati, R., & Spechler, S. J. (2022). ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. *The American Journal of Gastroenterology, 117*(1), 27–56. https://doi.org/10.14309/ajg.0000000000001538
10. National Institute for Health and Care Excellence. (2019). *Gastro-oesophageal reflux disease and dyspepsia in adults: Investigation and management: Clinical guideline.*
11. Wang, Z., Jin, J., Wang, G., Zhou, G., & Jiang, H. (2026). Systematic analysis of proton pump inhibitors-related adverse reactions using the FDA adverse event reporting system database. *PLOS ONE, 21*(2), e0340684. https://doi.org/10.1371/journal.pone.0340684
12. Dutta, A. K., Sharma, V., Jain, A., Elhence, A., Panigrahi, M. K., Mohta, S., … Makharia, G. K. (2025). Inappropriate use of proton pump inhibitors in clinical practice globally: A systematic review and meta-analysis. *Gut, 74*(1), e5–e5.
13. Othman, F., Card, T. R., & Crooks, C. J. (2016). Proton pump inhibitor prescribing patterns in the UK: A primary care database study. *Pharmacoepidemiology and Drug Safety, 25*(9), 1079–1087.

14. Bhatnagar, M. S., Choudhari, S., Pawar, D., & Sharma, A. (2024). Long-term use of proton-pump inhibitors: Unravelling the safety puzzle. *Cureus, 16*(1), e52773. https://doi.org/10.7759/cureus.52773
15. Jaynes, M., & Kumar, A. B. (2018). The risks of long-term use of proton pump inhibitors: A critical review. *Therapeutic Advances in Drug Safety, 10*, 2042098618809927. https://doi.org/10.1177/2042098618809927
16. Ambizas, E. M., & Etzel, J. V. (2017). Proton pump inhibitors: Considerations with long-term use. *US Pharmacist, 42*(7), 4–6.
17. Ward, R. M., & Kearns, G. L. (2013). Proton pump inhibitors in pediatrics: Mechanism of action, pharmacokinetics, pharmacogenetics, and pharmacodynamics. *Paediatric Drugs, 15*(2), 119–131. https://doi.org/10.1007/s40272-013-0012-x
18. El Rouby, N., Lima, J. J., & Johnson, J. A. (2018). Proton pump inhibitors: From CYP2C19 pharmacogenetics to precision medicine. *Expert Opinion on Drug Metabolism & Toxicology, 14*(4), 447–460. https://doi.org/10.1080/17425255.2018.1461835
19. Lam, J. R., Schneider, J. L., Zhao, W., & Corley, D. A. (2013). Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. *JAMA, 310*(22), 2435–2442. https://doi.org/10.1001/jama.2013.280490
20. Attwood, S. E., Ell, C., Galmiche, J. P., Fiocca, R., Hatlebakk, J. G., Hasselgren, B., Långström, G., Jahreskog, M., Eklund, S., Lind, T., & Lundell, L. (2015). Long-term safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions: Data from the SOPRAN and LOTUS studies. *Alimentary Pharmacology & Therapeutics, 41*(11), 1162–1174. https://doi.org/10.1111/apt.13194
21. Shikata, T., Sasaki, N., Ueda, M., Kimura, T., Itohara, K., Sugahara, M., Fukui, M., Manabe, E., Masuyama, T., & Tsujino, T. (2015). Use of proton pump inhibitors is associated with anemia in cardiovascular outpatients. *Circulation Journal, 79*(1), 193–200. https://doi.org/10.1253/circj.CJ-14-0582
22. Zhou, B., Huang, Y., Li, H., Sun, W., & Liu, J. (2016). Proton-pump inhibitors and risk of fractures: An update meta-analysis. *Osteoporosis International, 27*(1), 339–347. https://doi.org/10.1007/s00198-015-3365-x
23. Fraser, L. A., Leslie, W. D., Targownik, L. E., Papaioannou, A., Adachi, J. D., & CaMos Research Group. (2013). The effect of proton pump inhibitors on fracture risk: Report from the Canadian Multicenter Osteoporosis Study. *Osteoporosis International, 24*(4), 1161–1168. https://doi.org/10.1007/s00198-012-2112-9
24. van der Hoorn, M. M. C., Tett, S. E., de Vries, O. J., Dobson, A. J., & Peeters, G. M. E. E. G. (2015). The effect of dose and type of proton pump inhibitor use on risk of fractures and osteoporosis treatment in older Australian women: A prospective cohort study. *Bone, 81*, 675–682. https://doi.org/10.1016/j.bone.2015.08.024
25. Lazarus, B., Chen, Y., Wilson, F. P., Sang, Y., Chang, A. R., Coresh, J., & Grams, M. E. (2016). Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Internal Medicine, 176*(2), 238–246. https://doi.org/10.1001/jamainternmed.2015.7193
26. Antoniou, T., Macdonald, E. M., Hollands, S., Gomes, T., Mamdani, M. M., Garg, A. X., Paterson, J. M., & Juurlink, D. N. (2015). Proton pump inhibitors and the risk of acute kidney injury in older patients: A population-based cohort study. *CMAJ Open, 3*(2), E166–E171. https://doi.org/10.9778/cmajo.20140074
27. Engstrand, L., & Graham, D. Y. (2020). Microbiome and gastric cancer. *Digestive Diseases and Sciences, 65*(3), 865–873. https://doi.org/10.1007/s10620-020-06101-z
28. Janarthanan, S., Ditah, I., Adler, D. G., & Ehrinpreis, M. N. (2012). Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: A meta-analysis. *The American Journal of Gastroenterology, 107*(7), 1001–1010. https://doi.org/10.1038/ajg.2012.179
29. Trifan, A., Stanciu, C., Girleanu, I., Stoica, O. C., Singeap, A. M., Maxim, R., Chiriac, S. A., Ciobica, A., & Boiculese, L. (2017). Proton pump inhibitors therapy and risk of Clostridium difficile infection: Systematic review and meta-analysis. *World Journal of Gastroenterology, 23*(35), 6500–6515. https://doi.org/10.3748/wjg.v23.i35.6500
30. Su, T., Lai, S., Lee, A., He, X., & Chen, S. (2018). Meta-analysis: Proton pump inhibitors moderately increase the risk of small intestinal bacterial overgrowth. *Journal of Gastroenterology, 53*(1), 27–36. https://doi.org/10.1007/s00535-017-1371-9
31. Xu, H. B., Wang, H. D., Li, C. H., Ye, S., Dong, M. S., Xia, Q. J., Zhang, A. Q., Pan, K., Ge, X. L., & Dong, J. H. (2015). Proton pump inhibitor use and risk of spontaneous bacterial peritonitis in cirrhotic patients: A systematic review and meta-analysis. *Genetics and Molecular Research: GMR, 14*(3), 7490–7501. https://doi.org/10.4238/2015.July.3.25
32. Ortiz-Guerrero, G., Amador-Muñoz, D., Calderón-Ospina, C. A., López-Fuentes, D., & Nava Mesa, M. O. (2018). Proton pump inhibitors and dementia: Physiopathological mechanisms and clinical consequences. *Neural Plasticity, 2018*, 5257285. https://doi.org/10.1155/2018/5257285
33. Haenisch, B., von Holt, K., Wiese, B., Prokein, J., Lange, C., Ernst, A., Brettschneider, C., König, H. H., Werle, J., Weyerer, S., Luppa, M., Riedel-Heller, S. G., Fuchs, A., Pentzek, M., Weeg, D., Bickel, H., Broich, K., Jessen, F., Maier, W., & Scherer, M. (2015). Risk of dementia in elderly patients with the use of proton pump inhibitors. *European Archives of Psychiatry and Clinical Neuroscience, 265*(5), 419–428. https://doi.org/10.1007/s00406-014-0554-0

34. Moayyedi, P., Eikelboom, J. W., Bosch, J., Connolly, S. J., Dyal, L., Shestakovska, O., Leong, D., Anand, S. S., Störk, S., Branch, K. R. H., Bhatt, D. L., Verhamme, P. B., O'Donnell, M., Maggioni, A. P., Lonn, E. M., Piegas, L. S., Ertl, G., Keltai, M., Bruns, N. C., … COMPASS Investigators. (2019). Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology, 157*(3), 682–691.e2. https://doi.org/10.1053/j.gastro.2019.05.056
35. Desai, M., Nutalapati, V., Srinivasan, S., Fathallah, J., Dasari, C., Chandrasekhar, V. T., Mohammad, B., Kohli, D., Vaezi, M., Katz, P. O., & Sharma, P. (2020). Proton pump inhibitors do not increase the risk of dementia: A systematic review and meta-analysis of prospective studies. *Diseases of the Esophagus, 33*(10), doaa041. https://doi.org/10.1093/dote/doaa041
36. Li, M., Luo, Z., Yu, S., & Tang, Z. (2019). Proton pump inhibitor use and risk of dementia: Systematic review and meta-analysis. *Medicine, 98*(7), e14422. https://doi.org/10.1097/MD.0000000000014422
37. Freedberg, D. E., Kim, L. S., & Yang, Y. X. (2017). The risks and benefits of long-term use of proton pump inhibitors: Expert review and best practice advice from the American Gastroenterological Association. *Gastroenterology, 152*(4), 706–715. https://doi.org/10.1053/j.gastro.2017.01.031
38. Nassar, Y., & Richter, S. (2018). Proton-pump inhibitor use and fracture risk: An updated systematic review and meta-analysis. *Journal of Bone Metabolism, 25*(3), 141–151. https://doi.org/10.11005/jbm.2018.25.3.141
39. Cheungpasitporn, W., Thongprayoon, C., Kittanamongkolchai, W., Srivali, N., Edmonds, P. J., Ungprasert, P., O'Corragain, O. A., Korpaisarn, S., & Erickson, S. B. (2015). Proton pump inhibitors linked to hypomagnesemia: A systematic review and meta-analysis of observational studies. *Renal Failure, 37*(7), 1237–1241. https://doi.org/10.3109/0886022X.2015.1057800
40. Imhann, F., Bonder, M. J., Vich Vila, A., Fu, J., Mujagic, Z., Vork, L., Tigchelaar, E. F., Jankipersadsing, S. A., Cenit, M. C., Harmsen, H. J., Dijkstra, G., Franke, L., Xavier, R. J., Jonkers, D., Wijmenga, C., Weersma, R. K., & Zhernakova, A. (2016). Proton pump inhibitors affect the gut microbiome. *Gut, 65*(5), 740–748. https://doi.org/10.1136/gutjnl-2015-310376
41. Clooney, A. G., Bernstein, C. N., Leslie, W. D., Vagianos, K., Sargent, M., Laserna-Mendieta, E. J., Claesson, M. J., & Targownik, L. E. (2016). A comparison of the gut microbiome between long-term users and non-users of proton pump inhibitors. *Alimentary Pharmacology & Therapeutics, 43*(9), 974–984. https://doi.org/10.1111/apt.13568
42. Maes, M. L., Fixen, D. R., & Linnebur, S. A. (2017). Adverse effects of proton-pump inhibitor use in older adults: A review of the evidence. *Therapeutic Advances in Drug Safety, 8*(9), 273–297. https://doi.org/10.1177/2042098617715381
43. Pakkir Maideen, N. M., Jumale, A., & Balasubramaniam, R. (2017). Drug interactions of metformin involving drug transporter proteins. *Advanced Pharmaceutical Bulletin, 7*(4), 501–505. https://doi.org/10.15171/apb.2017.062
44. Savarino, V., Marabotto, E., Zentilin, P., Furnari, M., Bodini, G., De Maria, C., Pellegatta, G., Coppo, C., & Savarino, E. (2018). Proton pump inhibitors: Use and misuse in the clinical setting. *Expert Review of Clinical Pharmacology, 11*(11), 1123–1134. https://doi.org/10.1080/17512433.2018.1531703
45. Sattayalertyanyong, O., Thitilertdecha, P., & Auesomwang, C. (2020). The inappropriate use of proton pump inhibitors during admission and after discharge: A prospective cross-sectional study. *International Journal of Clinical Pharmacy, 42*(1), 174–183. https://doi.org/10.1007/s11096-019-00955-8
46. Boster, J., Lowry, L. E., Bezzant, M. L., Kuiper, B., & Surry, L. (2020). Reducing the inappropriate use of proton pump inhibitors in an internal medicine residency clinic. *Cureus, 12*(1), e6609. https://doi.org/10.7759/cureus.660
47. Targownik, L. E., Fisher, D. A., & Saini, S. D. (2022). AGA clinical practice update on de-prescribing of proton pump inhibitors: Expert review. *Gastroenterology, 162*(4), 1334–1342. https://doi.org/10.1053/j.gastro.2021.12.247