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Navigating the Long-Term Use of Proton Pump Inhibitors: Clinical Efficacy and Safety Concerns

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ABSTRACT:

Proton pump inhibitors (PPIs) have been extensively used for over two decades as the cornerstone therapy for acid-related gastrointestinal disorders, including gastroesophageal reflux disease, peptic ulcer disease, and Zollinger-Ellison syndrome. Their clinical efficacy in suppressing gastric acid secretion and promoting mucosal healing is well established. However, widespread and often prolonged use has prompted growing concerns regarding safety issues associated with long-term therapy. This article provides a comprehensive review of the current evidence on the clinical benefits and potential risks of extended PPI use. Common adverse effects such as nutrient malabsorption (magnesium, calcium, vitamin B12), increased susceptibility to infections (Clostridioides difficile, pneumonia), renal complications, and possible cardiovascular and gastrointestinal risks are discussed in detail. The role of pharmacovigilance data in monitoring these safety concerns is highlighted. Additionally, evidence-based deprescribing strategies are presented to guide appropriate tapering and discontinuation of PPIs when long-term use is not warranted. The critical involvement of clinicians and pharmacists in ensuring rational prescribing, patient education, and adverse effect management is emphasized. Lifestyle modifications that may reduce dependence on pharmacologic therapy are also reviewed. This balanced overview underscores the importance of individualized therapy, regular reassessment, and interdisciplinary collaboration to optimize patient outcomes while minimizing adverse events related to long-term PPI therapy.

1. Introduction

Proton pump inhibitors (PPIs) have become some of the most widely prescribed medications globally due to their potent ability to suppress gastric acid secretion. Their primary indications include acid-related gastrointestinal conditions such as gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger-Ellison syndrome.[1] Since their introduction over 25 years ago, PPIs have transformed the treatment landscape by effectively promoting mucosal healing and providing

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symptomatic relief for these conditions. Their strong efficacy and favorable short-term safety profile have led to extensive use in clinical practice.[2] However, the increased utilization and sometimes extended or indefinite duration of therapy have raised significant concerns about the long-term safety and the overall balance of benefits versus risks associated with prolonged PPI use.

Emerging evidence from observational studies, pharmacovigilance data, and meta-analyses suggests that long-term PPI therapy may be associated with various adverse effects, including nutrient malabsorption, increased risk of infections such as Clostridioides difficile and pneumonia, renal complications, and potential cardiovascular and neurological concerns.[1,3] These findings have challenged the longstanding assumption that PPIs are entirely safe for extended use and have highlighted the need for careful patient selection and periodic re-evaluation of ongoing therapy.

This article comprehensively reviews the clinical efficacy of long-term PPI therapy while critically examining the spectrum of safety concerns reported in the literature. It also proposes evidence-based deprescribing strategies to minimize unnecessary exposure and optimize treatment duration.[2] Moreover, it underscores the crucial roles of clinicians and pharmacists in ensuring rational prescribing, monitoring adverse events, and educating patients to achieve the best therapeutic outcomes with minimal harm. Through a balanced understanding of efficacy and safety, healthcare professionals can navigate the complexities of long-term PPI use to improve patient care.

2. PPIs and its Mechanism of Action

Proton pump inhibitors are a class of medications designed to potently and selectively suppress gastric acid secretion by targeting the stomach's acid-producing cells, known as parietal cells. Their mechanism of action involves entering the bloodstream after oral absorption, reaching the parietal cells, and irreversibly inhibiting the hydrogen/potassium adenosine triphosphatase (H+/K+ ATPase) enzyme system, commonly referred to as the gastric proton pump.[4,5] This enzyme mediates the final step in the process of gastric acid secretion, exporting hydrogen ions into the gastric lumen in exchange for potassium ions. By forming covalent bonds with the sulfhydryl groups of cysteine residues on the proton pump, PPIs block its activity until new enzymes are synthesized.[1] The profound reduction of gastric acid secretion achieved by PPIs underpins their efficacy in treating acid-related disorders, such as gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger-Ellison syndrome.

3. Clinical Efficacy of Long-Term PPI Use

Proton pump inhibitors (PPIs) produce their therapeutic effects through a highly specific mechanism that targets the gastric acid production process. These drugs act by irreversibly inhibiting the hydrogen-potassium adenosine triphosphatase enzyme system, commonly known as the proton pump, which is situated in the membrane of the gastric parietal cells. This enzyme system is the final and rate-limiting step in the secretion of gastric acid into the stomach lumen.[6] By binding covalently and permanently to the proton pump, PPIs block the exchange of hydrogen ions (protons) for potassium ions, thereby suppressing the secretion of gastric acid effectively.

This potent acid inhibition underlies the clinical success of PPIs in the management of acid-peptic disorders. In gastroesophageal reflux disease (GERD), continuous long-term PPI therapy helps maintain remission by reducing acid exposure to the esophageal mucosa, which prevents esophagitis and decreases the risk of complications such as Barrett's esophagus—a precancerous condition.[1,5] Clinical evidence consistently shows that sustained acid suppression with PPIs reduces symptom recurrence and promotes mucosal healing better than intermittent or placebo treatments.

In peptic ulcer disease, particularly when linked to Helicobacter pylori infection or nonsteroidal anti-inflammatory drug (NSAID) use, PPIs accelerate ulcer healing and reduce recurrence risk by neutralizing gastric acidity, which favors mucosal repair and suppresses injury progression.

Moreover, PPIs are indispensably used in managing Zollinger-Ellison syndrome, a rare but severe disorder characterized by gastrin-producing tumors that provoke excessive gastric acid secretion.[7] In such cases, lifelong, often high-dose acid suppression is required to prevent ulceration and complications.

PPIs also address stress-related mucosal bleeding in critically ill patients, where acid suppression and

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mucosal protection are crucial. Despite these demonstrated benefits, clinical guidelines advocate for regular reassessment of PPI indications during long-term use. This is to avoid unnecessary indefinite treatment, which may expose patients to risks without additional therapeutic gains.[4] Periodic evaluation ensures that continued PPI therapy is tailored to ongoing clinical need, optimizing benefits while mitigating potential harms associated with extended acid suppression.

4. Are PPI Over-prescribed

Proton pump inhibitors (PPIs) are widely regarded as effective agents for managing acid-related disorders; however, there is substantial evidence to suggest that they are frequently overprescribed. Studies have shown that a significant proportion of PPI prescriptions, ranging from 25% to as high as 70%, are given without appropriate clinical indications. This trend is observed across both primary and secondary care settings worldwide.[2,5] Common factors contributing to overprescription include initiating PPIs for prophylaxis during hospital stays without clear justification and failure to reassess or discontinue therapy upon discharge. Many patients continue PPIs for extended periods unnecessarily, sometimes for years, without documented indications or scheduled review.[8] Overprescribing not only exposes patients to avoidable safety risks but also incurs considerable healthcare costs. Despite their proven efficacy and relative safety, the inappropriate long-term use of PPIs highlights the urgent need for stewardship programs, regular medication reviews, and clinician education to ensure prescriptions are evidence-based and periodically re-evaluated. Addressing overuse is critical to minimize adverse effects, drug interactions, and resistance patterns while optimizing resource utilization in healthcare systems.

5. Safety Concerns and Adverse Effects of Long-Term Use

The expanding use of proton pump inhibitors (PPIs) beyond their FDA-approved indications, often without clear re-assessment, has raised significant concerns about safety risks from prolonged acid suppression.[1-4] Numerous observational studies and meta-analyses have reported associations between long-term PPI use and diverse adverse effects, though establishing definitive causality remains complex due to confounding factors.

One major concern is nutrient malabsorption. PPIs reduce gastric acidity, which is essential for the absorption of minerals such as magnesium and calcium and vitamins like B12. This can lead to hypomagnesemia, characterized by muscle cramps or cardiac arrhythmias, and impaired calcium absorption, contributing to osteoporosis and an elevated fracture risk, particularly hip fractures among the elderly.

Long-term acid suppression also alters the gastrointestinal environment, leading to an increased risk of infections. Reduced acid barrier function may predispose patients to gastrointestinal infections such as Clostridioides difficile-associated diarrhea—an infection notorious for causing severe colitis—and to respiratory infections including community-acquired pneumonia.[9] The mechanism is thought to involve bacterial overgrowth in the upper gastrointestinal tract and subsequent aspiration or colonization.

Renal complications have emerged as another safety concern. Chronic use of PPIs is linked to acute interstitial nephritis, an immune-mediated kidney injury, and a modestly increased risk of chronic kidney disease, raising the importance of monitoring renal function during prolonged therapy.

Cardiovascular safety remains a debated topic. Some studies suggest an association between PPIs and increased cardiovascular events, particularly in patients on antiplatelet therapy like clopidogrel, possibly due to drug interactions affecting platelet aggregation or endothelial function. However, evidence is mixed, and no definitive causal link has been confirmed.[6]

Gastrointestinal effects related to compensatory hypergastrinemia include enterochromaffin-like cell hyperplasia and fundic gland polyps, potentially altering gastric mucosal integrity. Small intestinal bacterial overgrowth has also been observed in long-term users.

Emerging but still inconclusive data suggest possible connections between chronic PPI use and dementia risk, liver disease, and stomach cancer. These associations warrant further robust studies to clarify clinical relevance.[10]

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Table 1. Common Adverse Effects Associated with Long-Term Proton Pump Inhibitor Use.

Adverse Effect	Possible Mechanism	Clinical Implications
Hypomagnesemia	Reduced absorption	Neuromuscular symptoms, cardiac arrhythmias
Vitamin B12 Deficiency	Decreased gastric acid for absorption	Neurological symptoms, anemia
Osteoporosis-related Fractures	Impaired calcium absorption	Increased fracture risk
Clostridioides difficile Infection	Altered gastric pH favoring pathogens	Diarrhea, colitis
Pneumonia	Aspiration of altered flora	Respiratory infections
Acute Interstitial Nephritis	Immune-mediated renal injury	Acute kidney injury
Chronic Kidney Disease	Progressive renal damage	Long-term renal impairment
Cardiovascular Events	Possibly drug interaction or endothelial effects	Myocardial infarction, stroke (controversial)
Enterochromaffin-like Cell Hyperplasia	Hypergastrinemia	Fundic gland polyps, gastric mucosal changes

6. Pharmacovigilance Data

Active pharmacovigilance systems play an essential role in detecting, assessing, and preventing adverse effects associated with long-term proton pump inhibitor (PPI) use. These systems serve as vital post-marketing surveillance tools, capturing real-world data that extend beyond pre-approval clinical trials, where follow-up durations are typically short and sample sizes limited. Databases such as the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS), the European Medicines Agency's EudraVigilance, and the World Health Organization's VigiBase aggregate spontaneous reports from healthcare professionals, patients, and pharmaceutical manufacturers.[5,11] Analysis of these large datasets has consistently revealed safety signals implicating chronic PPI use in various adverse outcomes, including hypomagnesemia, renal complications like acute interstitial nephritis and chronic kidney disease, osteoporosis-related fractures, and increased risk of infections such as Clostridioides difficile colitis and community-acquired pneumonia.[2-6] These findings have informed updates to drug labeling, clinical guidelines, and patient monitoring recommendations.

Cross-regional variations in pharmacovigilance data provide insights into how genetic factors, prescribing patterns, local antimicrobial resistance, and healthcare access influence the risk profile of PPIs across populations.[12,13] For example, higher rates of renal adverse event reporting in some Western cohorts contrast with more infection-related signals in Asian databases, reflecting distinct environmental exposures and prescribing habits. Such observational diversity underscores the necessity of regional pharmacovigilance collaboration and context-specific policy formulation.[14] In addition, signal strength analyses have shown that certain risks, particularly metabolic and renal complications, appear to be dose- and duration-dependent, indicating that excessive or prolonged suppression of gastric acid may disrupt physiological homeostasis over time.

Pharmacovigilance efforts also emphasize the dynamic nature of PPI risk-benefit assessment. Continuous feedback from these monitoring systems allows for early identification of emerging adverse events, refinement of clinical practice guidelines, and implementation of

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deprescribing strategies.[2] Regular re-evaluation of therapy duration, dosage adjustment, and consideration of on-demand or step-down approaches can significantly reduce unnecessary PPI exposure. Clinicians and pharmacists, as primary contributors to these safety databases, have a pivotal role in reporting adverse events accurately and promoting awareness among patients about potential risks.[15-18] Their participation ensures data integrity and fosters proactive patient management through counseling on symptom-based PPI use, dietary modifications, and monitoring for early signs of adverse reactions.

Active pharmacovigilance transforms post-marketing surveillance into a continuous learning process, strengthening medication safety frameworks globally.[4] By integrating data analytics, regulatory oversight, and clinical vigilance, these systems not only help validate observed associations but also guide evidence-based decision-making for safer long-term PPI therapy.[1] The synergy between pharmacovigilance data and clinical practice reinforces the overarching principle that while PPIs remain indispensable for managing acid-related disorders, individualized prescribing, periodic review, and timely deprescribing are critical for optimizing patient outcomes and minimizing harm.

7. Deprescribing Strategies and Pathways

Deprescribing proton pump inhibitors (PPIs) has become an important strategy to reduce unnecessary long-term use and mitigate associated safety risks.[17] Deprescribing involves a structured, patient-centered approach to tapering or discontinuing PPI therapy when the original indication for treatment has resolved or when the risks of continued use outweigh potential benefits.[19,20] The first essential step is confirming that the ongoing need for PPI therapy is justified by reviewing the patient's clinical condition and, if necessary, conducting further diagnostic assessments.[2] This ensures that patients with lasting indications such as Barrett's esophagus, severe esophagitis, or a history of bleeding ulcers are appropriately excluded from deprescribing attempts without specialist input.

Once eligibility for deprescribing is established, clinicians may choose to reduce the daily dose gradually or switch the patient to on-demand (as-needed) PPI use, which has been shown to successfully decrease overall medication burden while maintaining symptom control for many patients.[15] In situations where dose tapering alone provokes rebound acid hypersecretion and symptom recurrence, adjunctive therapies such as H2-receptor antagonists or antacids can be utilized to ease the transition and improve tolerability. Patient education plays a crucial role in managing expectations and encouraging adherence, focusing on potential symptom rebound, lifestyle modifications (e.g., weight loss, dietary changes, head-of-bed elevation), and reassurance that PPI therapy can be resumed if symptoms recur.[21]

Monitoring during and after deprescribing is critical to assess symptom control and patient wellbeing, with follow-up visits scheduled typically at 4 to 12 weeks post-dose adjustment.[10] If symptoms persist or worsen significantly, clinicians should reconsider the dose or investigate other causes, including Helicobacter pylori infection. Overall, evidence-based deprescribing protocols emphasize a gradual, individualized approach that balances symptom management with minimizing exposure to unnecessary long-term acid suppression, improving patient safety and quality of care.[2,5]

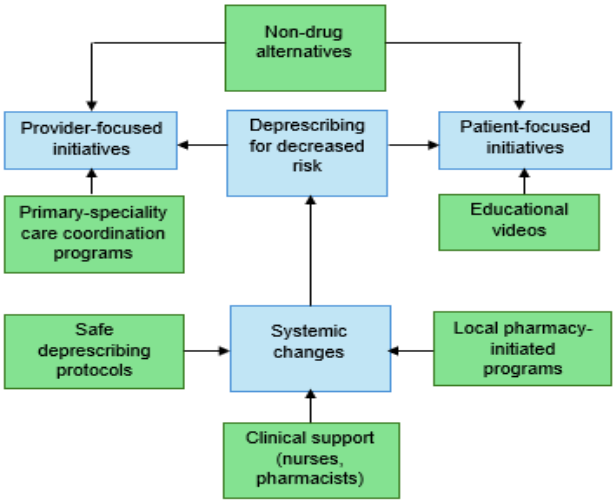

Figure 1. Schematic representation of a multidisciplinary deprescribing framework

8. Role of Clinicians and Pharmacists

Clinicians and pharmacists play a pivotal role in ensuring the rational, safe, and effective use of proton pump inhibitors (PPIs) throughout all stages of therapy.[22] Their collaboration begins at the point of initiation, where clinicians assess clinical indications such as gastroesophageal reflux disease, peptic ulcer disease, or

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NSAID-induced ulcer prophylaxis, confirming that PPI use aligns with validated guidelines and appropriate dosing regimens.[23] This careful evaluation prevents unnecessary or empiric prescribing, which remains one of the key drivers of prolonged and unjustified PPI use. Once therapy has commenced, clinicians are responsible for setting clear treatment objectives and duration limits, documenting these in patient records, and scheduling periodic reviews to reassess the ongoing need for acid suppression.[5] Regular evaluation helps identify patients who may benefit from dose reduction, step-down therapy, or gradual discontinuation, minimizing cumulative exposure to the potential risks associated with chronic PPI therapy.

Monitoring for adverse effects forms another cornerstone of clinical responsibility. Long-term PPI users should be periodically evaluated for signs of nutrient deficiencies, renal function impairment, and infection risks.[24] Laboratory monitoring such as serum magnesium, vitamin B12, and renal parameters can aid in early detection of emerging issues. Clinicians must also recognize and manage adverse effects promptly, discontinuing the medication where appropriate or switching to alternative therapeutic options. In parallel, pharmacists enhance patient safety by performing comprehensive medication reconciliation to detect possible drug-drug interactions.[17] Given that PPIs can influence the metabolism of drugs like clopidogrel, warfarin, and certain antifungals through cytochrome P450 interactions, pharmacists provide critical recommendations to optimize therapy and prevent clinically significant interactions.

Pharmacists also serve as vital educators, guiding patients on the correct timing and administration of PPIs—ideally 30 to 60 minutes before meals—to achieve optimal acid suppression.[25] They reinforce adherence, counsel on the expected therapeutic response, and address common misconceptions about the need for indefinite therapy.[5] Importantly, pharmacists assist patients in adopting lifestyle modifications that complement pharmacologic treatment, including dietary adjustments, weight reduction, decreased alcohol and caffeine intake, and smoking cessation. Such counseling not only improves symptom control but may also reduce dependence on pharmacotherapy.

A key shared responsibility between clinicians and pharmacists is implementing structured deprescribing strategies once the therapeutic goal has been achieved or when ongoing PPI use is no longer clinically justified.[9] Gradual tapering or step-down to as-needed dosing helps minimize rebound acid hypersecretion and discourages unnecessary reinitiation. Through interdisciplinary coordination, healthcare providers can ensure seamless transitions, mitigate withdrawal symptoms, and maintain patient trust during therapy adjustment.

Ultimately, this interprofessional model fosters a culture of continuous medication review, proactive risk mitigation, and patient-centered care.[18] By integrating clinical judgment with pharmacological expertise, clinicians and pharmacists collectively safeguard against adverse outcomes, optimize therapeutic success, and uphold responsible medication stewardship in the management of long-term PPI therapy.

9. Conclusion

Proton pump inhibitors (PPIs) have revolutionized the management of acid-related gastrointestinal disorders by providing potent and sustained suppression of gastric acid secretion, which leads to significant clinical efficacy in healing mucosal damage and alleviating symptoms. Their introduction transformed therapeutic strategies for conditions like gastroesophageal reflux disease, peptic ulcers, and Zollinger-Ellison syndrome, contributing to improved patient outcomes and quality of life. However, the benefits of PPIs must be carefully weighed against emerging evidence of safety concerns linked to their long-term use. Prolonged suppression of gastric acid can predispose patients to adverse effects including nutrient deficiencies, infections, renal and cardiovascular complications, and other systemic sequelae. These potential risks necessitate vigilant clinical monitoring and periodic reassessment of the ongoing need for therapy to ensure that the benefits continue to outweigh harms.

Incorporating deprescribing strategies has become crucial as part of responsible PPI management. Systematic deprescribing involves evaluating indications, tapering doses, and transitioning patients off unnecessary or prolonged therapy with appropriate support to minimize symptom recurrence or rebound acid hypersecretion. This approach reduces exposure to avoidable risks and enhances patient safety.

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Furthermore, the active engagement of healthcare professionals, particularly clinicians and pharmacists, is essential. Their proactive roles include initiating therapy only when indicated, reviewing treatment regularly, managing complications, educating patients on lifestyle modifications, and applying deprescribing protocols. Through interdisciplinary collaboration, they ensure precision in prescribing, optimize therapeutic outcomes, and minimize adverse effects, thus striking a critical balance between efficacy and safety in long-term PPI use. This holistic approach ultimately fosters safer medication use, improves patient care, and mitigates the burden of preventable complications associated with chronic acid suppression.

References

1. Freedberg DE, Kim LS, Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. Gastroenterology. 2017;152(4):706-715.
2. Scarpignato C, Gatta L, Zullo A, Blandizzi C. Effective and safe proton pump inhibitor therapy in acid-related diseases—a position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016;14:179.
3. Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. JAMA. 2013;310(22):2435-2442.
4. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol. 2012;107(7):1001-1010.
5. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016;176(2):238-246.
6. Xie Y, Bowe B, Li T, et al. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney Int. 2017;91(6):1482-1494.
7. Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. CMAJ. 2011;183(3):310-319.
8. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006;296(24):2947-2953.
9. Bangia A, Jindal SK. Proton pump inhibitors: mechanism, efficacy and safety in the treatment of gastroesophageal reflux disease in adults. Expert Opin Drug Saf. 2017;16(4):421-434.
10. Janisch T, Grischke EM, Janisch H, Büchler P, Ritz JS. Proton pump inhibitors and risk of dementia: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2020;76(11):1529-1540.
11. Maura G, Ludovic B, Joumana F, et al. Proton pump inhibitors and risk of myocardial infarction: A systematic review and meta-analysis. Pharmacol Res. 2021;164:105438.
12. Larsen AM, Bruun JM, Nielsen TS, et al. Proton pump inhibitor-induced hypomagnesemia: A case series and review of the literature. Am J Med Sci. 2021;361(5):540-550.
13. Kanno T, Noshiro H, Hosoya K, et al. Pharmacokinetic drug interactions with proton pump inhibitors: clinical implications. J Clin Pharmacol. 2015;55(8):839-851.
14. Bhurwal A, Golemi I, Kim K, et al. Interaction of clopidogrel with proton pump inhibitors: a systematic review and meta-analyses. Pharmacol Res Perspect. 2019;7(6):e00542.
15. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. Ther Adv Drug Saf. 2013;4(3):125-133.
16. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk-benefit considerations. Am J Gastroenterol. 2010;105(3):497-500.
17. Gyawali CP. Proton pump inhibitor deprescribing: guidelines and clinical

experience. Curr Gastroenterol Rep. 2022;24(9):279-286.

18. Reeve E, Gnjidic D, Long J, Hilmer S. A systematic review of the emerging definition of "deprescribing" with network analysis: implications for future research and clinical practice. Br J Clin Pharmacol. 2015;80(6):1254-1268.
19. US Food and Drug Administration. Clopidogrel bisulfate drug interactions with proton pump inhibitors - FDA drug safety communication. 2023.
20. Xie Y, Bowe B, Al-Aly Z. Proton pump inhibitors and risk of incident CKD and progression to ESRD. Kidney Int. 2016;89(5):1059-1071.
21. Dore MP, Bibbo S, Pes GM, et al. Vonoprazan, a novel potassium-competitive acid blocker: pharmacology and clinical trial evidence. Therap Adv Gastroenterol. 2020;13:1756284820968686.
22. Candelli M, Cremonini F, Bartolozzi F, et al. Long-term safety concerns of proton pump inhibitors: mechanisms and clinical implications. Ther Adv Drug Saf. 2024;15:20420986241032198.
23. Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104(3):728-738.
24. Muñoz-Torrero JJ, García-Navarro S, Navarro-Caballero A. Pharmacovigilance in proton pump inhibitors: an overview of reports and safety signals. Pharmacoepidemiol Drug Saf. 2024;33(7):683-692.
25. Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton pump inhibitors and risk for recurrent Clostridium difficile infection. Arch Intern Med. 2010;170(9):772-778.