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Proton Pump Inhibitors - Clinical Use and Long-Term Safety in Adults

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ABSTRACT

Background: Proton pump inhibitors (PPIs) are widely prescribed for gastrointestinal disorders. Their potent and persistent inhibition of gastric acid ensures efficacy but has raised concerns about adverse effects during long-term therapy.

Aim: To summarize current evidence on the indications and clinical benefits of proton pump inhibitors in adults, and to review major long-term adverse effects and drug–drug interactions to guide safer treatment strategies.

Material and methods: A narrative literature review was conducted using PubMed/MEDLINE for articles published between January 2016 and November 2025. Peer-reviewed human studies and major reviews on adults receiving oral PPIs were included if they addressed utilization, indications, duration of therapy, long-term adverse effects, drug-drug interactions, or deprescribing strategies. Pediatric studies, purely animal research, and non-peer-reviewed articles were excluded.

Results: PPIs remain first-line treatment in gastroesophageal reflux disease, peptic ulcer disease, *Helicobacter pylori* eradication, and selected hypersecretory conditions. However, many patients receive these medications chronically without a clear ongoing indication or regular reassessment. Long-term PPI therapy can be linked to nutrient and electrolyte disturbances, increased fracture risk, renal complications, infections, and clinically relevant interactions with drugs such as clopidogrel and methotrexate. Cardiovascular and neurological risk signals remain inconclusive.

Conclusions: PPIs should not be withheld from patients with justified indications, but must be prescribed thoughtfully. Clinicians need to use the lowest effective dose for the shortest necessary duration, regularly review indications, and educate patients to limit unnecessary chronic exposure while preserving the substantial benefits of PPI therapy.
Keywords: Proton Pump Inhibitors, Gastroesophageal Reflux, Peptic Ulcer; Drug-Related Side Effects and Adverse Reactions, Inappropriate Prescribing

1. Introduction

Proton pump inhibitors (PPIs) are one of the most commonly used medications worldwide, serving as standard therapy for gastrointestinal disorders. Since their introduction in 1989, PPIs have spread rapidly across the globe, replacing H_2-receptor antagonists because of their superior gastric acid suppression. Their high effectiveness and fast symptom relief have made PPIs an essential part of multiple treatment strategies in acid-related conditions.[1–3]

PPIs rank among the top ten prescribed medications in many countries. Over-the-counter availability and cheaper generic substitutes have led to increased use, often without proper medical assessment. Research shows that a large share of adults have received a PPI at some point in their lives. The widespread use of PPIs reflects their medical benefits, but it has also raised concerns about potential overprescription and long-term adverse effects.[4–6]

PPIs are first-line medications for acid-related conditions, including gastroesophageal reflux disease (GERD) and peptic ulcer disease. They are also used in hypersecretory disorders such as Zollinger-Ellison syndrome, as part of eradication therapy for *Helicobacter pylori*, and for the prevention of stress-related mucosal bleeding.[2,7]

The primary mechanism of PPIs involves irreversible blockade of the gastric H^+/K^+-ATPase in parietal cells, leading to a significant reduction in gastric acid at its source. This mechanism of action makes them the most powerful acid-suppressing agents and establishes their position as core therapy for multiple gastrointestinal conditions.[1,2]

The first evaluations of PPIs showed them to be safe and reliable medications.[1] However, after long-term use became common, an increasing number of reports described possible adverse effects related to PPI therapy.[5,8,9] Observational studies demonstrate that extended

PPI treatment may result in intestinal infections with *Clostridioides difficile*, micronutrient deficiencies (vitamin B12 and magnesium), bone deterioration with elevated fracture risks, and kidney damage such as interstitial nephritis and chronic kidney disease.[5,8,9] Research suggests possible connections with cardiovascular diseases, dementia, and other health issues; however, a definitive connection has never been proven.[10–12] These potential risks do not outweigh the major advantages that PPIs offer, but the existence of many possible complications should influence doctors when making treatment decisions. The current guidelines suggest that patients should receive the lowest effective dose for the shortest period of time, with scheduled assessments of indications for therapy.[2,7,13]

In practice, healthcare providers need to establish a proper balance between the control of acid-related diseases and the avoidance of unnecessary prolonged exposure. This literature review will examine the global spread of PPIs, their medical applications, the mechanism of action, and the assessment of adverse effects in clinical practice.[2,5]

2. Research materials and methods

This article is a narrative literature review that synthesizes current evidence on the global use, indications, and safety concerns of proton pump inhibitors (PPIs), with particular focus on gastroesophageal reflux disease, peptic ulcer disease, long-term adverse reactions, and patterns of inappropriate prescribing in everyday clinical practice.

A structured search of PubMed/MEDLINE was conducted for articles published between January 2016 and November 2025. We used MeSH terms and free-text keywords related to PPIs, their main indications, and safety outcomes (e.g., “proton pump inhibitors”, “omeprazole”, “gastroesophageal reflux”, “peptic ulcer”, “*Helicobacter pylori*”, “chronic kidney disease”, “hypomagnesemia”, “*Clostridioides difficile*”, “drug interactions”, “deprescribing”), combined with Boolean operators. The reference lists of key papers and major guidelines were manually screened. Grey literature, conference abstracts, and non-peer-reviewed sources were excluded.

We included peer-reviewed studies and reviews on oral PPIs in adults that reported on utilization, indications and dosing, duration of therapy, long-term adverse effects (nutrient and electrolyte disturbances, bone disease, renal complications, infections, cardiovascular or neurological signals), drug-drug interactions, or strategies for deprescribing and optimization of therapy. Eligible designs comprised randomized controlled trials, observational studies (prospective, retrospective, cohort, case-control), systematic reviews, meta-analyses, clinical practice guidelines, and high-quality narrative reviews. Exceptionally, well-documented case

reports or very small case series were considered when they described rare but clinically important adverse outcomes. We excluded publications focused solely on pediatric populations, purely animal studies without clear translational relevance, non-English papers, and opinion pieces without primary data.

3. Results

3.1. Global Use of Proton Pump Inhibitors

Proton pump inhibitors (PPIs) represent one of the most commonly prescribed medications throughout the world, and they have become the primary treatment for acid-related gastrointestinal disorders since the late 1980s. The high occurrence of gastroesophageal reflux disease (GERD), peptic ulcers, and dyspepsia means that many patients require potent acid suppression, and PPIs provide this treatment. As a result, PPIs maintain their position among the most widely used medications throughout Europe, North America, and Asia.[1,4]

Observational studies show that most patients who use PPIs chronically do not have any medical reason for continuing therapy. According to research, PPIs are taken regularly by one-quarter of adult patients. Approximately 25% of PPI users extend their treatment duration past one year, and some remain on treatment for several years. Reports indicate that long-term PPI prescriptions do not receive adequate medical attention, and many of them lack sufficient documentation. In clinical practice, once PPI therapy is started, it is rarely reassessed, so patients continue unnecessary therapy for a long time.[4,5,14,15]

The high availability of over-the-counter (OTC) medications has led to the increased use of PPIs. In many countries, PPIs, such as omeprazole and esomeprazole, are sold without a prescription for patients with heartburn or dyspepsia. This results in better access to short-term symptom management but also allows prolonged unmonitored use. After OTC approval of PPIs, consumption among the entire population has increased rapidly. The image of PPIs as being extremely safe has further reduced the bar for prescription.[1,4,5]

The use of PPIs has also increased in low- and middle-income countries. Due to healthcare systems growing and lower generic prices, PPI prescriptions became more common for empiric treatment of gastrointestinal disorders, without prior testing, including endoscopy or pH monitoring, which are often unavailable in such regions.[4,5]

3.2. Mechanism of Action

Proton pump inhibitors (PPIs) reduce the secretion of gastric acid by irreversibly blocking the H^+/K^+-ATPase enzyme complex on the secretory surface of gastric parietal cells, also known as the proton pump. All PPIs are taken as inactive prodrugs; after oral absorption, they reach

the stomach through the systemic circulation. When parietal cells are stimulated to release acid, a PPI enters the acidic canaliculi of the cells, becomes protonated, and is activated. The medication then covalently reacts with cysteine residues on the proton pump, permanently inhibiting its function.[1,2]

Since each inhibited pump is not active until new enzymes are synthesized, the secretion of gastric acid is suppressed for at least 24 hours. A single daily dose of a PPI usually maintains gastric pH at a level of approximately 4 or higher for most of the day. PPIs block basal acid secretion as well as the high post-meal acid surge, and they do not show tachyphylaxis (tolerance). This effective, long-lasting acid inhibition enhances the healing of peptic ulcers and erosive esophagitis and provides greater symptomatic relief than older acid-blocking agents in clinical practice.[1,2]

3.3. Clinical Applications of Proton Pump Inhibitors

3.3.1. Gastroesophageal Reflux Disease (GERD)

Proton pump inhibitors (PPIs) are the first-line pharmacotherapy for gastroesophageal reflux disease (GERD) due to their strong inhibition of gastric acid secretion. By increasing the pH of the stomach environment, they provide fast symptom relief and promote mucosal healing in erosive lesions. Research shows that all PPIs are effective in managing GERD-related complaints. In clinical practice, a standard dosage of PPI in erosive esophagitis is 20-40 mg of omeprazole, which should be taken 30-60 minutes before breakfast to maximize beneficial results. In most patients, significant improvement occurs within several weeks. In severe or chronic cases of GERD, long-term maintenance therapy may be needed. To ensure patient safety and decrease the risk of potential adverse effects, it is essential to periodically re-evaluate the need for ongoing treatment.[2,7,13]

3.3.2. Peptic Ulcer Disease

Proton-pump inhibitors (PPIs) are considered the main treatment for peptic ulcer disease, as they reduce gastric acid secretion and promote ulcer healing. Due to their outstanding performance, they have replaced histamine H_2-receptor antagonists as primary medications. Normal regimens lead to approximately 80-90% healing of active gastric or duodenal lesions in 4-8 weeks.[1,2] PPIs have been shown to be effective in eliminating ulcers of any etiology, including *Helicobacter pylori*-associated or idiopathic ulcers, and are also used to prevent recurrence in high-risk patients, such as those taking chronic nonsteroidal anti-inflammatory drugs. PPIs reduce ulcer pain by raising gastric pH and are often continued at lower

maintenance doses in patients with recurrent ulcers or a history of gastrointestinal bleeding.[16,17]

3.3.3. *Helicobacter pylori* Eradication

One of the most important elements of the treatment plan to eradicate *Helicobacter pylori* is the use of proton pump inhibitors (PPIs). They are prescribed in combination with antibiotics because an increase in gastric pH improves the chemical stability and antimicrobial activity of the administered drugs.[1,2]

In clinical practice, PPIs are most often used in triple therapy with clarithromycin and amoxicillin or metronidazole, or in quadruple therapy with bismuth. Treatment usually lasts for 10 to 14 days. These protocols achieve eradication rates of approximately 80-90%. Notably, PPIs are the only approved antisecretory drugs that are included in all standardized eradication regimens.[2,7]

3.3.4. Prevention of NSAID-Induced Ulcers

Long-term therapies, which include nonsteroidal anti-inflammatory drugs (NSAIDs), are associated with higher rates of gastric and duodenal ulceration. This risk is significantly reduced by co-prescription of a proton pump inhibitor (PPI) with an NSAID. This preventive therapy is particularly important for those with known risk factors for ulcer disease, such as a history of peptic ulcers, the use of corticosteroids or anticoagulants, and advanced age. Pantoprazole remains the main agent in such cases. It is usually prescribed at a dose of 20-40 mg once daily alongside the NSAID regimen. Research demonstrates that this combination reduces the risk of NSAID-related stomach ulcers and bleeding complications. PPI co-therapy is generally considered to be safe and essential in patients who must have prolonged exposure to NSAIDs to prevent severe gastrointestinal adverse events.[16,17]

3.3.5. Hypersecretory Conditions

In some rare hypersecretory conditions, such as Zollinger-Ellison syndrome (gastrinoma), gastric acid production can become extremely high. The risk of mucosal ulceration requires strong gastric acid suppression; therefore, proton pump inhibitors remain the primary treatment in such disorders. To sufficiently reduce acid production, medical professionals should prescribe PPIs at high doses; a dose of omeprazole 60-120 mg per day in divided doses is commonly used to maintain gastric acid at a desirable level. Since the possibility of curing gastrinoma is limited, most patients require lifelong PPI therapy. Effective acid suppression is

essential to prevent diarrhea and refractory peptic ulcer disease in Zollinger-Ellison syndrome.[1,2]

3.3.6. Additional or Off-Label Uses

Aside from their well-defined indications, proton pump inhibitors (PPIs) are also used for a variety of non-specific or extraesophageal symptoms. In everyday practice, patients who suffer from a long-term cough, hoarseness, or laryngopharyngeal reflux are frequently prescribed PPIs in the hope of managing occult GERD. In a similar way, empirical PPI treatment can be applied to patients with functional dyspepsia or non-ulcer dyspeptic complaints. However, these off-label applications are not always supported by strong evidence, and the effectiveness of PPIs in these settings is not consistent. Due to extensive and sometimes unnecessary use of PPIs, medical specialists emphasize the importance of periodic re-examination of current treatment. Clinicians should regularly review their PPI prescriptions and pay attention to indications that are no longer valid. Careful monitoring remains essential to reduce the risk of possible adverse effects in patients who no longer benefit from PPI therapy.[2,13,14]

3.4. Adverse Effects of Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are commonly used to treat patients with gastrointestinal conditions. They are highly effective and well-tolerated medications, yet observational studies show that long-term therapy can be associated with several adverse effects, such as nutrient deficiencies, kidney problems, bone fractures, and infections.[5,8,9] Many of these reports remain speculative; however, they emphasize the importance of careful PPI prescription, especially in patients without established indications.[12,18,19]

3.4.1. Nutrient and Electrolyte Disturbances

Prolonged proton pump inhibitor (PPI) therapy may increase the risk of electrolyte imbalance, including hypochlorhydria, which affects the digestion and intestinal absorption of several vitamins and minerals. For example, the bioavailability of vitamin B12 depends on gastric acid-mediated release from dietary proteins, a process also associated with pepsin. As a result of insufficient acid secretion, vitamin B12 absorption is reduced, leading to deficiency. Similarly, the absorption of non-heme dietary iron depends on acid-driven reduction of ferric (Fe^{3+}) iron to ferrous (Fe^{2+}) iron in the gastric environment. Thus, prolonged acid suppression limits iron uptake and can cause iron-deficiency anemia. A systematic review has shown a link

between long-term PPI use and deficiencies in vitamin B12, iron, magnesium, and calcium, as well as other micronutrients.[5,9,18]

Hypomagnesemia is a common electrolyte imbalance that may be observed in patients on long-term therapy with PPIs. Chronic use is often associated with significantly low concentrations of magnesium. In clinical practice, hypomagnesemia can present with neuromuscular irritability (muscle cramps, tetany, and in severe cases, seizures) and cardiac arrhythmias, as determined by electrocardiography. In patients affected by this adverse effect, urinary magnesium excretion remains unusually low, which suggests that gastrointestinal uptake of magnesium is decreased. The mechanism of malabsorption seems to be related to a higher intestinal pH and changes in transporter activity. Research shows that PPIs downregulate the magnesium channel (TRPM6) in enterocytes. Calcium balance may also be disrupted, considering that the solubility of calcium carbonate is highly pH-dependent and declines significantly when gastric pH increases. In a controlled study, the representative PPI omeprazole reduced calcium absorption in elderly women. These nutrient and electrolyte deficiencies usually develop gradually and may go unnoticed without proper monitoring.[12,20,21]

3.4.2. Bone Health and Fracture Risk

Alterations in mineral homeostasis during long-term use of proton pump inhibitors (PPIs) have been frequently associated with a small but significant increase in fracture risk. Large meta-analyses show that the rates of osteoporotic fractures in chronic PPI therapy are approximately 20-50% higher than in patients who do not use these medications. For instance, one meta-analysis found that the risk of hip fracture was about 22% higher and the risk of spinal (vertebral) fracture was approximately 49% higher for patients who were exposed to PPIs. Although the absolute risk for any given person remains small, these results are significant given the widespread clinical use of PPIs.[5,9,20,22]

Possible mechanisms of these adverse effects include changes in both calcium and bone metabolism. PPIs significantly decrease the solubility of calcium by suppressing gastric acid production. In practice, this implies that less dietary calcium is absorbed during PPI treatment, which, over time, can result in impaired bone mineralization. There is also an indication that PPIs may have a particular effect on bone cells: in vitro studies suggest that omeprazole inhibits osteoclast proton pumps and interferes with bone remodeling. Reduced calcium uptake, along with altered bone turnover, offers a credible explanation for the observed fracture associations. However, studies of bone density itself have been mixed. In summary, while PPIs should not

be discontinued in patients with a clear indication, long-term therapy requires ongoing evaluation and monitoring for nutrient deficiencies and fracture risk.[12,20,21]

3.4.3. Renal Complications

Proton pump inhibitors (PPIs) have been linked to multiple forms of renal injury, but the possibility of such events is relatively low. A single, well-documented, but rare adverse effect is acute interstitial nephritis, an immune-mediated condition that can manifest itself as sudden renal failure in patients taking PPIs. Observational studies indicate that there is a higher incidence of acute kidney injury in hospitalized or high-risk patients during PPI therapy and imply that even subclinical nephritis or other subtle renal damage may occur in certain cases.[5,9,23]

Long-term PPI treatment is also associated with chronic deterioration of renal function. Numerous large-scale studies have found that patients who are prescribed PPIs have a higher incidence of chronic kidney disease (CKD) compared with control groups. Such a relationship has also been evident in some cohorts in which vulnerable patients have developed end-stage renal disease at a faster pace. All these results are based on retrospective studies and, therefore, the possibility of confounding factors, such as advanced age or comorbidities, cannot be absolutely dismissed. However, renal monitoring is often advised for patients who receive long-term PPI treatment.[23–26]

3.4.4. Infections

Long-term acid suppression caused by proton pump inhibitors (PPIs) interferes with the natural microbial protection system of the stomach. As a result, the likelihood of certain infectious complications is increased. This association has been particularly noted in *Clostridioides difficile* infection; when gastric pH is increased, PPIs enable this pathogen to survive beyond the acidic gastric environment and proliferate in the colon. The risk is exceptionally high in situations where exposure to medications has disrupted the normal gut microbiota. In addition, PPI therapy is linked to small intestinal bacterial overgrowth (SIBO) and other gastrointestinal infections.[27–29]

Studies have reported a moderately higher incidence of community-acquired pneumonia soon after the start of PPI therapy, an effect that may be due to aspiration of less acidic gastric contents; however, this association is less significant and may be confounded by other factors.[30] These results suggest that the general risk of infection is increased in patients who are prescribed PPIs, especially in the presence of comorbid risk factors. Therefore, medical professionals should be cautious when prescribing long-term PPI therapy to elderly or

immunocompromised patients, with careful consideration of these additional risk factors.[5,8,9,30]

3.4.5. Cardiovascular and Neurological Concerns

Proton pump inhibitors (PPIs) in long-term use have been the subject of scholarly interest in terms of cardiovascular and neurological sequelae; nonetheless, conclusive evidence has not been found. Multiple observational studies have reported a small increase in the rate of myocardial infarction and ischemic stroke in patients on PPI treatment, but randomized controlled trials have failed to support a causal relationship. The suggested pathophysiological mechanisms include endothelial dysfunction. PPIs can increase plasma concentrations of asymmetric dimethylarginine and reduce nitric oxide bioavailability, which may lead to impaired vasodilatory capacity and disrupted electrolyte homeostasis. One of the outcomes involves hypomagnesemia, which can predispose to arrhythmogenic events. Persistent acid inhibition has also been shown to impair the absorption of vitamin B12 and other micronutrients, raising hypotheses about the neurocognitive implications related to chronic consumption of PPIs. Although some analyses have stated a relatively small increase in the rate of dementia in patients on long-term PPI therapy, methodologically stronger meta-analyses and bias-corrected reviews have failed to find clear evidence of an increase in the risk of Alzheimer's disease or more general dementias. The link between chronic PPI treatment and cardiovascular or neurodegenerative disorders remains unproven; as a result, these issues do not outweigh the health benefits of PPIs in patients with the established indications.[10–12]

3.5. Drug Interactions

Proton pump inhibitors (PPIs) can interact with multiple medications that patients are currently using and affect their established effectiveness and safety profiles. The interaction between PPIs (in particular, omeprazole and esomeprazole) and the antiplatelet drug clopidogrel is one of the most important ones. When these two drugs are administered together, PPIs inhibit cytochrome P450 isoenzyme 2C19 (CYP2C19), which is the main catalyst in the conversion of clopidogrel into its active metabolite. This mechanism leads to a reduced antiplatelet effect of clopidogrel. By increasing gastric pH, PPIs may also disrupt the uptake of medications that are better absorbed in an acidic environment. For example, azole antifungals, including itraconazole and ketoconazole, and some antiretroviral drugs, such as atazanavir and rilpivirine, have pH-dependent absorption kinetics. When gastric acid secretion is suppressed, their bioavailability may be reduced. Another interaction involves high-dose methotrexate therapy, in which PPIs have been linked to slower clearance of methotrexate and, as a result,

its increased toxicity. A possible explanation is inhibition of excretory pathways in the kidneys. Clinicians should be particularly cautious when these two drug classes are used together. Other interactions can occur with nutrient supplements or minerals, such as iron salts, which require an acidic environment to dissolve properly; however, they have a low clinical impact.[2,5,18]

In everyday practice, medical professionals should closely monitor the drug regimens of their patients. Establishing the correct timing of drug administration and choosing other medications in situations of high risk of drug interactions is essential to provide beneficial and safe treatment.[2,7,13]

4. Discussion

Since proton pump inhibitors (PPIs) have revolutionized the therapy of acid-related diseases, they serve as a fundamental treatment in gastrointestinal conditions.[1–3] The review demonstrates that PPIs can provide powerful symptom relief in many disorders through their effectiveness in inhibiting gastric acid.[2,3] They are most commonly used in patients suffering from gastroesophageal reflux disease and peptic ulcer disease.[1,2] They are also a part of all *Helicobacter pylori* eradication programs, and help with much rarer hypersecretory disorders such as Zollinger-Ellison syndrome.[1,3] Their wide availability and good short-term safety profile explain why they are among the most frequently used drugs in the world.[4,6,15]

At the same time, research demonstrates clear signs of overuse and inappropriate long-term prescribing.[4,6,15] Many patients remain on PPIs for months or years without a documented indication or regular reassessment, and over-the-counter formulations make unsupervised self-medication easier still.[4,6,13] In this context, even relatively uncommon adverse effects become important at the population level.[5,8,9]

The reviewed data suggest that chronic PPI therapy may contribute to nutrient and electrolyte disturbances, specifically deficiencies of vitamin B12, iron, magnesium, and calcium.[8,9,21] These abnormalities may, in turn, promote bone demineralization and a modest increase in fracture risk, particularly in older adults.[20,22] Observational studies also link long-term PPI use with renal complications, such as acute interstitial nephritis and chronic kidney disease [23–25], and with an increased risk for certain infections, including *Clostridioides difficile* and small intestinal bacterial overgrowth.[27–29] Furthermore, clinically relevant reactions with other medications, most notably with clopidogrel and a high dose of methotrexate, also give reason for careful review of prescriptions.[2,18,19]

Most information on the adverse effects of PPIs is available from observational research, which is prone to confounding and cannot establish causality for many of the proposed

cardiovascular and neurological risks.[10–12] For this reason, PPIs should not be withheld from patients with clear indications out of fear of uncertain long-term harm.[3,7,14]

The key implication for clinical practice is not to abandon PPI therapy, but to use it with thoughtfulness.[2,7,13] To avoid adverse effects associated with prolonged use of PPIs, specialists should prescribe the lowest effective dose for the shortest possible time and regularly monitor patients for any severe complications.[5,18,19] It is also essential to perform regular assessments to establish if previous indications are still justified.[6,15] Education at both the prescriber and patient levels is important in limiting unnecessary chronic use, without losing the substantial benefits of PPIs for appropriate candidates.[4,7]

5. Conclusions

Proton pump inhibitors have revolutionized the treatment of acid-related diseases and have become the mainstay of therapy worldwide. The potent and sustained inhibition of gastric acid secretion enables highly effective treatment for gastroesophageal reflux disease, peptic ulcer disease, the eradication of *Helicobacter pylori* infection, and rare hypersecretory disorders. Easy availability, simple dosing, and a benign short-term safety profile have made these drugs very common in both hospital and outpatient settings.

However, this review shows that PPIs are often continued for prolonged periods, even after the initial indication has resolved, and without scheduled reassessment. Chronic therapy can be linked to a higher risk of nutrient and electrolyte imbalances, including vitamin B12, iron, magnesium, and calcium deficiencies. It is also associated with reduced bone mineral density, renal complications, and microbiome-related infections such as *Clostridioides difficile* infection. PPIs interact with various medications when administered concomitantly, which may alter their safety profile and effectiveness. For several potential cardiovascular and neurological risks, the current evidence remains inconclusive, and causality has not been definitively established.

This paper indicates the need for more careful and individualized use of PPIs. They should be prescribed at the lowest effective dose for the shortest duration of treatment necessary to provide symptom relief and mucosal healing. It is also important to schedule regular reviews of the indication for ongoing PPI therapy. Well-designed studies are required to specifically address remaining safety concerns and to better define which patients are most at risk of possible adverse effects. A thoughtful, evidence-informed approach can preserve the undeniable benefits of PPIs while minimizing the risks of long-term therapy.

Disclosure

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