Proton pump inhibitors: potential adverse effects

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Purpose of review
This review summarizes adverse effects of potential proton pump inhibitors (PPIs), including nutritional deficiencies (B12 and magnesium), rebound acid hypersecretion, acute interstitial nephritis, gastric carcinoid tumor, cardiovascular risk with clopidogrel and PPI coprescription, bone fractures, enteric infections and pneumonia. An epidemiologic framework is applied to assess clinical relevance and reinforce best practice recommendations.

Recent findings
The evidence for PPI adverse events is limited by the absence of Level 1 (randomized controlled trial) studies. The best evidence supports *Clostridium difficile* and bone fractures in susceptible populations. A substantial reduction in gastrointestinal bleeding risk without increase in cardiovascular events was observed in the COGENT trial when clopidogrel was coprescribed with omeprazole. The risk of pneumonia is inconsistent, and although acute interstitial nephritis, nutritional deficiencies (including B12 and hypomagnesemia), gastric carcinoid and rebound hyperacidity are biologically plausible, studies have failed to demonstrate supportive clinical relevance.

Summary
Prescribe PPI for robust indications only. Strong data supporting risk of adverse events are lacking; however, exercise caution in the elderly and in patients with other risk factors for bone fractures or *C. difficile* infection.

Keywords
B12 deficiency, bone fractures, *Clostridium difficile*, hypomagnesemia, pneumonia, proton pump inhibitor side effects

INTRODUCTION

Proton pump inhibitors (PPIs) are the third highest-selling drug in the United States, generating $13.9 billion annually [1]. Robust clinical indications for a PPI include gastroesophageal reflux disease (GERD), esophagitis, acid hypersecretory states, peptic ulcers and eradication of *Helicobacter pylori*. PPIs are also used for treating dyspepsia and prophylaxis of peptic ulcers in the intensive care setting, and among high-risk patients prescribed aspirin, NSAIDs, antiplatelets and anticoagulants [2]. This review critically evaluates evidence regarding potential PPI-related adverse effects.

NUTRITIONAL DEFICIENCIES

PPIs may contribute to deficiencies of B_{12}, iron and magnesium [3▪▪].

B_{12} deficiency

Acid suppression interferes with the acid-activated proteolytic digestion of dietary protein-bound vitamin B_{12} in the stomach [4,5] and promotes bacterial overgrowth in the duodenum [6]. Studies of PPI use and vitamin B_{12} deficiency have yielded mixed results. Absorption decreased from 3.2 to 0.9% ($P = 0.031$) in patients on omeprazole 20 mg daily, and from 3.4 to 0.4% in patients on higher doses [7]. Chronic PPI therapy was associated with a 46% decline in median serum B_{12} levels and subnormal levels in 10% of patients [8]. Others have reported no decreased absorption of vitamin B_{12} [4,9]. Older patients are at greatest risk and more likely to have borderline baseline levels [10]. Data supporting an association are from small, nonrandomized retrospective studies or sporadic case reports with varying

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KEY POINTS

- High-dose, chronic proton pump inhibitor (PPI) use is prevalent.
- The evidence for PPI adverse events is limited by the absence of randomized controlled trials. The best evidence supports an increased risk of *Clostridium difficile* and bone fractures in susceptible populations.
- PPI prescription must be tailored, using an individualized approach that limits use to robust indications.
- Decrease inappropriate use among the elderly, the highly comorbid, the hospitalized patient on broad-spectrum antibiotics and the individual with risk factors for metabolic bone disease.

methods for measuring B_{12} levels [3▪▪,9]. Prospective studies [11,12] demonstrate reduced B_{12} levels that are within the normal range, suggesting that the risk of deficiency may be clinically insignificant [3▪▪]. Consumption of a normal diet will safeguard against clinically significant B_{12} deficiency when taking a PPI. The elderly and malnourished patient may be at a higher risk [3▪▪].

Hypomagnesemia

Severe hypomagnesemia, refractory to supplementation, has been reported with long-term PPI use [13]. No case was associated with renal disease or malabsorptive disorders, and symptoms resolved within 2 weeks of PPI discontinuation. Hypomagnesemia is rare but appears to be a class effect, persisting after substitution of PPI [14]. Normally, low-serum magnesium results from impaired absorption or intake, excessive losses (urinary or gastrointestinal), redistribution from extracellular to intracellular sites or acquired deficiencies in transient receptor potential cation channels, subfamily M, member 6 (TRPM6) and member 7 (TRPM7) [13]. The biological mechanism of deficiency in PPI users is poorly understood; however, consider discontinuation of PPI or switching to an H2RA if patients present with unexplained hypomagnesemia.

REBOUND ACID HYPERSECRETION

Rebound acid hypersecretion (RAH) results in gastric acid secretion above pretreatment levels after acid suppression [15,16]. PPI therapy leads to diminished acid secretion and antral D-cell release of somatostatin, while increasing G-cell release of circulating gastrin [3▪▪]. The increased gastrin concentration exerts a trophic effect on oxyntic mucosa, causing hyperplasia and increased functional capacity of the enterochromaffin-like (ECL) cell and parietal cell [17]. Increased acid secretion due to sustained hypergastrinemia is not apparent during PPI therapy but appears with drug cessation [18] theoretically, leading to acid-related heartburn, acid regurgitation or dyspepsia [15]. Four studies present conflicting data due to differences in RAH definition and heterogeneity in populations. It remains unclear whether conclusions from normal volunteer trials [15,19] are clinically relevant. The fact that healthy volunteers receiving placebo reported symptoms in both trials may indicate that the volunteers were sensitized to report symptoms. It is also possible that PPI-treated volunteers were reporting side effects of therapy rather than symptoms of GERD [20▪]. Finally, measurement of acid secretion differed between the studies, complicating interpretation of the data. Until consistent and compelling data that PPI withdrawal produces symptomatic rebound, continue to follow the evidence-based guidelines [21] recommending empiric PPI therapy in patients with uncomplicated heartburn and maintenance PPI therapy in patients with erosive esophagitis. Most patients with GERD symptoms severe enough to warrant PPI therapy require long-term PPI for adequate symptom control. Use the lowest effective dose for symptom control [20▪,21]. Patients with dyspepsia or mild, uncomplicated heartburn can be managed with antacids or H2RA drugs, which cause negligible RAH and can be discontinued later with little difficulty [18].

INTERSTITIAL NEPHRITIS

Acute interstitial nephritis (AIN) is a humoral and cell-mediated hypersensitivity reaction that causes inflammation of the renal interstitium and tubules [13], causing acute renal failure [22]. Medications account for 60% of cases [22,23], including antibiotics, NSAIDs, diuretics and PPIs. All PPIs have been associated with AIN [22]. The most commonly implicated is omeprazole, and the least is rabeprazole [22]. PPI-related AIN is rare, idiosyncratic and, therefore, difficult to predict [22]. A major limitation of the literature is the source of data, limited to observational case reports and case series that do not adequately control for confounding factors. The mainstay of therapy for drug-induced AIN is early diagnosis, identification and discontinuation of the causative agent [23].

GASTRIC CARCINOID TUMOR

Carcinoid tumors are rare (1–2 per 1000 individuals), but their incidence has increased [3▪▪,24],

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prompting concerns that PPI use may increase the risk [3▪▪]. Marked trophic effects of PPI-induced hypergastrinemia caused major concerns during early animal safety tests when rats on long-term omeprazole developed carcinoid tumors [17]. Long-standing hypergastrinemia coupled with other factors, such as genetic abnormality of multiple endocrine neoplasia type 1 (MEN-1), can produce gastric ECL carcinoids in humans [25]. Hypergastrinemia alone, however, has not been documented to induce carcinoid formation in humans [25]. It may be associated with gastric ECL hyperplasia or redistribution but has not been associated with neoplastic changes [25]. Given the low incidence of gastric carcinoid tumors, prospective studies would not be feasible; thus, it is unlikely that the rat hypotheses will ever be proved in humans.

CARDIOVASCULAR RISK

Concern regarding increased myocardial infarction, stroke and cardiovascular death associated with PPI and clopidogrel coprescription has been discussed in depth previously [26▪▪]. Although initially thought due to competitive inhibition of clopidogrel metabolism by PPI at the shared CYP 450 pathway [27▪], subsequent data have refuted this hypothesis [28,29]. Pharmocokinetic and pharmacodynamic studies did suggest a differential response between various PPIs, with omeprazole showing the greatest effect on clopidogrel activity [26▪▪,28,30]. However, no increase in cardiovascular events was observed in major trials or well adjusted observational studies, even when omeprazole was used [29], undermining the clinical relevance of avoiding clopidogrel and omeprazole coprescription.

Current evidence points to individual genetic polymorphism as causative for impaired clopidogrel activity. Data support the presence of a reduced-function CYP2C19∗2 allele, common in Asian Americans (51%) and African Americans (33%), and a four-fold increased risk of poor cardiac outcomes [31–34]. One copy is associated with a 47% reduction in clopidogrel activity and two copies with a 65% reduction in clopidogrel activity [33]. The potential role of the ABCB1 3435 TT genotype, CYP2C19 metabolic status and ITGB3 PLA2 carriage as independent risk factors for early stent thrombosis has also been published [35▪], supporting genetic polymorphism as the primary cause of impaired clopidogrel activity when compared with the risk associated with PPI coprescription. The third-generation thienopyridines (i.e. prasugrel and ticagrelor) activity is unaffected by variants in the CYP2C19 genotype [36▪,37]. Emerging data will reveal whether these drugs are affected by other key genetic polymorphisms.

BONE FRACTURES

The mechanism behind impaired bone strength among PPI users hinges on profound acid suppression and its triple effect of impairing vitamin B_{12} and calcium absorption, and resulting in hypergastrinemia. Impaired B_{12} absorption decreases osteoblastic activity, decreasing bone formation while increasing homocysteine levels, which negatively affects collagen cross-linking, resulting in reduced metabolic bone density and bone strength. Hypergastrinemia causes parathyroid hormone release from hyperplastic parathyroid glands, contributing to increased bone absorption and decreased metabolic bone density and bone strength. Diminished calcium absorption negatively influences calcium homeostasis and reduces plasma calcium levels, turning on parathyroid hormone release with subsequent increase in circulating parathyroid hormone, furthering the decline in metabolic bone density and bone strength [13].

Case–control studies support a weak association between prolonged PPI use and increased bone fracture risk [38▪,39–41], ranging from 20% [odds ratio (OR) 1.2; 95% confidence interval (CI), 1.1–1.3] to 60% (OR 1.6; 95% CI, 1.4–1.8), respectively [39,41]. The magnitude of ORs is low (<2), and no experimental evidence supports a mechanism of action. These studies are subject to confounding variables that may bias results. PPI use for up to 5 years has not been associated with osteoporosis, even at a high dose [42], and marginally affects 3-year bone mineral density of the hip in postmenopausal women [43]. Kaye and Jick [44] and Corley *et al.* [45] examined PPI and bone fractures, adjusting for other key independent risk factors (i.e. alcohol abuse, arthritis, diabetes, kidney disease, glucocorticoids, cerebrovascular disease, dementia, epilepsy, visual impairment, anxiolytics and preexisting osteoporosis), showing no increase in fracture. Corley *et al.* [45] did demonstrate a 20% increase (OR 1.2; 95% CI, 1.2–1.3) in fracture risk among PPI users when one or more other independent risk factors for bone fractures were present. A meta-analysis [46▪▪] revealed an OR of 1.3 (95% CI, 1.1–1.4) for fracture risk. However, the pooled studies demonstrated significant heterogeneity and were of very low quality (i.e. great uncertainty about the estimate) [47]. In summary, chronic PPI use is not associated with increased osteoporosis risk or accelerated bone mineral density loss, and any association between PPI use and hip fractures is likely related to other independent risk factors for osteoporosis.

PROTON PUMP INHIBITOR AND INFECTION RISK

Gastric acidity is a major defense mechanism of the body – it sterilizes contents entering the digestive

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tract, prevents bacterial colonization of the upper gastrointestinal tract and influences the composition of normal intestinal flora. PPIs increase gastric pH, resulting in more bacterial colonization of the stomach [48]. Chronic PPI use may also impair leukocyte function by increasing basal cytosolic calcium concentrations in neutrophils and decreasing intracellular and extracellular reactive oxygen species impairing bactericidal activity [49].

ENTERIC INFECTIONS

A 2007 meta-analysis [50] was first to suggest a potential three-fold increased risk in enteric infections, including salmonella, campylobacter and shigella, among PPI users. However, significant heterogeneity in the five pooled studies could not be explained by subgroup analyses. In 2012, physicians were alerted to a two- to three-fold increased risk of *C. difficile*-associated diarrhea among elderly patients with chronic comorbidity and on broad-spectrum antibiotics [51▪▪,52]. In both meta-analyses, significant heterogeneity requires interpretation of data with caution [50,51▪▪]. Until trial data are available, clinicians should consider the risks and benefits of continuing chronic PPI therapy in hospitalized patients on broad-spectrum antibiotics; the elderly; and, possibly, those travelling to endemic areas. *C. difficile*-associated diarrhea should be considered in hospitalized patients taking PPIs who develop refractory diarrhea. Too little data are available to assess risk and PPI dose or duration of over-the-counter PPI use.

RESPIRATORY INFECTIONS

Data supporting an association between chronic PPI and increased respiratory infections are weak. Native gastric pH is 1–2, an environment inhospitable to community-acquired lung pathogens. Chronic acid suppression may permit intermittent bacterial survival and possible colonization of the upper gastrointestinal tract, facilitating microaspiration or translocation into the lungs. Laheij *et al.* [53], using a nested case–control analysis of the general practice database in the Netherlands, suggested a 73% increased risk of pneumonia (OR 1.73; 95% CI, 1.33–2.25). A Danish cohort suggested a 50% increase in risk among PPI users (OR 1.5; 95% CI, 1.30–1.70) [54]. Both studies demonstrated an inverse relationship between magnitude of association and chronicity of PPI use, with the weakest association among patients who were prescribed a PPI for the longest duration of time, highlighting likely residual confounding caused by a higher comorbidity in pneumonia cases on PPI. When data

Table 1. Epidemiologic evidence supporting an association between proton pump inhibitors and adverse effects

Potential PPI adverse effects	Assessment criteria			
	Strength of association	Consistency of association	Biologically plausible mechanism	Supportive experimental evidence
B_{12} deficiency	Low magnitude (Ratio <2)	Inconsistent	Interaction biologically plausible	Failed to demonstrate an association
Hypomagnesemia	Low magnitude (Ratio <2)	Inconsistent	Interaction biologically plausible	Failed to demonstrate an association
Rebound acid hypersection	Low magnitude (Ratio <2)	Inconsistent	Interaction biologically plausible	Failed to demonstrate an association
Acute interstitial nephritis	Low magnitude (Ratio <2)	Inconsistent	Interaction biologically plausible	Failed to demonstrate association
Gastric carcinoid tumor	Low magnitude (Ratio <2)	Inconsistent	Interaction biologically plausible	Failed to demonstrate an association
Cardiovascular risk (clopidogrel interaction)	Low magnitude (Ratio <2)	Inconsistent	Interaction biologically plausible	Failed to demonstrate an association
Bone fractures	Low magnitude (Ratio <2)	Inconsistent	Interaction biologically plausible	Mixed results
Enteric infections	Higher magnitude (Ratio >2)	Inconsistent	Interaction biologically plausible	Mixed results
Respiratory infections	Low magnitude (Ratio <2)	Inconsistent	Interaction biologically plausible	Failed to demonstrate an association

PPI, proton pump inhibitor.

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were adjusted for confounding variables, no significant increase in pneumonia risk was demonstrated [55]. A meta-analysis of seven randomized controlled trials (RCTs) evaluating efficacy of PPIs that recorded respiratory adverse events failed to show a significant association between PPIs and respiratory infections (OR 1.4; 95% CI, 0.9–2.3) [56], even among ventilator-assisted patients on chronic PPI, in whom abnormal gastric colonization exists and the theoretical risk of increased microaspiration or translocation would be greatest [56].

EPIDEMIOLOGIC AND CLINICAL SUMMARY OF THE EVIDENCE

With an epidemiologic framework and pragmatic scrutiny of clinical relevance, few adverse event concerns appear pertinent in clinical practice (Table 1). Evidence for long-term complications is weak at best, limited by the absence of Level 1 (RCT) data. The best evidence supports a relevant risk of increased *C. difficile*-associated diarrhea among hospitalized patients, the elderly and those prescribed broad-spectrum antibiotics on chronic PPI therapy.

CONCLUSION

High-dose, chronic PPI use is prevalent, despite a high degree of comorbidity in the target population and significant treatment failures [57]. Clinicians must remain cognizant of potential threats and ensure vigilance in their prescribing habits. PPI prescription must be tailored, using an individualized approach that limits use to robust indications [2] and actively responds to opportunities to decrease inappropriate use, especially among the elderly, highly comorbid individuals with independent risk factors for metabolic bone disease and hospitalized patients receiving broad-spectrum antibiotics.

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Conflicts of interest

The views expressed are those of the author and not necessarily those of the Department of Veterans Affairs and/or Baylor College of Medicine or the US Government. Dr Abraham has no conflict of interest.

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