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Proton Pump Inhibitors: Review of Emerging Concerns

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Learning Objectives: On completion of this article, you should be able to (1) recognize US Food and Drug Administration–approved indications for use of proton pump inhibitors, (2) summarize the reported adverse effects of long-term proton pump inhibitor use and describe which consequences are most likely and least likely to be causative, and (3) describe current recommendations for the optimal administration and continued monitoring of patients using proton pump inhibitors.

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Abstract

First introduced in 1989, proton pump inhibitors (PPIs) are among the most widely utilized medications worldwide, both in the ambulatory and inpatient clinical settings. The PPIs are currently approved by the US Food and Drug Administration for the management of a variety of gastrointestinal disorders including symptomatic peptic ulcer disease, gastroesophageal reflux disease, and nonulcer dyspepsia as well as for prevention of gastrointestinal bleeding in patients receiving antiplatelet therapy. PPIs inhibit gastric acid secretion, and the most commonly associated adverse effects include abdominal pain, diarrhea, and headache. Although PPIs have had an encouraging safety profile, recent studies regarding the long-term use of PPI medications have noted potential adverse effects, including risk of fractures, pneumonia, *Clostridium difficile* diarrhea, hypomagnesemia, vitamin B_{12} deficiency, chronic kidney disease, and dementia. These emerging data have led to subsequent investigations to assess these potential risks in patients receiving long-term PPI therapy. However, most of the published evidence is inadequate to establish a definite association between PPI use and the risk for development of serious adverse effects. Hence, when clinically indicated, PPIs can be prescribed at the lowest effective dose for symptom control.

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Proton pump inhibitors (PPIs), which reduce the production of gastric acid through irreversible binding to the hydrogen/potassium ATPase enzyme found on gastric parietal cells, were first approved for use in 1989. Over the past several decades, PPIs have become one of the most commonly prescribed medications in the United States with use in nonhospitalized patients doubling between 1999 and 2012 and accounting for more than $11 billion in expenditures annually.[1] Currently, long-term PPI use is approved for prevention and symptom control of gastroesophageal reflux disease, for Barrett esophagus, as prophylaxis for nonsteroidal anti-inflammatory drug (NSAID)—associated bleeding, and for pathologic hypersecretory conditions including Zollinger-Ellison syndrome (Table 1). Recent studies, however, have suggested an association between PPI use and several adverse effects. These studies have been well publicized and have been a source of major concern to both patients and physicians. The majority of results were reported from retrospective, observational studies with accepted statistical methods, which revealed mild to moderate overall associations but did not prove cause and effect. Therefore, the purpose of this review was to analyze recently published literature regarding several of the emerging concerns related to long-term use of PPIs and to determine whether the adverse effects mandate changes to our current practices (Table 2).

ASSOCIATION LIKELY CAUSATIVE

Hypomagnesemia

Hypomagnesemia associated with PPI use was first described in 2006 in patients who had been taking PPIs for more than 1 year and presented with carpopedal spasm.[2] Moreover, serum magnesium levels normalized with discontinuation of PPI therapy. Impaired absorption of magnesium may contribute to the development of hypomagnesemia. A meta-analysis of 9 observational studies and 109,798 patients reported a 43% increased risk of hypomagnesemia in patients receiving PPIs, thus suggesting a causative association.[3]

In 2011, the US Food and Drug Administration (FDA) issued a safety warning regarding the association between PPI use and hypomagnesemia and recommended monitoring of magnesium levels in patients receiving long-term PPI therapy. Some guidelines suggest monitoring patients, particularly those concomitantly using diuretics or those with malabsorption disorders, because PPIs appear to be causative in this relationship.

Vitamin B_{12} Deficiency

Data from the National Health and Nutrition Examination Survey have revealed low serum vitamin B_{12} levels in 3.2% of adults.[4] Gastric acid is required for the release of vitamin B_{12} from dietary proteins to facilitate absorption in the terminal ileum. In a study performed at Kaiser Permanente, 25,956 patients with vitamin B_{12} deficiency were compared with 184,199 patients without vitamin B_{12} deficiency to assess the association with acid suppression therapy. Those who had received PPI treatment for more than 2 years had a 65% increased risk for vitamin B_{12} deficiency when compared with nonusers. Use of $1\frac{1}{2}$ or more pills per day was also significantly associated with vitamin B_{12} deficiency (odds ratio [OR], 1.95; 95% CI, 1.77-2.15).[5] Of note, this increased relative risk (RR) of B_{12} deficiency would increase the prevalence of vitamin B_{12} deficiency in this population (≥50 years) from 2.3% to 3.8%. Current guidelines do not recommend monitoring vitamin B_{12} levels in patients receiving long-term PPI treatment.

Small Intestine Bacterial Overgrowth

Small intestine bacterial overgrowth (SIBO) has been associated with PPI use. Decreased gastric

TABLE 1. FDA-Approved Indications for Proton Pump Inhibitor Therapy

Treatment of gastroesophageal reflux disease
Healing of erosive esophagitis
Maintenance treatment for healed erosive esophagitis
Treatment of gastric and duodenal ulcers
Treatment and prophylaxis for NSAID-induced ulcers
Treatment of *Helicobacter pylori* infection in combination with antibiotics
Management of pathologic hypersecretory conditions (including Zollinger-Ellison syndrome)

FDA = Food and Drug Administration; NSAID = nonsteroidal anti-inflammatory drug.

acid production associated with PPI use can lead to overgrowth of small-intestine bacteria. A meta-analysis of 11 studies found an increased risk for development of SIBO among PPI users compared with nonusers (OR, 2.28; 95% CI, 1.24-4.21). This risk was 7.5-times greater among studies that utilized the more sensitive and specific duodenal/jejunal aspirate for diagnosis of SIBO. Studies using the glucose hydrogen breath test for diagnosis, a less sensitive and less specific technique, did not find this relationship.[6] We suspect that this association is likely causative, although the clinical importance of SIBO remains controversial.

ASSOCIATION UNCLEAR

Bone Fractures

Osteoporosis-related fractures are a major health concern associated with significant morbidity and mortality: the lifetime risk is approximately 40% to 50% and 13% to 22% for females and males, respectively.[7] Based on data from observational studies, concern has grown over the potential association between long-term use of PPIs and fracture risk. In 2010, the FDA published a warning of the increased risk of PPI use and fractures of the spine, wrist, and hip.

Multiple studies have found an increased risk of bone fractures in PPI users. A recent meta-analysis of 18 observational studies revealed that PPI use was associated with a 33% increased risk for fracture at any site (RR, 1.33; 95% CI, 1.15-1.54), a 26% higher risk of hip fracture (RR, 1.26; 95% CI, 1.16-1.36), and a 58% increase in risk of spine fracture (RR, 1.58; 95% CI, 1.38-1.82). After limiting analysis to cohort studies, and thus eliminating heterogeneity, the risk of hip fracture was still moderately increased by 24%. Subgroup analysis, interestingly, found that both short-term (<1 year) and long-term use were associated with increased risk of hip fracture.[8]

The proposed mechanism for the increased fracture risk in patients receiving PPI therapy is reduced calcium absorption resulting in decreased bone mineral density (BMD). A placebo-controlled, double-blind, crossover trial in elderly postmenopausal women found that calcium carbonate absorption in the fasting state decreased after 1 week of omeprazole therapy.[9]

However, there is no clear evidence that PPI medications are associated with development of osteoporosis. The most thorough study assessed the relationship between PPI use and BMD of the lumbar spine (vertebrae L1-L4), femoral neck, and total hip at baseline and after 5 years and 10 years of PPI use.[10] A total of 8340 patients underwent initial BMD measurements, and 4512 patients completed BMD testing after 10 years. After adjusting for confounders, the results revealed that BMD was significantly lower at the total hip and femoral neck regions but not at the lumbar spine among individuals using PPIs at baseline. After regression analyses, among those patients receiving continuous PPI therapy, there was no significant rate of change in BMD at the previously described measurement sites over 5- and 10-year periods. Similar to other studies, PPI users had significantly higher fracture rates compared with nonusers at baseline, but this finding was likely impacted by having statistically lower overall BMD as well as risk factors that predispose to fracture, including older age, female sex, and concurrent use of medications including corticosteroids. Finally, the association of short-term PPI use with fractures similarly suggests that PPI-induced osteoporosis is not likely the cause of PPI-associated bone fractures.

Another hypothesized mechanism is the inhibition of osteoclastic activity by PPIs, which affect bone remodeling and structure. A study of 104 patients (52 PPI users for ≥5 years and 52 nonusers) found no significant differences between the 2 populations in mean T scores of the femoral neck, trochanter, total hip, and L1 through L4 vertebrae or in overall BMD, cortical or trabecular BMD, and cortical thickness, therefore concluding that long-term use of PPIs was not associated with adverse changes to bone structure.[11] Additionally, the relationship between PPI use and risk of fracture among 79,899 postmenopausal women differed only by smoking history; while current and former smokers had a 50% increased risk of fracture, there was no significant increase in fracture risk among nonsmokers who used PPIs.[12]

Although these studies have linked PPI use to development of hip fractures, recent data have been inconsistent and suggest that

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TABLE 2. Risks Associated With Long-term Proton Pump Inhibitor Use

Adverse effect	Relative risk/odds ratio (95% CI)	Quality of evidence	Practice recommendations
Likely causative			
Hypomagnesemia[3]	1.43 (1.08-1.88)	Low	Check serum magnesium levels in symptomatic patients
Vitamin B_{12} deficiency[5]	1.65 (1.58-1.73)	Low	Check CBC every 2 y and vitamin B_{12} every 5 y
Small-intestine bacterial overgrowth[6]	2.28 (1.24-4.21)		
Duodenal/jejunal aspirate	7.59 (1.81-31.89)	Low	Unclear clinical importance
Glucose hydrogen breath test	1.93 (0.69-5.42)		No recommendation to check for SIBO while using PPIs
Association unclear			
Bone fractures[8]	1.26 (1.16-1.36) for hip fractures 1.33 (1.15-1.54) for fractures at any site	Low	BMD screen per national guidelines Calcium and vitamin D intake per RDA recommendations
Clostridium difficile infection[14]	1.74 (1.47-2.85)	Low	No recommendations Cautious use of antibiotics
Chronic kidney disease[19]	1.50 (1.14-1.96)	Very low	Check serum creatinine level annually
Dementia[24]	1.44 (1.36-1.52)	Very low	No recommendations
Unlikely causative			
Community-acquired pneumonia[28]	1.27 (1.11-1.46)	Very low	No recommendations

BMD = bone mineral density; CBC = complete blood cell count; PPI = proton pump inhibitor; RDA = Recommended Dietary Allowance; SIBO = small intestine bacterial overgrowth.

although there may be a mild to moderate increase in the overall risk of fractures regardless of duration of therapy, long-term PPI use does not significantly affect the rate of bone density loss. However, clinicians should be aware of the potential for association with fracture risk, although the American Gastroenterological Association does not recommend routine BMD screening or increased calcium supplementation in patients receiving long-term PPI therapy.[13]

Clostridium difficile Infection

Clostridium difficile is a common cause of diarrhea associated with increasing morbidity and mortality. Studies have suggested a link between use of PPIs and development of *C difficile* infection (CDI), which led the FDA to issue a warning regarding risk of CDI in patients receiving PPI therapy and also recommend use of the lowest PPI dose for the shortest duration. A meta-analysis of 42 observational studies revealed an increased risk of both incident and recurrent CDIs in patients treated with PPIs (OR, 1.74; 95% CI, 1.47-2.85 and OR, 2.51; 95% CI, 1.16-5.44, respectively).[14] Although presenting less overall risk, the use of histamine 2 receptor antagonists was also associated with an increased risk for CDI, thus suggesting an overall role of acid suppression in development of CDI. All studies included were nonrandomized observational studies, had significant statistical heterogeneity, and were variable with regard to dose and duration of PPI treatment.

The association between CDI and PPI use is hypothesized to be due to survival of the *C difficile* vegetative form in the alkaline gastric pH. The emergence of SIBO in PPI users increases the luminal concentration of unconjugated bile acids, which may lead to conversion of the *C difficile* spores to the toxin-secreting vegetative form. Additionally, after 4 to 8 weeks of PPI therapy, there are alterations in the gut microbiome that predispose patients to development of CDI.[15]

A review of 23 observational studies with 288,620 patients found a 65% increase in CDI incidence among patients receiving PPIs.[16] An association between PPI use and CDI recurrence has also been reported.[17] However, studies with additional multivariate analysis established that PPI use was not associated with an increase in severe, complicated CDI, treatment failure, or recurrence of CDI.[18]

Hence, the association between PPI use and CDI has been inconsistent, suggesting an association without clear causation.

Acute and Chronic Kidney Disease

Reports have raised concerns regarding an association between use of PPIs and both acute kidney injury (AKI) and chronic kidney disease (CKD). In the prospective Atherosclerosis Risk in Communities Study, 10,482 participants with normal baseline renal function were followed up for a median of 13.9 years.[19] After adjusted analysis, the results revealed that PPI users had a 50% greater risk of development of CKD than nonusers, with a 10-year absolute risk increase of 3.3%. There was also a 64% increased risk of AKI among PPI users. These findings were replicated in a cohort of 248,751 patients from the Geisinger Health System who were followed up for a median of 6.2 years, during which there was a 17% increased risk of CKD among PPI users and higher risk with twice-daily dosing of PPIs when compared with a single daily dose.[19] However, among this population, there was a statistically significant increase in concomitant use of NSAIDs among PPI users, which is a confounding variable. The strengths of this study were inclusion of adjusted multivariate analysis and comparison between PPI users with propensity score–matched nonusers. Using the Department of Veterans Affairs national databases, Xie et al[20] also assessed renal outcomes among a cohort of 173,321 new PPI users vs 20,270 new users of histamine 2 receptor antagonists followed up for a period of 5 years. In comparison with patients using histamine 2 receptor antagonists, PPI users had a 28% increased risk for incident CKD, as well as increased risk for estimated glomerular filtration rate decline greater than 30%, doubling of serum creatinine level, and development of end-stage renal disease.[20] There was also a significant association between duration of exposure and worsening outcomes. Another population-based study of 290,592 patients older than 65 years found a 2.5-times increased risk for development of AKI and a 3-times increased risk for acute interstitial nephritis among elderly patients recently beginning PPI therapy.[21] Similarly, in a recent retrospective population study from Sweden, the risk of doubling of the serum creatinine level was 1.26-times greater after initiating PPI therapy compared with histamine 2 receptor antagonist therapy over a median follow-up of 2.7 years.[22]

The mechanism for development of CKD may be the result of subclinical acute interstitial nephritis, which if untreated progresses to injury of the nephron. Based on the results of these studies, initiation and cumulative use of PPIs have been associated with risk for kidney disease. No recommendations have been proposed for monitoring kidney function in patients receiving long-term PPI therapy, irrespective of dose. We believe that until this association is better clarified, it is reasonable to monitor estimated glomerular filtration rate annually, based on CKD guidelines for monitoring patients taking potentially nephrotoxic medications.[23]

Dementia

Recent observational studies have suggested an increased risk of dementia among PPI users. Two prospective studies have assessed the association between PPI use and the risk of dementia. Haenisch et al[24] studied 3076 patients 75 years or older with no history of dementia and after adjusting for confounders, found that PPI users had a 38% increased risk of dementia and a 44% increased risk of Alzheimer disease. Gomm et al[25] similarly conducted a prospective cohort study of 73,679 individuals 75 years or older without dementia at baseline and also found a significant 44% increased risk of dementia among patients receiving regular PPI medication. These findings contrast those of a recent prospective analysis of 13,864 middle-aged and older women enrolled in the Nurses' Health Study II, in which there was no definite evidence of association between the duration of PPI use and cognitive function.[26] Data from the Finnish nationwide health care registry also reported that among 70,718 newly diagnosed cases of Alzheimer disease, PPI use was not associated with increased risk.[27]

Accumulation of amyloid-β peptides is involved in the pathogenesis of Alzheimer disease, and studies have found that lansoprazole led to higher levels of amyloid-β levels in the brains of mice.[28] The PPIs increase amyloid synthesis and decrease amyloid degradation in the brain. In addition, association of PPI use with vitamin B_{12} deficiency can lead to neurologic

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symptoms including dementia. Thus, prospective clinical trials are required to further examine and establish this causal association.

ASSOCIATION UNLIKELY CAUSATIVE

Several studies have reported an association between PPI use and development of community-acquired pneumonia (CAP).[29] A meta-analysis of 8 observational studies found that the overall risk of pneumonia was increased by 27% with use of PPIs.[30] There was a temporal relationship of pneumonia with recent initiation of PPI treatment (≤7 days of index date). This temporal relationship would support a confounding rather than causative association between PPI use and CAP. Further subgroup analyses revealed that higher doses were correlated with greater risk of development of pneumonia and that this risk decreased with longer duration of therapy before the index date of diagnosis. To address the limitations of prior studies and examine the risk between PPIs and CAP, a meta-analysis of 8 cohort studies was conducted in patients initiating prophylactic PPIs while using NSAIDs. Results revealed that PPIs were not associated with increased risk of hospitalization for CAP in the 6 months immediately following initiation of NSAID therapy (OR, 1.05; 95% CI, 0.89-1.25).[31]

A recently published observational cohort study noted an increased risk of mortality with PPI use. However, this study had major limitations including the potential for residual confounders accounting for this association, selection bias, and limited generalizability of results.[32] Although we should not ignore these epidemiological associations, prospective controlled studies are needed in the future to establish a causative relationship between PPIs and the aforementioned diseases.

CONCLUSION

Use of PPIs has been reported to be associated with increased risk for development of a multitude of adverse effects. The majority of the data are based on results from retrospective observational studies, which have inherent biases, risk for confounding variables, and the inability to demonstrate a definite causal relationship. Most of these studies reported mild to moderate overall associations (with RRs of 1 to 2) between PPI use and the risks of bone fracture, CDI, pneumonia, vitamin and mineral deficiencies, kidney disease, and dementia. Thus, because many of these adverse effects are uncommon, the absolute risk to patients remains quite small.

Based on current recommendations, the American Gastroenterological Association does not recommend routine laboratory monitoring or use of supplemental calcium, vitamin B12, and magnesium in patients taking PPIs daily. However, as this story evolves, our current practice is to check creatinine levels yearly, complete blood cell counts every other year, and vitamin B12 levels every 5 years in patients receiving long-term PPI therapy. In summary, the best strategy is to prescribe PPIs at the lowest dose on a short-term basis when appropriately indicated so that the potential benefits outweigh any adverse effects associated with the use of PPIs.

Abbreviations and Acronyms: **AKI** = acute kidney injury; **BMD** = bone mineral density; **CAP** = community-acquired pneumonia; **CDI** = *Clostridium difficile* infection; **CKD** = chronic kidney disease; **FDA** = Food and Drug Administration; **NSAID** = nonsteroidal anti-inflammatory drug; **OR** = odds ratio; **PPI** = proton pump inhibitor; **RDA** = Recommended Dietary Allowance; **RR** = relative risk; **SIBO** = small-intestine bacterial overgrowth

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