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Safety Risks Associated with Long-Term Use of Proton Pump Inhibitors

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Proton pump inhibitors (PPIs) are the treatment of choice for gastrointestinal (GI) conditions such as gastro-esophageal reflux disease (GERD) and peptic ulcer disease (PUD).[1] PPIs currently found on the United States market include omeprazole, esomeprazole, pantoprazole lansoprazole, rabeprazole, and dexlansoprazole. Most people achieve relief of GERD symptoms with 8 weeks of PPI treatment.[1] However, many studies have found that people take PPIs for more than 8 weeks without a supporting indication.[1] This may be due to the availability of over-the counter PPIs, inappropriate continuation for stress ulcer prophylaxis upon hospital discharge, co-prescribing with non-steroidal anti-inflammatory drugs, or empiric treatment for nausea or cough.[1] This newsletter will review recently published evidence for long-term PPI safety and present guidance to assist with de-prescribing PPIs in eligible patients.

Guideline Recommendations for PPI Use

There are many indications which necessitate the use of PPIs including PUD, GERD, Zollinger-Ellison syndrome, *Helicobacter pylori* (*H. pylori*) eradication and non-steroidal anti-inflammatory drug (NSAID)-induced ulcers.[2] Treatment duration of PPI therapy is recommended based on diagnosis.[3] Duration of therapy for selected diagnoses managed with oral PPIs are presented in **Table 1** and comparative oral PPI dosing is provided in **Table 2**. Twice daily PPI dosing is recommended for treatment of *H. pylori*, refractory GERD, and Zollinger-Ellison Syndrome.[4,5]

Table 1. Treatment Duration of Oral PPI Therapy[4,5]

Diagnosis	Duration of Therapy
Peptic Ulcer Disease	4-8 weeks
Duodenal Ulcer	4 weeks
Gastric Ulcer	8 weeks
H. pylori infection	2 weeks
Gastroesophageal reflux disease	8 weeks
Nonsteroidal anti-inflammatory drug-induced ulcers	8 weeks
Barrett's esophagus	1 year
Zollinger-Ellison Syndrome	1 year

Table 2. Usual Oral PPI Dosage Ranges[4]

Generic Name	Brand Name	Dosage Range
Dexlansoprazole	Dexilant	30 to 60 mg once daily
Esomeprazole*	Nexium	20 to 40 mg once daily
Lansoprazole*	Prevacid	15 to 30 mg once daily
Omeprazole*	Prilosec	20 to 40 mg once daily
Pantoprazole	Protonix	40 mg once daily
Rabeprazole	Aciphex	20 mg once daily
*PPI's that are available over the counter (OTC)		

Long-term PPI Use

Without an ongoing indication, long-term PPI use may cause harm.[1] These harms include pill burden, medication-related costs, drug-drug interactions, and possible adverse effects related to long-term use.[1] Data from observational studies indicate that long-term use of PPI's is associated with increased risks of bone fracture, kidney injury, gastrointestinal infections, and magnesium deficiency, as reported in low-quality observational studies.[2] The Food and Drug Administration (FDA) issued safety announcements for PPIs regarding an association with increased risks of hip, wrist, and spine fractures (2014)[6] and with hypomagnesemia (2011)[7] when PPIs are taken more than one year. In 2012 the FDA issued a warning about diarrhea associated with *Clostridioides difficile* (*C. difficile*) with use of PPIs.[8]

Risk of Bone Fractures

Prolonged acid suppression with PPIs may interfere with calcium solubilization and absorption.[9] Two recently published case-control studies showed long-term use of PPIs may lead to a risk of fractures in high-risk patients.[10,11] The first case-control study investigated the risk of fracture associated with PPI use in women 65 years of age or older (n=65,262) within 1 year prior to the fracture date.[10] Relative to women with no history of PPI, those who had used PPIs for one year or more had a greater risk of fractures (adjusted odds ration [OR], 1.71; 95% confidence interval [CI], 1.55 to 1.89).[10]

In a large Korean case-control study, (n=2,388,137) patients 50 years of age and older were evaluated for fracture risk associated with use of PPIs compared with the use of histamine-2 receptor antagonists (H2RAs).[11] The odds ratio for osteoporotic fracture in PPI users compared to H2RA users was 1.11 (95% CI, 1.08 to 1.13).[11] Patients who used PPIs for 1 year or more were at greater risk for fracture (OR, 1.42; 95% CI, 1.32 to 1.52).[11]

Hypomagnesemia

The association between chronic PPI use and hypomagnesemia is controversial. Two meta-analyses of observational data concluded that long-term PPI use is significantly associated with hypomagnesemia,[12,13] while another 2 analyses concluded the risk of PPI-induced hypomagnesemia was unclear because of significant heterogeneity among studies.[14,15] The FDA suggests that health care providers should consider monitoring

magnesium levels before initiation of PPI treatment and then periodically.[7]

Routine monitoring of serum magnesium levels in all people taking a PPI is not recommended by the FDA. However, measuring serum magnesium levels should be considered before prescribing PPIs to people who will be taking them on a long-term basis and particularly to people who will also be receiving digoxin, diuretics or other treatments associated with hypomagnesemia.[7]

Gastrointestinal Infections

The use of PPIs has been associated with gastroenteritis involving *C. difficile* and other bacteria in observational studies.[16] Gastric acid secretion is inhibited by PPIs, creating a hypochloridic environment that may increase the risk of bacterial overgrowth.[17,18] A nationwide study of Danish adults evaluated the incidence of community-acquired *C. difficile* infection and exposure to PPIs.[16] Compared to individuals with no PPI use within one year of *C. difficile* treatment (n=2,172 events), those who were currently receiving PPI therapy had the highest adjusted incidence rate ratio (IRR) of *C. difficile* infection (2.03; 95% CI, 1.74 to 2.36).[16] The IRR was elevated even in those who utilized PPI therapy in the 6 to 12 months prior to infection, suggesting that the risk of infection remains elevated up to at least one year following PPI utilization.[16]

A randomized, placebo-controlled trial evaluating the safety of pantoprazole 40 mg once daily enrolled 17,598 patients from 33 countries.[19] Patients were followed for a median of 3 years.[19] The investigators observed that enteric infections were more frequent in the pantoprazole group (OR, 1.33; 95% CI, 1.01 to 1.75) compared with placebo.[19] The number needed to harm was 301.[19] There were no statistically significant between-group differences in any other safety outcomes.[19] Data appears to suggest that there is a greater risk of gastroenteritis, specifically C. difficile infection, with PPI use.[2] The 2022 American College of Gastroenterology (ACG) guidelines recommend evaluation of current PPI use and a subsequent risk/benefit discussion may if people develop gastroenteritis, especially *C. difficile*, without other identifiable causes,.[20]

Acute and Chronic Kidney Injury

Acute kidney injury (AKI) and chronic kidney disease (CKD) may be caused by PPI-induced acute interstitial nephritis (AIN), an idiosyncratic drug reaction.[21] A retrospective pharmacovigilance study examined 19,522 reports of PPI-related AKI events from the FDA Adverse Event Reporting System database from 2004 to 2019.[22] Patients younger than 65 years old were more affected than elderly patients (66.06% vs 33.94%).Middle-aged (45–64 years old) patients accounted for 53.04% of the reported cases.[22] Women were reported AKI more frequently than men (55.42% vs 44.58%).[22] The reported median time to onset of AKI was 446 days (interquartile range, 16 to 2176 days) after PPI administration.[22]

A cohort study evaluated the association of PPI use with increased risk of chronic renal outcomes in the absence of intervening AKI.[23] The Department of Veterans Affairs national databases were used to build a cohort of 144,032 patients who used acid suppression therapy.[23] The population included 125,596 PPI-treated patients and 18,436 H2RA-treated patients.[23] Over 5 years of follow-up, cohort participants were censored at the time of AKI occurrence.[23] Compared with people who took H2RAs, people treated with PPIs had an increased risk of an estimated glomerular filtration rate (eGFR) under 60 ml/min/1.73m^2 (hazard ratio [HR] 1.19; 95% CI 1.15 to 1.24), incident CKD (HR 1.26; 95% CI 1.20 to 1.33), eGFR decline over 30% (HR 1.22; 95% CI 1.16 to 1.28), and end stage renal disease (ESRD) or eGFR decline over 50% (HR 1.30; 95% CI 1.15 to 1.48).[23] The authors concluded PPI use is associated with an increased risk of chronic renal outcomes in the absence of intervening AKI. In addition, reliance on AKI as a warning sign to guard against the risk of CKD among PPI users is insufficient as a sole mitigation strategy.[23]

PPI-induced AIN is uncommon, often subtle, and without systemic allergic manifestations, which makes it challenging for clinicians to readily identify the issue.[21] The risk of AIN was added to the warning and precautions labeling for all PPIs in 2020.[24] Although it is not endorsed by guidelines, providers may consider renal monitoring for patients taking PPIs chronically and at risk for renal impairment.[2]

FDA Guidance: Risks of Long-Term Use of PPIs

- *Bone Fractures*: PPI use greater than 26 weeks in patients >50 years of age may increase risk of fracture
- *Acute and Chronic Kidney Disease*: Consider renal monitoring for patients taking chronic PPIs at risk for renal impairment
- *Hypomagnesemia*: Consider monitoring magnesium levels in patients on chronic PPI therapy and taking digoxin, diuretics, or other drugs that may cause hypomagnesemia
- *Gastrointestinal Infections*: For people taking chronic PPIs, monitor for development of *C. difficile* diarrhea

Patients with Cirrhosis Taking PPIs

Long-term PPI use in patients with cirrhosis has been associated with increased risk of spontaneous bacterial peritonitis (SBP) and other infections.[25-28] The degree of acid suppression induced by PPIs may play a role in the observed increases in infection risk.[29] The risk of adverse drug events in observational studies including hepatic decompensation, severe SBP and mortality appears to

increase as the dose and duration of the PPI increase.[30,31] Dutch guidance developed by an interdisciplinary panel of gastroenterologists, general practitioners and pharmacists in 2017 provides recommendations for safe use of PPIs in patients with cirrhosis.[32] Their recommendations suggest using esomeprazole, omeprazole (20 mg/day maximum) or rabeprazole (10 mg/day maximum) in patients with Child-Turcotte-Pugh (CTP) class A or B cirrhosis.[32] Only esomeprazole (20 mg/day maximum) is recommended in patients with CTP class C cirrhosis.[32] Pantoprazole and lansoprazole should be avoided in all patients with cirrhosis.[29]

Deprescribing PPIs

Deprescribing PPIs is achieved through drug discontinuation, dose reduction, or changing to on-demand H2RA use in adults who have completed a minimum of 4 weeks of PPI treatment for mild-to-moderate GI conditions with symptom resolution.[33] In 2022, the American Gastroenterological Association published PPI de-prescribing guidance based on expert review.[1]

To determine whether a PPI's potential benefits outweigh the potential harms, all patients taking a PPI should have an annual review of the ongoing indications for use and documentation of that indication.[1] Patients with an indication for chronic PPI use who take twice-daily dosing should be considered for step down to once-daily PPI (refer to T**able 2** for dosing recommendations). All patients without a definitive indication for chronic PPI should be considered for trial of de-prescribing.[1] The decision to discontinue PPIs should be based solely on the lack of an indication for PPI use, and not because of concern for PPI-associated adverse events.[1] In general, patients with these diagnoses should not be considered for de-prescribing:[1]

- Severe erosive esophagitis
- Esophageal ulcer or peptic stricture
- Barrett's esophagus, eosinophilic esophagitis, or idiopathic pulmonary fibrosis
- High risk for upper GI bleeding

Patients who discontinue long-term PPI therapy should be advised that they may develop transient upper GI symptoms due to rebound acid hypersecretion.[1] These symptoms can be managed with over-the-counter antacids and nonpharmacological strategies such as avoiding dietary triggers and eating meals before bedtime. Tapering off of PPI's may reduce symptoms of rebound acid hypersecretion. When de-prescribing PPIs, either dose tapering or abrupt discontinuation can be considered.[1]

Another reputable resource is the Canadian organization, desprescribing.org. Their website provides links to an evidence based deprescribing guideline, a deprescribing algorithm, and patient information. The website can be accessed here: PPI Deprescribing Resources.

Oregon Health Plan Policies

The Health Evidence Review Committee placed long-term (greater than 8 weeks) medical treatment of GERD below the OHP funding line on the Prioritized List of Services effective January 1, 2015.[34] To align with this guidance, the Oregon Health Plan (OHP) restricts duration of therapy for non-preferred PPIs to 8 weeks for treatment of GERD. Coverage duration for PPIs used to treat *H. pylori* is 2 weeks. Other funded conditions such as Barrett's esophagus, Zollinger-Ellison, and upper GI bleeding allow for PPI duration of therapy up to one year. The Preferred Drug List status for PPIs is provided in Figure 1. Specific prior authorization criteria for Oregon Medicaid Fee-For-Service (FFS) can be accessed here: OHP FFS PA Criteria for PPIs.

Figure 1. OHP Preferred Drug List for PPIs and H2RAs

Preferred PPIs: (tablets and capsules) granules)	***Nonpreferred PPIs: (suspension, packets,***
Dexlansoprazole	Esomeprazole
Lansoprazole	Omeprazole/Sodium Bicarbonate
Omeprazole	
Pantoprazole	
Rabeprazole	
Preferred H2RAs	***Nonpreferred H2RAs***
Famotidine	Nizatidine
Ranitidine	Cimetidine

Conclusions

Observational studies have reported that long-term use of PPI's has been associated with increased risks of bone fracture, kidney injury, gastrointestinal infections, and magnesium deficiency.[2] The risk of adverse drug events including hepatic decompensation, severe SBP, and mortality appears to increase as the dose and duration of the PPI increase.[30,31] Although these adverse effects are rare, the duration of PPI treatment should be limited to recommended durations of therapy to minimize pill burden and reduce the risk of drug-related complications. De-prescribing of PPIs should be considered in patients who are taking PPIs without a documented indication.

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