MAYO CLINIC

Proton Pump Inhibitors: Review of Emerging Concerns

Avinash K. Nehra, MD; Jeffrey A. Alexander, MD; Conor G. Loftus, MD; and Vandana Nehra, MD

From the Department of General Surgery (A.K.N.) and Division of Gastroenterology and Hepatology (J.A.A., C.G.L., V.N.), Mayo Clinic, Rochester, MN.

CME Activity

Target Audience: The target audience for *Mayo Clinic Proceedings* is primarily internal medicine physicians and other clinicians who wish to advance their current knowledge of clinical medicine and who wish to stay abreast of advances in medical research.

Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. *Mayo Clinic Proceedings* aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

Accreditation Statement: In support of improving patient care, Mayo Clinic College of Medicine and Science is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the healthcare team.

Credit Statements:

AMA: Mayo Clinic College of Medicine and Science designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*.™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOC: Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1 MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

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.

Disclosures: As a provider accredited by ACCME, Mayo Clinic College of Medicine and Science (Mayo School of Continuous Professional Development) must ensure balance, independence, objectivity, and scientific rigor in its educational activities. Course Director(s), Planning Committee members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off-label and/or investigational use of pharmaceuticals or instruments discussed in their presentation. Disclosure of this information will be published in course materials so that those participants in the activity may formulate their own judgments regarding the presentation. In their editorial and administrative roles, Karl A. Nath, MBChB, Terry L. Jopke, Kimberly D. Sankey, and Jenna M. Pederson, have control of the content of this program but have no relevant financial relationship(s) with industry. Dr Alexander has a stock investment in Meritage Pharmacia, Inc, and has received research funding from Shire. However there is no association with this research. The other authors report no competing interests.

Method of Participation: In order to claim credit, participants must complete the following:

1. Read the activity.
2. Complete the online CME Test and Evaluation. Participants must achieve a score of 80% on the CME Test. One retake is allowed.

Visit www.mayoclinicproceedings.org, select CME, and then select CME articles to locate this article online to access the online process. On successful completion of the online test and evaluation, you can instantly download and print your certificate of credit.

Estimated Time: The estimated time to complete each article is approximately 1 hour.

Hardware/Software: PC or MAC with Internet access.

Date of Release: 2/1/2018

Expiration Date: 1/31/2020 (Credit can no longer be offered after it has passed the expiration date.)

Privacy Policy: http://www.mayoclinic.org/global/privacy.html

Questions? Contact dletcsupport@mayo.edu.

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.

 ■ Mayo Clin Proc. 2018;93(2):240-246

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.