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## Cover Page Footnote

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# The Adverse Effects of Proton Pump Inhibitors and How to De-Escalate Therapy

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## ABSTRACT

Many patients, both inpatient and outpatient, are initiated on proton pump inhibitors (PPIs) for stomach acid related symptoms, as well as for prophylaxis. When being treated with PPIs, many patients can be discontinued within a short time after initiation. However, these medications may inadvertently be continued long-term. Chronic use of PPIs can result in adverse events, such as vitamin deficiencies, community-acquired pneumonia, and an increased risk for *Clostridium difficile* infection. Clinicians should periodically evaluate the need for PPIs in patients and discontinue as appropriate.

## INTRODUCTION

Proton pump inhibitors (PPIs) are frequently prescribed in inpatient and outpatient settings. They are used to treat esophagitis, gastroesophageal reflux disease (GERD), peptic ulcer disease, Zollinger-Ellison Syndrome, helicobacter pylori, and other off label indications. Additionally, they can be given to patients to prevent nonsteroidal anti-inflammatory drug-induced ulcers as well as stress ulcers.<sup>1</sup> Most commonly, PPIs are initiated in the outpatient setting, as a prescription or over-the-counter medication, when patients are experiencing GERD. They are typically trialed for a period of 8 weeks and then discontinued if there is adequate response of lessened GERD symptoms. If symptoms persist, patients should receive an endoscopy to evaluate the esophageal mucosa to determine if the PPI should be continued long-term.<sup>2</sup> However, most patients never attempt to discontinue the PPI and an endoscopy is not performed. In the inpatient setting, PPIs are mostly used in patients with a considerable risk of upper gastrointestinal bleeding or as a continuation of their outpatient regimen. Currently, FDA-approved PPIs are omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole.<sup>1</sup>

PPIs are one of the most prescribed medication classes and are used in more than 30% of adults. They must be taken daily, as the full effectiveness is not shown for days after beginning therapy.<sup>3</sup> Other classes of medications, such as histamine-2 receptor antagonists (H2RAs) and antacids, can be used as needed as they have a quicker onset of action to relieve GERD. In addition to having a faster onset, these medications are less potent than PPIs and have a shorter duration of action. Thus, some patients may feel more benefit with PPIs than H2RAs and antacids.<sup>4</sup>

PPIs work by decreasing stomach acid. Parietal cells in the stomach contain the enzyme H<sup>+</sup>/K<sup>+</sup> ATPase,

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**Table 1.** AGA best practice statements<sup>9</sup>

1	A regular review and documentation of indication for use performed by the primary care provider (PCP)
2	No definitive indication for chronic PPI patient should be considered for deprescribing trail
3	No definitive indication for chronic twice daily dosing should consider a trail of step-down dosing to once daily
4	Patients with a history of complicated GERD* should not be considered for discontinuation
5	Patient with known Barrett's esophagus, eosinophilic esophagitis, or idiopathic pulmonary fibrosis generally should not be considered discontinuation
6	Assess for the risk of upper gastrointestinal (GI) bleeding using evidence-based strategy before discontinuation
7	Patients with a high-risk upper GI bleeding should not be considered for discontinuation
8	Counsel patients on the possibility to develop RAHS
9	Either tapering or abrupt discontinuation can be considered for patients who are deprescribed PPIs
10	Decision to discontinue PPIs should be based on the lack of indication for the use of PPI not the concern for PPI-associated adverse events (PAAEs)

\*Erosive esophagitis, esophageal ulcer, or peptic stricture

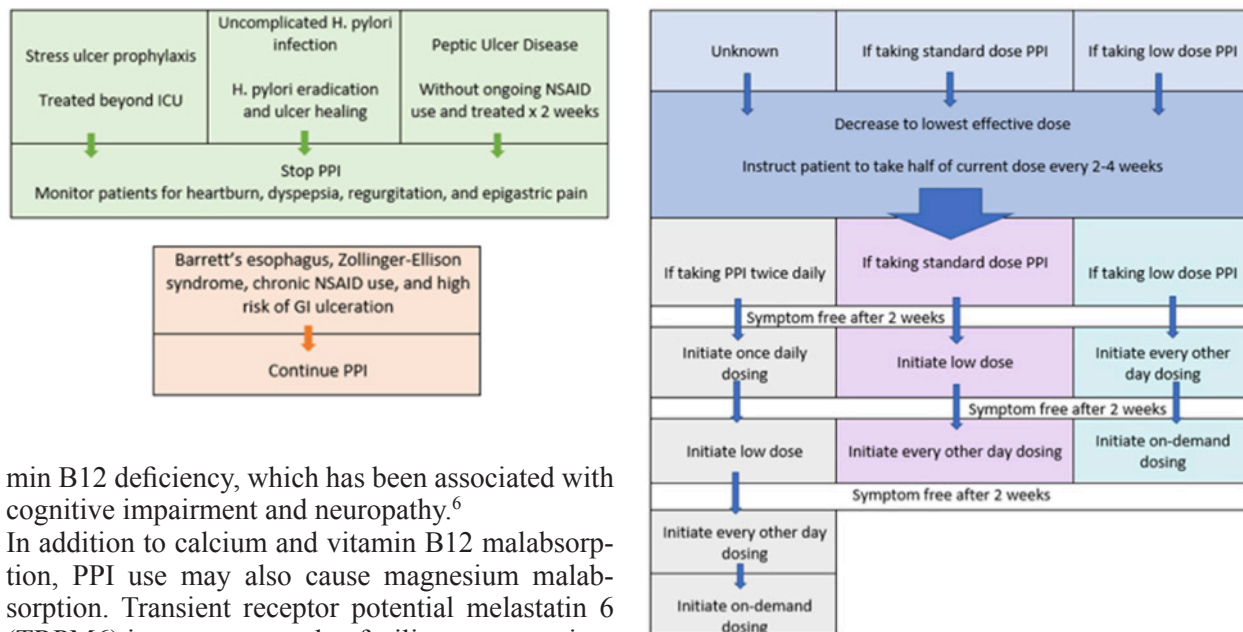
known as the proton pump. This enzyme serves as the ultimate step for stomach acid secretion. PPIs block the proton pump, thus preventing stomach acid from being secreted. PPIs are metabolized by hepatic CYP450 enzymes, with different PPI medications having different CYP450 enzymes degrading them. With individuals having different variations of these enzymes, some PPIs may be more beneficial in certain patients than others. Moreover, as individuals age, the bioavailability of PPIs increases, and the elderly population requires decreased doses. Because proton pumps cycle through regeneration about every 37 hours, PPIs will take a few days to become fully effective and may not cause immediate relief in individuals who are feeling discomfort.<sup>5</sup>

When using proton pump inhibitors, it is important for patients and providers to be aware of the risks and benefits. They can be useful in helping patients restore their quality of life by reducing symptoms of increased stomach acids but can lead to many adverse events when used long-term. It is essential that patients be routinely evaluated for possible discontinuation of PPIs so that a patient is no longer at an increased risk for an adverse event.

## LONG-TERM ADVERSE EFFECTS

While proton pump inhibitors may be beneficial when used for appropriate durations, long-term use of PPIs can result in a higher risk of adverse effects. Because PPIs reduce the acidity of the stomach, they affect the pH-dependent absorption of certain vitamins and minerals in the body. Calcium is a mineral that is important for bone formation and health. It is primarily obtained from diet and from oral supplementation.<sup>6</sup> Calcium requires a low pH to facilitate absorption into the bloodstream. Higher stomach pH results in a reduction in absorption and increased calcium excretion in the stool.<sup>6</sup> Calcium malabsorption from PPI use can lead to an increased risk of bone fractures. In a study of post-menopausal women taking PPIs, it was shown that the risk of hip fractures increased by as much as 35% in women who used PPIs regularly for at least two years, with an even higher risk for longer durations of therapy.<sup>6</sup> Similar to calcium, vitamin B12 also requires an acidic environment for absorption. In the stomach, gastric acid and pepsin release vitamin B12 from food proteins, allowing it to be absorbed into the blood.<sup>6</sup> PPI-induced elevated pH may lead to vita-

FIGURE 1. Summary of PPI deprescribing algorithm<sup>9</sup>



min B12 deficiency, which has been associated with cognitive impairment and neuropathy.<sup>6</sup>

In addition to calcium and vitamin B12 malabsorption, PPI use may also cause magnesium malabsorption. Transient receptor potential melastatin 6 (TRPM6) is a transporter that facilitates magnesium absorption into the blood from the intestines.<sup>6</sup> It is hypothesized that TRPM6 is more active in an acidic environment.<sup>6</sup> Therefore, in the setting of PPI use, TRPM6 activity is reduced, and magnesium absorption decreases. Hypomagnesemia may precipitate tetany, seizures, muscle weakness, delirium, and cardiac arrhythmias. However, the incidence of PPI-induced hypomagnesemia is rare.<sup>1</sup>

Due to their reduction of the acidity of the stomach, PPIs have been associated with an increased risk of infections. As part of normal flora, the bacteria *Clostridium difficile* (*C. diff*) resides in the large intestine, where the pH is higher than that in the stomach.<sup>6</sup> PPI use increases the pH of the stomach, facilitating the growth of *C. diff* there. In a multi-center case-control study, people taking PPIs had a 2.9-fold increase in developing *C. diff*-associated diseases compared to those not taking PPIs.<sup>6</sup> *C. diff* infections can cause severe, infectious diarrhea and most often will require antibiotics to treat.

Community-acquired pneumonia is also associated with PPI use. Similar to how PPIs provide a more basic environment for *C. diff* to grow, the reduction of gastric acid by PPIs can cause bacterial colonization in the upper gastrointestinal tract, increasing the risk for bacterial aspiration.<sup>1,6</sup>

**DE-PRESCRIBING OF PROTON PUMP INHIBITORS**

As PPIs continue to be overly prescribed with substantial long-term cost and health adverse effects,

it is important to consider deprescribing this class of medication when there is no definitive indication requiring continuation. The American Gastroenterological Association (AGA) published best practice recommendations to educate providers on the complex decision-making process when discontinuing PPIs (*Table 1*).<sup>7</sup> These statements are directed to providers, therefore, counseling of patients is crucial for their understanding. Counseling should focus on rebound acid hypersecretion (RAHS) and supplying patients with other as-needed options for short-term symptom control, such as H2RAs or antacids.

Deprescribing of PPIs can be done in several ways, including abrupt discontinuation, tapering, or change in prescription frequency to an as needed basis.<sup>8</sup> According to a recent analysis, there are two factors that lead to the most successful strategies when deprescribing PPIs. Factors include a protocol that is simple in nature, with patient education on the measures to follow in the event of reappearing symptoms, along with proper training of physicians responsible for deprescribing.<sup>8</sup> Physicians do not have to be the only health care providers who engage in monitoring patients for the possibility of deprescribing or deescalating therapy. The implementation of a pharmacist-led algorithm looking at the appropriateness of PPIs in a geriatric ambulatory office showed a significant decrease of inappropriate usage (38.5% difference;  $P < 0.0001$ ).<sup>9</sup> Additionally, PPIs are on the Beers Criteria published by The

American Geriatric Society, recognizing that this patient population is at an increased risk of unwanted adverse effects. Overall, de-prescription can be accomplished by following the AGA best practice statements (*Table 1*), by appreciating the two factors leading to successful strategies seen in a meta-analysis, and by implementing a treatment algorithm like the geriatric ambulatory office (*Figure 1*).

## CONCLUSION

PPIs treat and prevent conditions like GERD, peptic ulcer disease, and gastrointestinal ulcers. Due to their use and efficacy for multiple indications, they are common in inpatient and outpatient settings. Some patients require PPIs chronically, while others do not. Unfortunately, patients who do not require long-term use take these agents for extended periods due to a lack of patient and provider education.

Although PPIs are effective, long-term use is not benign due to their reduction in stomach acidity. Absorption of acid-dependent vitamins such as calcium, B12, and magnesium becomes impaired and may result in complications. When gastrointestinal calcium absorption is disrupted, less calcium is available to maintain bone health. Inadequate calcium can subsequently put patients at an increased risk for fractures. Similarly, decreased gastrointestinal acidity prevents proper B12 release from food and reduces the amount available for absorption into the systemic circulation. Low B12 puts patients at a higher risk for cognitive impairment, which can be irreversible if left untreated. Less common than calcium and B12 deficiency, PPIs can cause hypomagnesemia through neutralization of the stomach acid. Even though this is rare, low magnesium can lead to complications such as seizures and cardiac arrhythmias. In addition to the effects on vitamin absorption, the reduction of acidity in the gastrointestinal tract caused by PPIs results in the alteration of normal flora. The increase in pH cultivates the growth of bacteria that do not typically reside in the stomach, which may lead to C. diff infections or pneumonia.

Due to the multitude of adverse health effects PPIs can precipitate, deprescribing is an important consideration. The AGA provides best practice guidelines to help practitioners optimize PPI use in their patients, which focuses on deprescribing. Although it would be ideal for deprescribing to simply mean discontinuation, that is not the case. Some patients require PPIs for adequate treatment. In these situations, deprescribing may mean getting a patient to the lowest effective dose. Additionally, there are times deprescribing should not be considered.

These situations include when patients have Barrett's esophagus, Zollinger-Ellison syndrome, who chronically use NSAIDs, or are at elevated risk of gastrointestinal ulceration. Deprescribing can be accomplished in several ways and is most successful with provider training and the implementation of a protocol. Additionally, patients should be educated on RAHS and be given alternative agents (H2RAs or antacids) to use as needed should this occur. Overall, adhering to AGA recommendations, understanding successful deprescribing factors, and adopting treatment algorithms can aid providers in limiting PPI use in all healthcare settings.

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