

# Review of the Long-Term Effects of Proton Pump Inhibitors

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Proton pump inhibitors are widely used, but up to 70% of patients take them without an appropriate indication and face risk of adverse effects associated with long-term use.

**P**roton pump inhibitors (PPIs) are one of the most frequently used drug classes, given that they are readily accessible over-the-counter as well as via prescription. About 100 million PPI prescriptions dispensed annually.<sup>1</sup> One study showed that between 25% and 70% of patients taking a PPI do not have an appropriate indication.<sup>2</sup> It is common for patients to be prescribed a PPI during and following an inpatient hospital stay. Upon discharge, many of these patients continue taking PPIs without proper documentation or a planned termination date.

The human stomach uses 3 primary neurotransmitters that regulate gastric acid secretion: acetylcholine (ACh), histamine (H), and gastrin (G). The interactions between these neurotransmitters promote and inhibit hydrogen ion (H<sup>+</sup>) generation. Stimulation of their corresponding receptors draws H<sup>+</sup> into parietal cells that line the stomach. Once in the cell, a H<sup>+</sup>-K<sup>+</sup>-ATPase (more commonly known as the proton pump) actively transports H<sup>+</sup> into the lumen of the stomach. The H<sup>+</sup> bind with

chlorine ions to form hydrochloric acid, which increases stomach acidity.<sup>5</sup> Histamine receptors were thought to be responsible for the greatest degree of stimulation. Hence, histamine type 2-receptor antagonists (H<sub>2</sub>RAs) became a novel means of therapy to reduce stomach acidity. While utilizing H<sub>2</sub>RAs was effective, it was theorized the downstream inhibition of the action of all 3 neurotransmitters would serve as a more successful therapy. Therefore, PPIs were developed to target the H<sup>+</sup>-K<sup>+</sup>-ATPase

Over the past decade, many studies have evaluated the long-term PPI adverse effects (AEs). These include calcium and magnesium malabsorption, vitamin B<sub>12</sub> deficiency, *Clostridium difficile* (*C difficile*) associated disease (CDAD), and community-acquired pneumonia (CAP). Within the past year, data have become available linking PPI use to dementia and chronic kidney disease (CKD).<sup>3,4</sup> The following article reviews literature on the safety of long-term PPI use and proposes recommendations for proper use for their most common indications.

## MALABSORPTION

### Calcium & Long-Term Fracture Risk

Calcium is an essential component in bone health and formation. In

fact, 99% of all calcium found in the body is stored in bones.<sup>6</sup> The primary source of calcium is through diet and oral supplements. After it is ingested, calcium is absorbed from the stomach into the blood in a pH dependent manner. If the pH of the stomach is too high (ie, too basic) calcium is not absorbed into blood and remains in the gastrointestinal (GI) tract for fecal excretion. Without sufficient calcium, the body's osteoclasts and osteoblasts remain inactive, which hinders proper bone turnover.<sup>7</sup>

The decrease in acidity leads to calcium malabsorption and increases fracture risk long-term.<sup>8</sup> Khalili and colleagues surveyed 80,000 postmenopausal women to measure the incidence of hip fracture in women taking PPIs. The study found that there was a 35% increase in risk of hip fracture among women who regularly used PPIs for at least 2 years (age-adjusted hazard ratio [HR] 1.35; 95% confidence interval [CI], 1.13 -1.62). Adjusted HRs for 4-year and 6- to 8-year use of a PPI was 1.42 (95% CI, 1.05-1.93) and 1.55 (95% CI, 1.03-2.32), respectively, indicating that the longer women were on PPI therapy, the higher the risk of hip fracture. The study also evaluated the time since stopping PPI and the risk of hip fracture. Women who

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stopped PPI use more than 2 years prior had a similar risk to that of women who never used a PPI, indicating that the effect was reversible.<sup>9</sup>

### Magnesium

Magnesium is an important intracellular ion that has a number of key functions in metabolism and ion transport in the human body. Once ingested, magnesium is absorbed into the bloodstream from the small and large intestines via passive and active transport. Transient receptor potential melastatin 6 (TRPM6) is one of the essential proteins that serve as a transporter for magnesium.<sup>10</sup> The high affinity for magnesium of these transporters allows them to maintain adequate levels of magnesium in the blood. In states of low magnesium (hypomagnesemia), the body is at risk for many AEs including seizures, arrhythmias, tetany, and hypotension.<sup>11</sup>

Proton pump inhibitors have been linked to hypomagnesemia, and recent evaluation has clarified a potential mechanism.<sup>12</sup> TRPM6 activity is increased in an acidic environment. When a PPI increases the pH of the stomach, TRPM6 and magnesium levels decrease.<sup>12</sup> Luk and colleagues identified 66,102 subjects experiencing AEs while taking a PPI. Hypomagnesemia had a prevalence rate of 1% in these patients. According to the researchers, PPIs were associated with hypomagnesemia and that pantoprazole had the highest incidence among all other PPIs studied (OR, 4.3; 95% CI, 3.3 – 5.7;  $P < .001$ ).<sup>13</sup>

### Vitamin B<sub>12</sub>

In recent years, vitamin B<sub>12</sub> has been the subject of many studies. An area of concern is vitamin B<sub>12</sub>'s neurologic effect, as it has been successfully demonstrated that vitamin B<sub>12</sub> is essential for proper cognitive function.<sup>14</sup> Some data suggest that de-

generation is present in parts of the spinal column in patients with cognitive decline or neurologic problems. These lesions are due to improper myelin formation and are specific to vitamin B<sub>12</sub> deficiency.<sup>15</sup> In 2013 the CDC published the Healthy Brain Initiative, which stated cognitive impairment can be caused by vitamin B<sub>12</sub> deficiency.<sup>16</sup>

Similar to calcium, vitamin B<sub>12</sub> needs an acidic environment to be digested and absorbed.<sup>17</sup> Vitamin B<sub>12</sub> is released from food proteins via gastric acid and pepsin. Once free, the vitamin B<sub>12</sub> pairs with R-binders secreted in the stomach. Pancreatic enzymes then degrade this complex into a form that can be absorbed into circulation by the intestine. Given that PPIs reduce the acidity of the stomach, they also reduce the body's ability to release vitamin B<sub>12</sub> from food proteins and be paired with the R-binders.<sup>18</sup>

In 2013, Lam and colleagues evaluated the association between vitamin B<sub>12</sub> deficiency and the use of PPIs and H<sub>2</sub>RAs. An extensive evaluation was performed on 25,956 patients with a diagnosis of vitamin B<sub>12</sub> deficiency and 184,199 patients without. About 12% of patients with vitamin B<sub>12</sub> deficiency had received more than a 2-year supply of a PPI, whereas only 7.2% of the patients without vitamin B<sub>12</sub> deficiency received a 2-year supply of a PPI. Four point 3 percent of patients with vitamin B<sub>12</sub> deficiency received more than a 2-year supply of an H<sub>2</sub>RA. Only 3.2% of patients without vitamin B<sub>12</sub> deficiency received more than a 2-year supply of H<sub>2</sub>RA. The study concluded that a 2-year or greater history of PPI (OR, 1.65; 95% CI, 1.58-1.73) or H<sub>2</sub>RA (OR, 1.25; 95% CI, 1.17-1.34) use was associated with vitamin B<sub>12</sub> deficiency.<sup>19</sup>

## PPIS AND INFECTIONS

### *Clostridium difficile*-associated disease

Nationwide CDAD has become a prevalent infection nationwide. In 2011, *C difficile* caused nearly 500,000 infections and was associated with 29,000 deaths in the U.S.<sup>20</sup> One study stated that *C difficile* is the third most common cause of infectious diarrhea in people aged >75 years.<sup>21</sup>

*C difficile* is part of the body's normal flora in the large intestine. It grows and colonizes in an environment of low acidity. Therefore, in the stomach, where the pH is relatively low, *C difficile* is unable to colonize.<sup>22</sup> When a PPI is introduced, the increased gastric pH increases the risk for CDAD.

Dial and colleagues conducted a multicenter case control study to determine whether gastric acid suppression increases the risk of CDAD. Compared with patients who did not take a gastric acid suppressant, those taking a PPI had a 2.9-fold increase in developing CDAD (95% CI, 2.4-3.4). Comparatively, H<sub>2</sub>RAs had a 2.0-fold increase for CDAD (95% CI, 1.6 to 2.7). These results correlated with the fact that PPIs have a greater impact on gastric pH than do H<sub>2</sub>RAs.<sup>23</sup>

### Community-Acquired Pneumonia

Community-acquired pneumonia (CAP) has become a growing concern in the U.S. According to the Infectious Disease Society of America (IDSA) and American Thoracic clinical consensus guidelines, CAP remains one of the top reasons for hospitalizations in the U.S., and about 10% of patients admitted to the hospital for CAP end up in the intensive care unit (ICU).<sup>24</sup> In the past, PPIs have been linked to patients' predisposal for developing

CAP.<sup>25</sup> Although controversial, available evidence suggests a direct association. In 2008 Sarker and colleagues theorized a mechanism that the acid reduction of the gastric lumen allows for increased bacterial colonization in the upper part of the GI tract.<sup>26</sup> Since the acidity of the stomach serves as a defense mechanism against many ingested bacteria, many pathogens will be able to survive in the more basic environment.<sup>25</sup>

Sarkar and colleagues went on to evaluate 80,000 cases over 15 years. The objective was to examine the association between PPI use and the date of diagnosis of the CAP infection, known as the index date. The study demonstrated that PPI use was not associated with increased CAP risk in the long-term (adjusted odds ratio (OR), 1.02; 95% CI, 0.97-1.08). The study did find a strong increase in the risk of CAP if a PPI was started within 2 days (adjusted OR, 6.53; 95% CI, 3.95-10.80), 7 days (adjusted OR, 3.79; 95% CI, 2.66-5.42), and 14 days (adjusted OR, 3.21; 95% CI, 2.46-4.18) of the index date.<sup>26</sup>

Four years later, de Jager and colleagues examined the differences in microbial etiology in CAP patients with and without an active PPI. Over a 4-year study period, 463 individuals were selected with clinical suspicion of CAP. The microbial etiology could be determined in 70% of those patients. The remaining 30% were excluded due to an alternative diagnosis. One of the most likely pathogens to cause a CAP infection is *Streptococcus pneumoniae* (*S pneumoniae*).<sup>27</sup> Patients prescribed a PPI were significantly more likely to be infected with *S pneumoniae* than those not prescribed a PPI (28% vs 11%). The study concluded that the risk of *S pneumoniae* in patients taking a PPI was 2.23 times more likely (95% CI, 1.28-3.75).<sup>28</sup>

**Table. Treatment of GERD in Adults**

Drug	Dose	Duration
Esomeprazole <sup>40</sup>	20 or 40 mg once daily	4-8 weeks
Lansoprazole <sup>41</sup>	30 mg once daily or 30 mg twice daily	Up to 8 weeks
Omeprazole <sup>42</sup>	20 or 40 mg once daily or 20 mg twice daily	Up to 4-8 weeks
Pantoprazole <sup>43</sup>	40 mg once daily or 40 mg twice daily	Up to 8 weeks

Abbreviation: GERD, gastroesophageal reflux disease.

**DEMENTIA**

In 2040, it is estimated that more than 80 million people will have from dementia.<sup>29</sup> This is expected to become a large fiscal burden on the health care system. In 2010, about \$604 billion was spent on therapy for dementia worldwide.<sup>30</sup> Although no cure for dementia exists, it is more feasible than in previous years to prevent its occurrence. However, many medications, including PPIs, are associated with the development of dementia; therefore, it is important to minimize their use when possible.

As noted earlier vitamin B<sub>12</sub> deficiency may lead to cognitive decline. Due to the malabsorption of vitamin B<sub>12</sub> that results from PPI use, it is hypothesized that PPIs may be associated with incidence of dementia. Badiola and colleagues discovered that in the brains of mice given a PPI, levels of β-amyloid increased significantly affecting enzymes responsible for cognition.<sup>31</sup> In a February 2016, *JAMA* article, researchers conducted a prospective cohort study evaluating 73,679 patients aged ≥75 years with no dementia at baseline. They went on to assess regular use of a PPI, defined as at least 1 PPI prescription every 3 months, and the incidence of

dementia. Patients with regular use of a PPI (≥ 1 PPI prescription every 3 months) had a 44% increase risk of incident dementia (HR, 1.44; 95% CI, 1.36-1.52; P < .001).<sup>3</sup> Therefore, it is theorized that avoiding PPI use in the elderly may prevent the development of dementia.

**CHRONIC KIDNEY DISEASE**

The prevalence of CKD has drastically increased in recent decades. It is estimated that up to 13% of people in the U.S. are affected by CKD.<sup>32</sup> Some studies suggest that dosing errors occur at much higher rates in patients with declined glomerular filtration rate (GFR).<sup>33</sup> The correct utilization use of medications becomes especially pertinent to this population. Several studies have already linked PPI use to acute interstitial nephritis (AIN) and acute kidney injury (AKI).<sup>34-36</sup>

Lazarus and colleagues evaluated the association between PPI use and the incidence of CKD. Their analysis was performed in a long-term running population-based cohort and replicated in a separate health care system. In the running cohort, patients receiving a PPI had a 1.45-fold greater chance of developing CKD (95% CI, 1.11-1.90; P = .006). In that same cohort, patients on a PPI

had a 1.72-fold increase risk of AKI (95% CI, 1.28-2.30;  $P < .001$ ).<sup>4</sup> Similar outcomes were seen in the replicated cohort. However, the replicated cohort did observe that twice daily dosing of a PPI (adjusted HR, 1.46; CI, 1.28-1.67;  $P < .001$ ) had a stronger association with CKD than once-daily dosing (adjusted HR, 1.15; 95% CI, 1.09-1.21;  $P < .001$ ). H<sub>2</sub>RAs exhibited no association with CKD in the running cohort (HR, 1.15; 97% CI, 0.98-1.36;  $P = .10$ ) or the replication cohort (HR, 0.93; 95% CI, 0.88-0.99;  $P = .03$ ).<sup>4</sup>

### CLINICAL PPI RECOMMENDATIONS

There are several FDA-approved and unapproved indications that warrant PPI therapy. Proton pump inhibitor indications include gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), *Helicobacter pylori*, and ulcers associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

#### GERD Recommendations

Optimal dosing and duration is important with all medications to maximize efficacy and minimize toxicity. In the case of PPIs, dosing and duration are of particular concern due to the aforementioned AEs. Table illustrates manufacturer-recommended dosing and duration for the most commonly prescribed PPIs. Although these dosing regimens are based on clinical studies, PPIs are commonly prescribed at higher doses and for longer durations. By extending the duration of therapy, the risk of potential long-term AEs increases dramatically. If durations are limited to the recommended window, risk of AEs can be reduced.

#### Alternative Therapies

There are several strategies that exist to limit the use of PPIs, including

lifestyle modifications to prevent GERD, supplementation of an alternative agent to prevent high doses of the PPI, or discontinuing PPI therapy all together. Lifestyle modifications provide additional benefit as monotherapy or to supplement a pharmacologic regimen.

The *American Journal of Gastroenterology* promoted lifestyle modifications that include:

- Weight loss for patients with GERD who are overweight and had a recent weight gain;
- Elevation of the head of the bed (if nighttime symptoms present);
- Elimination of dietary triggers;
- Fatty foods, caffeine, chocolate, spicy food, food with high fat content, carbonated beverages, and peppermint;
- Avoiding tight fitting garments to prevent increase in gastric pressure;
- Promote salivation through oral lozenges or chewing gum to neutralize refluxed acid;
- Avoidance of tobacco and alcohol; and
- Abdominal breathing exercise to strengthen the barrier of the lower esophageal sphincter.<sup>37</sup>

The above modifications may reduce the need for pharmacologic therapy, thereby reducing possible of long-term AEs.

If lifestyle modifications alone are not enough, it is reasonable to use a H<sub>2</sub>RA for acute symptom relief or reduce high doses and frequencies of a PPI. H<sub>2</sub>RAs are well studied and effective in the management of GERD. According to the American College of Gastroenterology 2013 clinical practice guidelines, H<sub>2</sub>RAs can serve as an effective maintenance medication to relieve heartburn in patients without erosive disease. The guideline also states that a bedtime H<sub>2</sub>RA can be used to supplement a once-

daily daytime PPI if nighttime reflux exists. This can eliminate the need to exceed manufacturer-recommended doses.<sup>37</sup>

One of the final challenges to overcome is a patient that has been maintained on chronic PPI therapy. However, caution should be exercised if choosing to discontinue a PPI. In a study by Nikleson and colleagues, after a 4-week course of pantoprazole given to healthy volunteers, those patients with no preexisting symptoms developed dyspeptic symptoms of GERD, such as heartburn, indigestion, and stomach discomfort. This correlation suggests that a rebound hypersecretion occurs after prolonged suppression of the proton pump, and therefore a gradual taper should be used.<sup>38</sup> Although no definitive national recommendations on how to taper a patient off of a PPI exist, one suggestion is a 2- to 3-week taper by using a half-dose once daily or full dose on alternate days.<sup>39</sup> This strategy has exhibited moderate success rates when used. Oral and written education on symptom management and the administration of H<sub>2</sub>RAs for infrequent breakthrough symptoms supplemented the reduction of the PPI.

### CONCLUSION

Proton pump inhibitors have become a popular and effective drug class for a multitude of indications. However, it is crucial to recognize the risk of long-term use. It is important to properly assess the need for a PPI and to use appropriate dosing and duration, since prolonged durations and doses above the manufacturer's recommendations is a primary contributor to long-term consequences. Both package inserts and clinical guidelines serve as valuable resources to help balance the risks and benefits



of this medication class and can help guide therapeutic decisions. ●

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