Proton Pump Inhibitor Therapy: Safety Concerns with Long-Term Use
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This newsletter is published by the New Mexico Medicaid Drug Utilization Review (DUR) Board to promote safe and cost-effective drug therapy in the New Mexico Fee-For-Service Program. It is our hope that this educational newsletter will be useful to your practice.

Introduction
Proton pump inhibitors (PPIs) are potent gastric acid suppressors that are used in the treatment of gastroesophageal reflux disease (GERD), gastric and duodenal ulcers, erosive esophagitis, and other gastric-acid related problems. The dose and length of therapy depend on the medication and the indication, and not all PPIs are approved for every indication. PPIs differ in how they are metabolized by the body and the length of time they are active in the body. However, there is no evidence that one PPI is more effective than another at treating any of the approved indications. Agents within this class include:

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Generic Available</th>
<th>Relative Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciphex®</td>
<td>Rabeprazole</td>
<td>Y</td>
<td>$$$</td>
</tr>
<tr>
<td>Dexilant®</td>
<td>Dexlansoprazole</td>
<td></td>
<td>$$$$$</td>
</tr>
<tr>
<td>Nexium®</td>
<td>Esomeprazole (Rx and OTC)</td>
<td>Y</td>
<td>$$</td>
</tr>
<tr>
<td>Prevacid®</td>
<td>Lansoprazole (Rx and OTC)</td>
<td>Y</td>
<td>$</td>
</tr>
<tr>
<td>Prilosec®</td>
<td>Omeprazole (Rx and OTC), Omeprazole magnesium (OTC)</td>
<td>Y</td>
<td>$</td>
</tr>
<tr>
<td>Protonix®</td>
<td>Pantoprazole</td>
<td>Y</td>
<td>$</td>
</tr>
<tr>
<td>Zegerid®</td>
<td>Omeprazole/sodium bicarbonate (Rx and OTC)</td>
<td>Y</td>
<td>$$$$$</td>
</tr>
</tbody>
</table>

The increased use of PPIs has led to a growing concern related to potential long-term adverse events. These include fracture risk, increased risk of infection, chronic kidney disease, and a link to dementia.

Pathophysiology:
The proton pump is a molecule in the parietal cells of the stomach. It “pumps” acid into the stomach. The proton pump takes a non-acidic potassium ion out of the stomach and replaces it with an acidic hydrogen ion. By putting more hydrogen ions into the stomach, the contents of the stomach become more acidic. PPIs effectively stop the acid secretion into the stomach by stopping the actions of the proton pump.

Proton Pump Inhibitor Areas of Treatment
Proton pump inhibitors are used for the treatment and prevention of gastric acid related conditions. They are commonly used to relieve symptoms of acid reflux or gastroesophageal reflux disease (GERD). GERD is a condition in which contents from the stomach move up into the esophagus. PPIs are also used in the healing and maintenance of erosive esophagitis. Erosive esophagitis is inflammation of damaged tissues of the esophagus which can result in an ulcer.
These agents can also be used in treatment of duodenal ulcer and gastric ulcer. Zollinger-Ellison syndrome, a rare disease, is another condition that is treated with proton pump inhibitors. Zollinger-Ellison syndrome is caused by an increase in gastric hormone which leads to too much stomach acid. Lastly, PPIs are effective when used in combination with certain antibiotics to eradicate *H. pylori* as discussed later in this newsletter.

### GERD Management

The * Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease* recommends an 8-week course of PPI therapy for symptom relief and healing of GERD. Most PPIs should be administered 30 to 60 minutes before a meal for greatest benefit. Dexilant® and Zegerid® may be administered without regard to meals. If there is a partial response to the first agent tried switching to a different PPI may provide additional symptom relief. Maintenance therapy of a PPI may be considered for patients who continue to have symptoms after the initial PPI course of treatment. It should be at the lowest effective dose, including on demand or intermittent therapy. Histamine-2-receptor antagonists (H2RAs) can also be used as maintenance options. In pediatric patients five of the available PPIs have an FDA-approved indication for the short-term treatment of symptomatic GERD. In the geriatric population there is increased concern regarding selected potential adverse events which will be discussed later.

Lifestyle modifications can also be important tools in the management of GERD. While diet does not cause GERD, what one eats and how one eats can have an influence on its symptoms. Large meals empty slowly from the stomach and are more likely to reflux and cause GERD symptoms. The tendency for reflux is also increased by lying down shortly after eating. Specific foods and beverages have variable effects depending on the individual, but some items are recognized as being associated with GERD symptoms. Many people with GERD find that fats, onions and chocolate may worsen symptoms as well as such beverages as coffee, cola and acidic juices (e.g. tomato or citrus). Alcohol is another beverage to avoid. It is known to cause heartburn symptoms because it stimulates gastric acid production. Smoking, or other forms of nicotine consumption, can also worsen the symptoms of GERD. Nicotine is known to relax the lower esophageal sphincter and make reflux more likely to occur.

### *H. pylori* Management

*H. pylori* is a bacteria found in the stomach of over 50% of the population, although there are no symptoms of infection in more than 80% of those individuals. The prevalence of *H. pylori* infections appears to be decreasing; however, it remains an important cause of dyspeptic symptoms, gastritis, and ulceration. Available testing for *H. pylori* includes both endoscopic and nonendoscopic tests. Unfortunately, testing remains controversial because none of the test methods is completely failsafe and many tests may remain positive following successful treatment. In addition, recent PPI use can affect the sensitivity of all endoscopic and nonendoscopic tests that identify active *H. pylori* infection. Among the nonendoscopic tests are a blood antibody test, a stool antigen test, and urea breath tests. All of these tests have concerns. The blood antibody test is not recommended if a patient has received prior therapy for *H. pylori*, while the polyclonal fecal antigen test has not been as well validated as the monoclonal method. The urea breath test is not consistently available. The most accurate method for detecting *H. pylori* infection is with a histological examination from two sites after an endoscopic biopsy.

The American College of Gastroenterology recommends *H. pylori* testing in the following scenarios, but deciding which test to use relies heavily upon whether a patient requires evaluation with upper endoscopy and an understanding of the strengths, weaknesses, and costs of the individual tests.

- In patients with active peptic ulcer disease, a past history of documented peptic ulcer, or gastric MALT (mucosa associated lymphoid tissue) lymphoma who have not previously been tested.
- The test-and-treat strategy for *H. pylori* infection. This is a proven management strategy for patients with uninvestigated dyspepsia who are less than 55 years of age and have no “alarm features” such as bleeding, anemia, early satiety, unexplained weight loss, progressive dysphagia, odynophagia, recurrent vomiting, family history of GI cancer, or previous esophagogastric malignancy.

For the treatment of *H. pylori*, The American College of Gastroenterology recommends either 14 days of a triple-drug regimen containing a proton pump inhibitor (PPI), clarithromycin, and either amoxicillin or metronidazole,
or 10-14 days of a quadruple-drug regimen containing a PPI or H2RA, bismuth, metronidazole, and tetracycline. There are marketed combination products available or the agents can be administered individually.

**Table 2: Marketed H. Pylori Combination Agents with PPIs**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Relative Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeclamox®</td>
<td>Omeprazole, amoxicillin, clarithromycin</td>
<td>$$$$$$$</td>
</tr>
<tr>
<td>Prevpac®</td>
<td>Lansoprazole, amoxicillin, clarithromycin</td>
<td>$$$$$</td>
</tr>
</tbody>
</table>

**Safety Concerns with the Overuse of PPI Therapy**

In general, proton pump inhibitors are well tolerated, and the incidence of short-term adverse effects is relatively low. Long-term use of PPIs has been studied less than short-term use, and the lack of data makes it difficult to make definitive statements in some areas. However, available data indicate long-term use of PPI therapy is associated with vitamin and mineral malabsorption and an increased risk of fractures, infections and potential gastrointestinal issues. A recent study has suggested an association between the long-term use of PPIs and chronic kidney disease while other studies have suggested an association with the risk of developing dementia in the elderly. Many of these risks have been found by association in claims data analysis of a retrospective nature. More controlled studies are generally needed to quantify those findings. The Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease state that PPIs should be used in care with patients that may be more susceptible to hip fracture and *Clostridium difficile* infection. The guidelines also mention that short-term use of PPIs may increase the risk of community acquired pneumonia, especially in the first 30 days after starting therapy, but they do not appear to elevate risk in long-term utilizers.³

In a meta-analysis by Yu, et al, the increased risk of hip, spine and any site fractures were escalated among PPI users. This risk did not increase for patients taking histamine-2-receptor antagonists.⁴ A large Canadian study over a 10 year period by Fraser, et al, found PPI use to be associated with an increased risk of fragility fracture.⁵ The increase risk of fracture is thought to be due to achlorhydria, or lack of gastric acid, which can lead to malabsorption of nutrients, such as calcium.⁶ Calcium is essential for maintaining bone structure and strength. In 2010, the FDA issued warnings regarding the increased risk of wrist, hip and spine fractures in long-term PPI users. Further research is needed to determine how long-term use of PPIs affects the absorption of vitamins and minerals, which may create other health concerns. In addition to calcium, the nutrients in question include iron, magnesium, and Vitamin B₁₂. These malabsorption issues may be especially problematic in the elderly.

It has also been found that lowering gastric acid with PPI therapy makes patients more susceptible to bacterial and parasitic infections. PPI use removes the barrier to infection created by low gastric pH. There is a two-fold increased risk of *Clostridium difficile* infection with PPI use. Studies support that colonized gastric contents (due to the absence of acid), if aspirated, may increase the rate of ambulatory pneumonia after short-term use of a PPI.¹³ Long-term risk assessment for community acquired pneumonia requires further studies ⁸.

Recent analyses have suggested associations between long-term PPI use and dementia in elderly and an association with development of chronic kidney disease (CKD). The association with dementia was found when looking at individuals 75 years of age and older. Those receiving regular PPIs had a significantly increased risk of incident dementia compared with the patients not receiving PPI medication (hazard ratio = 1.44 [95% CI, 1.36-1.52]).⁸ In another recent study PPI use was associated with development of CKD with an unadjusted analysis (hazard ratio = 1.45; 95% CI, 1.11-1.90). Twice-daily PPI dosing (adjusted HR = 1.46; 95% CI, 1.28-1.67) was associated with a higher risk than once-daily dosing (adjusted HR = 1.15; 95% CI, 1.09-1.21).⁹ These associations with dementia and CKD will need to be validated using more controlled methodology, but they are definitely concerning based on the volume of PPI use.

**Duration of PPI Use**

Recommended treatment courses for PPIs vary by indication, but do not involve chronic, maintenance therapy for most common uses. Over-The-Counter labeling of these medications does not recommend use for more than 14 continuous days. However, data shows that in the real world many individuals use PPIs chronically. If patients continue to have symptoms after an initial course of PPI treatment, options for continued treatment should include intermittent therapy or a change to an H2RA. Hypersecretion of gastric acid has been documented following
abrupt discontinuation of long-term PPI therapy. Gradual discontinuation, every other day therapy, or a switch to a different method of acid control may be useful to help such patients discontinue a PPI, but more research is needed to determine the most effective method.

**Conclusion:**

PPIs are generally quite effective at providing symptom relief for many conditions involving gastric acid secretion. In addition, they are generally well tolerated during short-term use. However, more studies are needed to determine the full effect of long-term use of PPIs. Current treatment guidelines for GERD recommend PPI therapy for eight weeks. If longer therapy with a PPI is required, the chosen agent should be used at the lowest effective dose or as intermittent therapy. Lifestyle modifications should also be stressed in individuals with chronic GERD complaints and a different method of gastric acid secretion control should be considered for longer courses of treatment.

**References:**


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Questions and/or comments about this newsletter may be directed to Diana Moya, R.Ph. at (505) 827-3174 or Dianaj.Moya@state.nm.us. DUR newsletters are posted on the New Mexico Human Services Department website: [http://www.hsd.state.nm.us/providers/utilization-review.aspx](http://www.hsd.state.nm.us/providers/utilization-review.aspx).