Proton Pump Inhibitors: Appropriate Use and Safety Concerns

**Introduction**

Proton pump inhibitors (PPIs) make up more than half of the gastrointestinal (GI) drug market, and are estimated to cost Americans 11 billion dollars each year.\(^1\) However, data suggest that only one-third of PPI use is appropriate.\(^2-4\) This misuse can have both negative financial and health-related consequences. Studies have shown there are risks associated with chronic use, and occasionally even short-term use, of PPIs.\(^5-7\)

Treatment guidelines, such as those for gastroesophageal reflux disease (GERD), help tease out appropriate use of these drugs based on the latest evidence for their benefits and risks.\(^8\) This document discusses the appropriate use of PPIs along with the safety concerns associated with them. We also have a PL Patient Education Handout, What You Should Know About Proton Pump Inhibitors, to teach patients how to take their PPIs correctly.

**Appropriate Use of PPIs**

PPIs are usually used short-term to heal gastric and duodenal ulcers, treat GERD, and eradicate *Helicobacter pylori* (H. pylori) infections. They may also be used short-term for stress ulcer prophylaxis in hospitalized patients. PPIs are used chronically for some conditions such as refractory GERD and pathologic hypersecretion of acid. PPIs may also be used longer term to prevent NSAID-induced ulcers.

Short-term use. Treatment guidelines for GERD recommend an initial eight-week course of therapy with a PPI.\(^8\) FDA-approved regimens for ulcer healing typically last for four to eight weeks.\(^9,39\)

Infection with *H. pylori* can contribute to the development of peptic ulcer disease, gastritis, and gastric cancer. The primary regimens recommended for treatment of *H. pylori* infection both include a PPI: triple therapy (a PPI, clarithromycin, and amoxicillin) or quadruple therapy (a PPI, tetracycline, metronidazole, and bismuth).\(^10\) See our PL Chart, *H. Pylori Treatment Regimens for Adults*, for more information on specific regimens.

Stress ulcer prophylaxis with a PPI should not be given to all hospitalized patients. It is indicated for patients during an intensive care unit (ICU) stay who have at least one of the following:\(^1\)

- Coagulopathy (platelet count <50,000 mm\(^3\), INR >1.5, or aPTT >2 times control);
- Mechanical ventilation for >48 hours;
- History of GI ulceration or bleeding within one year of admission;
- Glasgow Coma score ≤10;
- Thermal injury to >35% of body surface area;
- Partial heptectomy;
- Multiple trauma;
- Transplantation perioperatively in the ICU;
- Spinal cord injury;
- Hepatic failure;
- Two or more of the following risk factors:
  - Sepsis;
  - ICU stay of more than one week;
  - Occult bleeding lasting at least six days;
  - High-dose corticosteroids (>250 mg/day of hydrocortisone)

Longer-term use. Patients with GERD who require chronic therapy with a PPI may be able to switch to a lower dose, on-demand therapy, or intermittent therapy.\(^8\) In erosive esophagitis, a higher dose of PPI is initially used to heal the damaged area. Then, a lower dose of PPI is used as maintenance therapy. The dose and length of therapy is determined by the severity of disease and the specific PPI being used.\(^5,39\)

Most patients with hypersecretory conditions like Zollinger-Ellison syndrome are treated with a PPI indefinitely. Patients are typically started at a

More...
high dose which is then reduced as gastric output decreases. The dose should be adjusted based on patient response. PPIs are routinely given to reduce the risk of ulcers caused by NSAIDs. It is appropriate to use a PPI when starting an NSAID in a patient with another risk factor for GI bleeding such as older age or concomitant use of a corticosteroid, anticoagulant, or antiplatelet agent. PPIs can also be used to prevent recurrent ulcers in patients who take NSAIDs. In patients who have had a previous ulcer, the use of a PPI with an NSAID has been shown to decrease the incidence of recurrent bleeding ulcers by 4% to 6% over a six-month period. Studies show a PPI given with a selective cyclooxygenase-2 (COX-2) inhibiting NSAID decreases recurrent bleeds by almost 9% over one year compared to a selective COX-2 inhibitor alone. In general, the use of NSAIDs by patients with a previous GI bleed is not recommended because there is a significant risk of a recurrent bleed. However, when the use of an NSAID is unavoidable, a selective COX-2 inhibitor plus a PPI is preferred.

Overuse of PPIs

PPIs are routinely used in hospitals for stress ulcer prophylaxis. But, only about one-third of hospitalized patients actually need them. Stress ulcer prophylaxis should not be used in medical or surgical patients (non-ICU) as they are considered low risk for stress ulcers. When used for stress ulcer prophylaxis, suggest discontinuing a PPI as soon as the risk factors resolve. The PPI started in the hospital should be discontinued when the patient is discharged (at the latest) unless there is a clear indication for its continued use. A medication reconciliation process should be used during transitions in care to identify and prevent overprescribing of PPIs.

Rebound hypersecretion is observed in 60% to 90% of individuals who take PPIs for at least two to three months. Symptoms of rebound hypersecretion may last three months or more and may inappropriately encourage the continued use of PPIs. Patients who have taken PPIs for more than a few months without a clear indication should stop therapy. It may be worthwhile to taper PPIs before discontinuing them in patients using them for more than two or three months. Taper by first reducing the dose and then dosing every other day for a week or longer. An antacid or histamine-2 (H2) blocker can be used for breakthrough symptoms if needed. Some asthmatic patients are given a PPI to help manage asthma symptoms. It was thought that patients with poorly controlled asthma might have silent gastroesophageal reflux. However, a study published in 2009 found no relationship between the two conditions. Asthmatics receiving a PPI had the same type and severity of symptoms as patients receiving placebo. It was determined that PPIs added no benefit. Asthma patients should not be given a PPI without an appropriate indication for use.

Patients often self-medicate with PPIs due to symptoms of dyspepsia or GERD. Because these products are heavily advertised and many are available over-the-counter (OTC), many patients don’t realize these drugs do have safety risks. They should be reminded that PPIs should only be used short term unless indicated by a prescriber. Tell patients who self-medicate not to take a PPI for more than 14 days at a time, and to take no more than three courses per year. If more extensive therapy is required, suggest they contact their prescriber.

Provide your patients with instructions on the appropriate use of PPIs in order to optimize their effects. Ideally, the dose should be taken 30 to 60 minutes before breakfast to manage the gastric acid surge seen in the morning. (Dexlansoprazole is the exception, as it can be taken without regard to meals due to its dual-release mechanism.) PPIs should not be taken before every meal. Bedtime dosing is not useful for controlling most symptoms since the PPI level will not be high enough to decrease the morning gastric acid surge. Recommend the use of an H2-blocker if a patient has symptoms overnight (usually histamine mediated), but keep in mind relief may not last for more than a few weeks due to tachyphylaxis. Also, provide information on nonpharmacological ways that might be helpful for managing GERD symptoms (e.g., raising head of bed six inches; avoiding meals two to three hours before bedtime, losing weight). See our PL Patient Education Handout, What You Should Know About Proton Pump Inhibitors, for more helpful tips.

If GERD symptoms don’t respond to a PPI, switching PPIs or increasing the dose to twice daily can be tried. In addition, metoclopramide can be added for patients with refractory GERD.
**Drug Interactions**

PPIs inhibit the cytochrome P450 2C19 (CYP2C19) enzyme. Drug interactions can occur with other meds that use this enzyme pathway. One potentially significant interaction involves clopidogrel (Plavix). Strong to moderate CYP2C19 inhibitors can reduce its antiplatelet effect because clopidogrel is converted by CYP2C19 to its active metabolite. For example, omeprazole can decrease the antiplatelet activity of clopidogrel by 20% to 40%.\(^2\)

The interaction between clopidogrel and PPIs has received the attention of U.S. and Canadian regulating bodies. Both American and Canadian labeling recommend avoiding the use of clopidogrel with strong or moderate CYP2C19 inhibitors, such as omeprazole.\(^2,23\) However, GERD guidelines point out the most reliable data suggest there is not an increase of cardiovascular events in patients using clopidogrel with a PPI.\(^8\)

H2-blockers are an alternative to PPIs. However, they may not be as effective for preventing GI bleeding. Plus, cimetidine also inhibits CYP2C19 and may not be appropriate in patients taking clopidogrel.\(^24,25\)

PPIs can increase the serum concentrations of some drugs to toxic levels by decreasing their metabolism. See our *PL Chart, Cytochrome P450 Drug Interactions*, for more information.

Some meds require a more acidic pH for absorption. PPIs increase the gastric pH, making it less acidic. This may decrease the effectiveness of certain medications. The significance of this interaction can vary. A very significant interaction occurs with antiretroviral agents. Absorption of these drugs is not complete because there is not an acidic environment. Avoid concomitant use of a PPI with atazanavir (Reyataz) and nelfinavir (Viracept).\(^26\)

Some nutrients also require gastric acidity for optimal absorption. Absorption of calcium, iron, and vitamin B12 may be decreased with an increased gastric pH. However, the extent and significance of this interaction has not been established. Most patients will not need additional nutrient replacements while taking a PPI, especially if they are using the PPI short-term. If a calcium supplement is needed, the citrate salt is preferred. The absorption of calcium citrate may be less affected by low gastric acidity.\(^16\)

**Safety Concerns**

There is a concern that PPIs increase fracture risk in both men and women. PPI use has been associated with a 25% increase in overall fractures and a 47% increase in spinal fractures in postmenopausal women [Evidence level B; epidemiologic study].\(^3\) Some patients taking high doses and/or long-term therapy (at least one year) have been reported to have a higher incidence of hip, wrist, or spine fractures.\(^5,43\) Increased fracture risk has been reported in patients 50 and older, although other contributors were not accounted for.\(^16,20\)

The FDA has required this information about increased fracture risk be added to PPI product labeling. However, data suggest that PPIs do not actually increase the risk of osteoporosis and that the risk of hip fracture is only increased in patients with at least one other risk factor for hip fracture.\(^8\) The FDA has determined that PPIs probably don’t increase fracture risk when used short-term in low doses.\(^20\)

It is theorized that decreased calcium absorption caused by PPIs may be involved in any increased fracture risk. However, the role of decreased calcium absorption in these patients has not been determined.\(^16,20\) Also there is no conclusive relationship between the use of PPIs and bone mineral density.\(^6\)

It is prudent to encourage the use of calcium (citrate salt) and vitamin D supplementation in those at risk for osteoporosis. In addition, patients should use the lowest effective PPI dose for the shortest time period to minimize any fracture risk.\(^20\) For patients with GERD, treatment guidelines recommend that those with known osteoporosis can remain on PPI therapy. In addition, concern of a negative impact on bone mineral density or increased risk for fractures should not be a factor influencing the use of PPIs unless the patient has other risk factors for hip fracture.\(^8\)

**Magnesium absorption may be decreased** when PPIs are used. This can occur as soon as three months after being on a PPI but risk is higher if therapy is for more than a year.\(^27,28\) This may be concerning in patients who take other meds that lower magnesium levels such as thiazide and loop diuretics. Digoxin toxicity can occur in patients with low magnesium levels. Symptoms of hypomagnesemia include muscle
cramps, heart palpitations, dizziness, tremors, or seizures.  

Consider a baseline magnesium level for patients who are likely to be on a PPI long-term.  
For patients on PPIs long-term, especially those taking digoxin or on meds that decrease magnesium, consider checking levels during PPI therapy.  
Magnesium levels aren't usually included in the standard electrolyte panel and need to be specifically ordered. An ICD-9 code (ICD-10 code starting October 2015) may be required for reimbursement. The following ICD-9 code may be appropriate:  

275.2 – hypomagnesemia (ICD-10 code will be E83.42).  

Recommend an OTC product (e.g., Slow-Mag, MagOx, etc) to treat low magnesium.  
Warn patients that a common side effect with higher magnesium doses is diarrhea.  
For more information on the treatment of low magnesium, see our PL Detail-Document, Treating Magnesium Deficiency.  

Magnesium levels won’t always improve in patients taking a PPI. In this situation, the PPI may need to be replaced with an H2-blocker. In some cases, IV magnesium supplementation is required, such as if magnesium is less than 1 mEq/L or patients are symptomatic.  
Normal serum magnesium levels vary by lab but are typically 1.8 to 2.3 mg/dL (1.5 to 1.9 mEq/L).  

**Increased risk for infections** is another safety concern with the use of PPIs. PPIs increase pH, which may allow more bacterial growth. The resulting change in GI and respiratory flora may increase the risk for infection. Even short-term use (under one week) may increase the incidence of infections.  

The incidence of pneumonia may be increased with PPI therapy. Hospitalized patients on mechanical ventilators while taking a PPI are at greatest risk of developing hospital-acquired gram-negative pneumonia.  
In one study, one additional case of hospital-acquired pneumonia was seen for every 111 non-ICU patients treated with a PPI for at least three days.  
In another study, there was about one extra case of community-acquired pneumonia for every 226 or more patients treated with a PPI for five months.  
However, meta-analyses have produced conflicting results regarding the risk of community-acquired pneumonia with the use of PPIs. One analysis suggests that short-term use of PPIs may be associated with a higher risk of community-acquired pneumonia, whereas chronic use is not.  
There was significant heterogeneity among the studies included, but there have been other studies that have supported this conclusion.  
In order to remove some of the potential confounding factors associated with GERD, a meta-analysis was conducted in patients on PPIs for prevention of GI adverse effects from NSAIDs. They found that PPIs did not increase the risk of hospitalization for community-acquired pneumonia.  
And, a retrospective analysis of pooled patient data from 24 randomized controlled trials concluded that there was no causal association between treatment with esomeprazole and a higher risk of community-acquired pneumonia over 180 days.  
The use of PPIs may also lead to an increase in *Clostridium difficile* infections and diarrhea.  
For every 533 patients receiving a daily PPI in the hospital, at least one will develop *C. difficile*. This number may seem small until you consider the large number of patients receiving PPIs daily.  
Patients being treated for *C. difficile* while taking a PPI are at a 42% increased risk of having a recurrent infection within 90 days.  
These infections may be decreased by limiting PPI use to patients who truly need them. GERD guidelines point out that PPIs should be used with caution in patients at risk for *C. difficile* infection, such as those taking antibiotics.  
The use of H2-blockers may also increase the risk of *C. difficile* but to a lesser extent than PPIs.  
Some incidence of gastric and colon cancers had been suspected to be associated with PPI use. However, evidence does not support an increased incidence of cancer in patients on PPIs.  
There has also been concern that long-term use of omeprazole or esomeprazole might increase the risk of cardiovascular events such as heart attack, heart failure, and heart-related sudden death. In 2007, based on available evidence, the FDA concluded that there was no relationship between PPIs and adverse cardiac events.  
A new, 2015 data-mining study supports the association of PPI exposure with risk for myocardial infarction in the general population. One proposed mechanism for this possible increased risk is an increased plasma level of symmetric dimethylarginine (ADMA) and decreased nitric oxide levels, attributed to PPIs. Elevated ADMA is associated with an increased risk for...
cardiovascular disease. It is important to know that this increased risk is an association that has not been proven. Randomized clinical trials do not show an increased risk for myocardial infarction with the use of PPIs.

**Conclusion**

PPIs are clearly indicated for treating a variety of GI-related conditions. They are well tolerated and very effective. Patients benefit from their appropriate use. However, it is more common for PPIs to be used inappropriately or longer than necessary. This may needlessly expose patients to risks such as drug interactions, certain infections, and other adverse effects.

Patients should be evaluated to determine the appropriateness of PPI therapy (e.g., indication, duration of therapy, dose). Continue to use PPIs for patients with appropriate indications such as GI ulcers, GERD, *H. pylori*, and hypersecretory conditions, and for those at high risk for a GI bleed when starting NSAID therapy or at high risk for stress ulcers. Remind patients using OTC PPIs to contact their health care provider if their symptoms are not relieved or if they are using a PPI for more than two weeks.

**Levels of Evidence**

In accordance with the trend towards Evidence-Based Medicine, we are citing the level of evidence for the statements we publish.

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
</tr>
</thead>
</table>
| A     | High-quality randomized controlled trial (RCT)  
High-quality meta-analysis (quantitative systematic review) |
| B     | Nonrandomized clinical trial  
Nonquantitative systematic review  
Lower quality RCT  
Clinical cohort study  
Case-control study  
Historical control  
Epidemiologic study |
| C     | Consensus  
Expert opinion |
| D     | Anecdotal evidence  
In vitro or animal study |


**References**


More...


More...


