Overview:

Proton pump inhibitors (PPI) are used to treat gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), erosive esophagitis and pathologic hypersecretory conditions; they are also used for stress ulcer prophylaxis for hospitalized patients. They are currently the third highest selling drug class in the United States, with annual sales greater than $14 billion. They are the most effective form of treatment for the above conditions with the exception of stress ulcer prophylaxis, in which there appears to be no difference among the different drug classes. PPIs have been associated with a number of adverse effects, including:

- increased risk of fracture
- increased risk for community-acquired pneumonia
- increased risk for re-infarction or rehospitalization in patients with CAD taking clopidogrel and a PPI concomitantly
- increased risk for iron deficiency
- increased risk for enteric infections, specifically *Clostridium difficile* colitis

As a general rule, the above adverse events linked to PPIs represent an appreciable increase relative risk. Absolute risk increase varies with the condition but is usually modest. Risk increases with age, duration of therapy and presence of co-morbid conditions. Elderly adults, especially those who are institutionalized, appear to be at highest risk of adverse events.

This guideline focuses primarily on preventing nosocomial/iatrogenic *Clostridium difficile* infections in hospitalized patients. One large cohort study of patients 70 years and older found a hazard ratio of 1.74 for once daily inpatient PPI use and 2.36 for greater than once daily use compared to no PPI therapy while hospitalized. It is important to note that this suggests a dose response effect. Another cohort study of both hospitalized and ambulatory care patients found a hazard ratio of 1.42 for all patients and 1.86 for those greater than 80 years of age compared to those not on PPI therapy.

One of the most common indications for patients to receive a PPI while hospitalized is “taking prior to admission.” In other words, if a patient takes a PPI as an outpatient, he or she will continue receiving this medication while in the hospital, where risk for *Clostridium difficile* is highest.

Patients who have non-erosive GERD without “Alarm Symptoms” are often over-treated with PPIs, both in dose and duration of therapy, sometimes without clear indication at all. For this

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reason, in light of the aforementioned adverse effects, this guideline seeks to review in which patients it may be appropriate to decrease or discontinue PPI therapy on an outpatient basis.

Recommendations:

- Patients with the following “Alarm Symptoms” should NOT be considered for cessation of PPI therapy:\(^4,5,6\)
  - Dysphagia / odynophagia
  - Unintentional weight loss
  - GI bleeding / iron deficiency anemia
  - Early satiety
  - Vomiting

- Patients being treated for the following conditions should NOT be considered for cessation of PPI therapy:\(^4,5,6\)
  - Erosive esophagitis
  - Barrett’s esophagus
  - PUD
  - Pathologic hypersecretory conditions (i.e. Zollinger-Ellison syndrome)
  - Esophageal adenocarcinoma
  - *Helicobacter pylori* infection

- Patients on long-term PPI therapy who have non-erosive GERD and no “Alarm Symptoms” may be candidates for dose reduction / cessation.\(^5,6\) Other therapy options are outlined below:
  - Try H2-receptor antagonists (H2RA) or antacids in place of PPIs (step down therapy)
  - Decrease PPI dose to the lowest effective dose
  - Evaluate the need for long-term daily therapy
    - On demand, patient-initiated therapy has been shown to be effective; many patients do not need daily suppressive therapy.
  - Implement lifestyle changes:
    - Elevated head of bed 6-8 inches
    - Avoid eating 4 hours prior to lying down
    - Smoking cessation
    - Weight loss
    - Smaller meal proportions

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- Less fatty meals
- Avoiding dietary triggers:
  - Alcohol, caffeine, peppermint, chocolate, garlic, onions, citrus, tomato.

Greater consideration should be given to reducing or stopping PPI’s in elderly patients and those with co-morbid conditions, as they are at higher risk of *Clostridium difficile* infection and have higher mortality rates once infected.

**Monitoring in Patients Who Require Long Term PPI Use:**

Patients on long term PPIs are at risk for malabsorption of calcium. FDA currently recommends that patients with additional risk factors for osteoporosis be monitored closely and treated with the lowest dose for the shortest course possible. Calcium Citrate is the best option for calcium supplementation for patients currently on a PPI.

- Long-term PPI use has been associated with an increased risk of osteoporosis and decreased bone mineral density (BMD), with a 35% increased risk of fractures. PPIs should be avoided in patients with another risk factor for hip fracture.

- Patients on long term PPIs are at risk for malabsorption of magnesium. FDA currently recommends that patients have a level checked prior to initiation of therapy with PPI and periodically during therapy. Hypomagnesaemia may occur years into therapy, and multiple electrolyte abnormalities can occur. Older patients are at greater risk as are those on concomitant diuretic therapy.

- Patients on long term PPIs are at risk for malabsorption of Vitamin B-12. In the presence of drug-induced hypochlorhydria, it has been theorized that patients may not make enough intrinsic factor to absorb B<sub>12</sub> appropriately. Levels should be monitored and supplemental B<sub>12</sub> given, if indicated. 8

**For Inpatient Physicians:**

For patients who are at highest risk for *Clostridium difficile* colitis (elderly, those with co-morbid conditions, patients on antibiotics), consideration should be given to assessing the need for continuation of outpatient PPI based on the patient’s history. If there are no alarm symptoms and no pathology beyond non-erosive GERD, consideration can be given to cessation of PPIs. H2RAs or antacid therapy can be substituted; these therapies mildly elevate risk for *Clostridium difficile* infection, but the risk is much lower when compared with PPIs. 2

**References:**

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7. [http://www.uspharmacist.com/content/d/feature/c/45678/](http://www.uspharmacist.com/content/d/feature/c/45678/)