MedStar Health

Outpatient use of Proton Pump Inhibitors
Clinical Practice Guideline

"These guidelines are provided to assist physicians and other clinicians in making decisions regarding the care of their patients. They are not a substitute for individual judgment brought to each clinical situation by the patient's primary care provider-in collaboration with the patient. As with all clinical reference resources, they reflect the best understanding of the science of medicine at the time of publication but should be used with the clear understanding that continued research may result in new knowledge and recommendations."

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.[1] They are the most effective form of treatment for the above conditions except for stress ulcer prophylaxis, for which there appears to be no difference among the different drug classes.[4,5,6]

The current FDA indications for PPI use are:

- Healing of erosive esophagitis
- Maintenance of healed erosive esophagitis
- Treatment of GERD
- Risk reduction for gastric ulcer associated with NSAIDs
- Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence in combination with antibiotics
- Hypersecretory conditions including Zollinger-Ellison syndrome
- Short-term and maintenance treatment of duodenal ulcer

In general, all PPIs are similarly effective in producing healing and providing symptom relief. Patients who do not respond to one PPI, however, may respond to another. PPIs are most effective when taken on an empty stomach. Tolerance does not develop with continued use. Because PPIs are metabolized partially by CYP2C19, patients who are rapid metabolizers may have a decreased response to PPI therapy. Conversely, Asian populations may be slow metabolizers, and dose reductions may be possible. PPIs are well-tolerated with common side effects including headache, nausea, abdominal pain, constipation, flatulence, and diarrhea.

In March 2017, the American Gastroenterological Association (AGA) published a review article, "The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association."[7] Its purpose was to evaluate the risks associated with the long term use of PPIs for three common indications: gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and non-steroidal anti-inflammatory drug (NSAID) bleeding prophylaxis. The recommendations come from expert opinion and a review of the literature. There has been no recent update to these recommendations.

Initial Approval Date and Reviews:	Most Recent Revision and Approval Date:	Next Scheduled Review Date:
December 2015, December 2017, December 2019, December 2021	December 2021	December 2023

Ambulatory Best Practice

As noted below, there remains much confusion about the long-term safety of PPIs. All expert opinion and review articles agree that PPIs should be prescribed for the shortest duration and lowest dose and for the appropriate indications. Periodically, efforts should be made to decrease the dose.

UpToDate recommends tapering the dose by 50% each week for patients who have been on PPIs for longer than 6 months.

Ten recommendations for Best Practice were made in the AGA article for the long-term use of PPIs:

***Best Practice Advice 1*: Patients with GERD and acid-related complications (i.e., erosive esophagitis or peptic stricture) should take a PPI for short-term healing, maintenance of healing, and long-term symptom control.**

***Best Practice Advice 2*: Patients with uncomplicated GERD who respond to short-term PPIs should subsequently attempt to stop or reduce them. Patients who cannot reduce PPIs should consider ambulatory esophageal pH/impedance monitoring before committing to lifelong PPIs to help distinguish GERD from a functional syndrome. The best candidates for this strategy may be patients with predominantly atypical symptoms or those who lack an obvious predisposition to GERD (e.g., central obesity, large hiatal hernia).**

***Best Practice Advice 3*: Patients with Barrett's esophagus and symptomatic GERD should take a long-term PPI.**

***Best Practice Advice 4*: Asymptomatic patients with Barrett's esophagus should consider a long-term PPI.**

***Best Practice Advice 5*: Patients at high risk for ulcer-related bleeding from NSAIDs should take a PPI if they continue to take NSAIDs.**

***Best Practice Advice 6*: The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition.**

***Best Practice Advice 7*: Long-term PPI users should not routinely use probiotics to prevent infection.**

***Best Practice Advice 8*: Long-term PPI users should not routinely raise their intake of calcium, vitamin B12, or magnesium beyond the Recommended Dietary Allowance (RDA).**

***Best Practice Advice 9*: Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium, or vitamin B12.**

***Best Practice Advice 10*: Specific PPI formulations should not be selected based on potential risks.**

And patients with Zollinger Ellison Syndrome should be on long term PPI's.

Potential Drug-Drug Interactions:

Drug interactions generally occur because of altered gastric pH, CYP2C19 metabolism, or CYP3A4 metabolism.

Interacting Medication	Interaction Management
Clopidogrel*	Avoid with omeprazole and esomeprazole, pantoprazole preferred
Calcium	Additional supplementation may be necessary Consider use of calcium citrate over calcium carbonate
Iron	Additional supplementation may be necessary Consider IV administration
Vitamin B12	Additional supplementation may be necessary Consider intranasal or intramuscular route of administration
Protease inhibitors	Avoid PPI use if possible Decreased to lowest possible dose if avoidance not possible Avoid atazanavir (even if boosted) if requiring PPI dose equivalent to >20mg omeprazole daily
Rilpivirine	Avoid PPI use if possible
Methotrexate	Avoid PPI use if possible Monitor methotrexate levels closely if PPI use cannot be avoided

*clinical significance of this interaction is not established

Patients receiving both PPI's and H2 blockers for refractory GERD symptoms should take the H2 blocker in the evening.

The safety of the long-term use of PPIs has been an area of conflicting data. PPIs have been associated with several adverse effects that are listed in the table below[1, 2,4,5,6,8]. Eusebi, et. al.[9] reviewed the evidence for many of these associated risks and found the strength of the association to be "weak" or "uncertain" for all of them except fundic gland polyps where they found "consistent" evidence.

An edition of the Medical Letter[10] published in August 2017 reviewed many of these same associated risks and concluded that there was conflicting data on fractures and no association between PPI use and osteoporosis. Hypomagnesemia has been reported rarely and in association with hypokalemia and hypocalcemia. Torsades de pointes has also been reported when there is significant hypomagnesemia. The long-term use of PPIs has been associated with an increased risk of kidney disease. Vitamin B-12 deficiency, especially with high doses in the elderly, has been noted due to decreased absorption. PPIs can also interfere with iron absorption, but the

clinical significance is unclear. The study cited was a case-control study. The conclusion for community acquired pneumonia was that there is no evidence of increased risk and that the data for C. difficile infection was conflicting. The evidence is likewise limited for PPI use as a risk factor for dementia. There is one observational study suggesting an association with PPIs and all-cause mortality. The Medical Letter concluded that while the list of safety concerns is growing, few are supported by consistent data. The article concluded, "For patients with a clear indication for long-term treatment with a PPI, the benefits probably outweigh the risks."

In February 2018, the Mayo Clinic published a review of the data on some of the safety concerns that have been raised and categorized as "Association Likely Causative" (hypomagnesemia, B12 deficiency and small intestine bacterial overgrowth), "Association Unclear" (bone fractures, C. difficile infection, acute and chronic kidney disease, and dementia) and "Association Unlikely Causative" (community acquired pneumonia and mortality).

Vaezi et al raised the concern about distinguishing carefully in observational studies between causality and association. In the article, they systematically evaluated the quality of the available studies and data against the Hill Criteria. The Hill Criteria were first proposed in 1965 and are 9 considerations to strengthen the notion of causality vs association. The Hill Criteria ask about the strength of the association, the consistency of the results in the various studies, the specificity of the outcome, is there a clear cause and effect, a relationship to dose and or duration, is there a biological rationale, is the data from experiments and are the other features of the association similar to the associations judged to be present. They applied the criteria to 16 of the reported associations. In the article they noted that, by and large, the evidence is weak (except fundic gastric polyps), consistency is often poor concluding that additional well-planned studies designed to address the questions that need to be answered should be undertaken.

The table below is an effort to organize the current state of confusion. The reader should understand that in ALL cases the evidence is weak except fundic gland polyps.

SAFETY CONCERNS—ASSOCIATION PROBABLY CAUSAL	
Increased risk for iron deficiency	Does interfere with Fe absorption, not clear if clinically significant unless on oral iron supplements
Increased risk for enteric infections, specifically *Clostridium difficile* colitis	Data is consistent for enteric infections Salmonella and Campylobacter
Small intestine bacterial overgrowth	Likely causative though clinical significance remains controversial
Kidney disease acute and chronic	Acute association with interstitial nephritis and CRF with long term use. Reasonable to monitor eGFR annually
Vitamin B-12 deficiency	Some sources recommend yearly monitoring esp. elderly
Hypomagnesemia	Likely causative, FDA recommends monitoring. Diuretic use and malabsorption disorders are risks.
Drug induced lupus	Yes, acute idiosyncratic
Fundic gland polyps	Yes, polyps but no specific association with progression to malignancy
SAFETY CONCERNS—ASSOCIATION MAY BE CAUSAL	
Dementia-- need more studies	Conflicting data. More studies needed

SAFETY CONCERNS—ASSOCIATION PROBABLY NOT CAUSAL	
Increased risk for community-acquired pneumonia	
Increased risk of fracture	There is an FDA warning, however AGA does not recommend BMD or ca supplement for PPI users
Gastric cancer	
Colon cancer	
Rhabdomyolysis	
Cardiovascular risk	
Increased risk for re-infarction or re-hospitalization in patients with CAD taking clopidogrel and a PPI[10] concomitantly.	

Individual Proton Pump Inhibitors

Medication	Typical Dosing	Additional Information	AWP*
Dexlansoprazole (Dexilant®)	**Dyspepsia**: 30mg daily **Nonerosive GERD**: 30mg daily **Erosive or severe GERD**: 60mg daily for 8 weeks, then 30mg daily	Consider tapering after 6 months if asymptomatic If unable to swallow capsules, open and sprinkle granules onto 1 tbsp of applesauce and swallow intact	Brand Only $370
Esomeprazole (Nexium®)	**Heartburn:** 20mg daily for 14 days (OTC); can repeat again after 4 months if needed **Symptomatic GERD**: 20mg daily for 4 weeks; can repeat for additional 4 weeks if still symptomatic	Capsule and tablet forms are best taken 1 hour before breakfast Can use granules or mix capsule contents with 1 tbsp of applesauce if unable to swallow whole	Capsule: $31 Tablet: Brand Only $20

Lansoprazole (Prevacid®)	**Mild/Intermittent and Nonerosive GERD**: 15mg daily for 8 weeks; can increase to 30mg if still symptomatic. Discontinue once asymptomatic for 8 weeks. **Severe or Erosive GERD**: 30mg daily. Discontinue once asymptomatic for 8 weeks. **Refractory GERD**: 30mg twice daily **Heartburn**: 15mg daily for 14 days (OTC); can repeat every 4 months as needed	Best given 30-60 minutes before breakfast if once daily or breakfast and then dinner if twice daily Capsule contents can be mixed with 1 tbsp of applesauce, cottage cheese, yogurt or strained pears and swallowed immediately if unable to swallow. Capsule contents can be emptied into 60mL orange juice, apple juice, or tomato juice and swallowed immediately if unable to swallow more solid food. Rinse glass with two or more volumes of the juice and swallow immediately to ensure that full dose is delivered.	Capsule: $794 Tablet: $946
Omeprazole (Prilosec®)	**Mild/Intermittent and Nonerosive GERD**: 10mg daily; can increase to 20mg daily after 4-8 weeks if needed. Discontinue once asymptomatic for 8 weeks	Best given 30-60 minutes before breakfast Capsule contents can be mixed with 1 tbsp of applesauce and swallowed immediately if unable to swallow whole.	Capsule: $222 Tablet: $263

	Severe or Erosive GERD: 20-40mg daily for at least 8 weeks once symptoms are controlled. Can taper to lowest effective dose or to discontinue once asymptomatic. **Heartburn**: 20mg daily for 14 days (OTC); can repeat every 4 months as needed	Oral suspension should be allowed to thicken for 2-3 minutes and administered within 30 minutes of reconstitution.	
Pantoprazole (Protonix®)	**Mild/Intermittent and Nonerosive GERD**: 20mg daily; can increase to 40mg daily after 4-8 weeks if needed. Discontinue once asymptomatic for 8 weeks. **Severe or Erosive GERD**: 40mg daily for at least 8 weeks once symptoms are controlled. Can taper to lowest effective dose or to discontinue once asymptomatic.	Best given 30-60 minutes before breakfast Oral suspension may be sprinkled on 1 tsp of applesauce and swallowed within 10 minutes or emptied into 5mL of apple juice, stirred for 5 seconds, and swallowed immediately. If using juice, rinse container twice with more apple juice and swallow immediately to assure delivery of full dose.	Tablet: $324

Rabeprazole (Aciphex®)	**Mild/Intermittent and Nonerosive GERD**: 20mg daily Discontinue once asymptomatic for 8 weeks **Severe or Erosive GERD**: 20mg daily for at least 8 weeks once symptoms are controlled. Can taper to lowest effective dose or to discontinue once asymptomatic.	Capsules can be opened and sprinkled on soft food or into small amount of liquid and administered within 15 minutes if unable to swallow whole	Capsule: $1448 Tablet: $344

*Average Wholesale Price for 30 days of generic medication at maximum dosing unless stated otherwise

GERD: gastroesophageal reflux disease

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