MedStar Health

Outpatient use of Proton Pump Inhibitors
Clinical Practice Guideline
December
2019

"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 with the exception of stress ulcer prophylaxis, in 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 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:

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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.

As noted below, there remains much confusion about the long-term safety of PPIs.
There is one thing that there is agreement on. 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
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

The safety of the long-term use of PPIs has been an area of conflicting data.
PPIs have been associated with a number of adverse effects that are listed in the table below,[1, 2,4,5,6,8]. Eusebi, et. al.[8] 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[9] 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 as 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.	

References:

1. Ament et al. "Reducing Adverse Effects of Proton Pump Inhibitors." *Am Fam Physician.* 2012 Jul 1;86(1):66-70
2. Howell MD, Novack V, Grgurich P, et al. Iatrogenic Gastric Acid Suppression and the Risk of Nosocomial Clostridium difficile Infection. *Arch Intern Med.* 2010;170(9):784-790. doi:10.1001/archinternmed.2010.89. Archives internal medicine "PPIs and risk for recurrent…"
3. Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton Pump Inhibitors and Risk for Recurrent The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association t Clostridium difficile Infection. *Arch Intern Med.* 2010;170(9):772-778. doi:10.1001/archinternmed.2010.73.
4. http://www.gastro.org/guidelines/2008/09/16/gastroesophageal-reflux-disease-gerd
5. http://www.med.umich.edu/1info/FHP/practiceguides/gerd/gerd.12.pdf
6. http://www.aafp.org/afp/2003/1001/p1311.html
7. Freedberg, Daniel et al. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. Gastroenterology. Volume 152, Issue 4, March 2017, Pages 706-715.
8. **Clinical Resource,** *Proton Pump Inhibitors: Appropriate Use and Safety Concerns. Pharmacist's Letter/Prescriber's Letter.* **February 2019**.
9. Eusebi, et al. Proton pump inhibitors: Risks of long-term use. Journal of Gastroenterology and Hepatology 32 (20170 1295-1302.
10. The Medical Letter August 14, 2017 Volume 59 Issue # 1527 p131-133 Safety of Long-Term PPI Use
11. UpToDate accessed November 16, 2019.
12. Vaezi, M, YangY., Howden, C. Complications of Proton Pump Inhibitor Therapy Gastroenterology, 2017-07-01, Volume 153, Issue 1, Pages 35-48,

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