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

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Table 1. Indications for Proton Pump Inhibitor Use

Indications					
Definitely indicated for long-term use (>8 wk)	Conditionally indicated for long-term use	Not indicated for long-term use	Definitely indicated for acute/short-term use (≤8 wk)	Conditionally indicated for acute/short-term use	Not indicated for acute/ short-term use
Barrett's esophagus Clinically significant (LA Classification grade C/D) erosive esophagitis Esophageal strictures from GERD (ie, peptic strictures) Zollinger-Ellison syndrome Eosinophilic esophagitis Gastroprotection in users of ASA/nonsteroidal anti-inflammatory drug at high risk for GI bleeding Prevention of progression of idiopathic pulmonary fibrosis	PPI-responsive endoscopy-negative reflux disease, with recurrence on PPI cessation PPI-responsive functional dyspepsia, with recurrence on PPI cessation PPI-responsive upper airway symptoms ascribed to laryngopharyngeal reflux, with recurrence on PPI cessation Refractory steatorrhea in chronic pancreatic insufficiency with enzyme replacement Secondary prevention of gastric and duodenal peptic ulcers with no concomitant antiplatelet drugs	Symptoms of nonerosive reflux disease with no sustained response to high-dose PPI therapy Functional dyspepsia with no sustained response to PPI therapy Steroid therapy in the absence of ASA/ nonsteroidal anti-inflammatory drug therapy Prevention of recurrent upper GI bleeding from causes other than: Peptic ulcer disease, including gastric and duodenal erosions Erosive esophagitis	*Helicobacter pylori* eradication Stress ulcer prophylaxis for ICU patients with risk factors Uninvestigated GERD/ dyspepsia Treatment of NSAID-related gastric and duodenal peptic ulcers	Initial or on-demand treatment of endoscopy-negative reflux disease Initial treatment of functional dyspepsia Uninvestigated dyspepsia Ulcer prevention after sclerotherapy or band ligation treatment of esophageal varices Prevention of rebleeding from Mallory-Weiss tears	Empiric treatment of laryngopharyngeal symptomatology Acute undifferentiated abdominal pain Acute nausea and vomiting not believed to be related to GERD/esophagitis Any isolated lower GI symptomatology

ASA, aspirin; ICU, intensive care unit; LA, Los Angeles.

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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.

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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.

To determine whether a PPI's potential benefits outweigh the potential harms, it is essential to know why the PPI was prescribed and the indications for continuing use. Without an ongoing indication or evidence of benefit for the prescribing indication, the PPI can only incur harm. These harms include pill burden, medication-related costs, and potential adverse effects related to long-term use. Therefore, clinicians should clearly document an acceptable indication for the drug and that the indication is ongoing. In the absence of an appropriate ongoing indication, the medication should be considered for de-prescribing.

Ten recommendations for Best Practice were made in the AGA article for the long-term use of PPIs:[15]

***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.

Table 2. Examples of Guidance Recommendations for Proton Pump Inhibitor Gastroprotection

Group	Year	Clinical focus	Populations for whom PPI gastroprotection is recommended
ACG[75]	2009	NSAIDs	Patients using NSAIDs who are at moderate or high risk of upper GI bleeding (1 or more risk factors, including prior ulcer, older than 65 years, high-dose NSAID therapy, concurrent use of aspirin (including low-dose), corticosteroids, or anticoagulants).
ACP[77,78]	2010, updated in 2019	Prior upper GI bleeding	Patients with prior ulcer bleeding who require an NSAID (the NSAID should preferably be a COX-2 inhibitor).
ACCF/ACG/AHA[73]	2010	Antiplatelet therapy	Patients with a history of upper GI bleeding or with multiple risk factors for GI bleeding who require antiplatelet therapy. Risk factors include advanced age; concurrent use of anticoagulants, steroids, or NSAIDs, including aspirin; and *Helicobacter pylori* infection.
ESC/EACTS[74]	2017	Dual antiplatelet therapy	Patients using dual antiplatelet therapy.
ACCP[79]	2018	Atrial fibrillation	Patients using aspirin and an oral anticoagulant.
ACC[76]	2020	Antithrombotics	Patients on 2 or more antithrombotic agents.

ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Chest Physicians; ACG, American College of Gastroenterology; ACP, American College of Physicians; AHA, American Heart Association; ESC, European Society of Cardiology; EACTS, European Association for Cardio-Thoracic Surgery.

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De-Prescribing of Proton Pump Inhibitors:
AGA published a clinical practice update on De-prescribing of Proton Pump Inhibitors in April 2022[16]
[Please see link attached: De-Prescribing Proton Pump Inhibitors (AGA April 2022]

As PPI use has become more common, the emerging literature has identified several adverse effects potentially linked to these drugs, from chronic kidney disease to fracture to dementia and, most recently, COVID-19. All studies to date reporting these specific associations have been observational and

therefore cannot establish causality. In contrast, randomized controlled trials (RCTs) comparing PPIs with placebo have not shown a higher rate of any adverse event among PPI users. Nonetheless, this body of literature has raised concerns among prescribers and patients about the long-term safety of PPIs. This concern may promote inappropriate discontinuation of PPIs when a strong indication for use exists. In this context, they developed a set of Best Practice Advice (BPA) statements about how to approach PPI de-prescribing— "the clinically supervised process of stopping or reducing the dose of medications when they cause harm or no longer provide benefit"—in ambulatory patients.

De-Prescribing of Proton Pump Inhibitors: Best Practice Advice Statements

Best Practice Advice 1
All patients taking a PPI should have a regular review of the ongoing indications for use and documentation of that indication. This review should be the responsibility of the patient's primary care provider.

Best Practice Advice 2
All patients without a definitive indication for chronic PPI should be considered for trial of de-prescribing.

Best Practice Advice 3
Most patients with an indication for chronic PPI use who take twice-daily dosing should be considered for step down to once-daily PPI.

Best Practice Advice 4
Patients with complicated gastroesophageal reflux disease, such as those with a history of severe erosive esophagitis, esophageal ulcer, or peptic stricture, should generally not be considered for PPI discontinuation.

Best Practice Advice 5
Patients with known Barrett's esophagus, eosinophilic esophagitis, or idiopathic pulmonary fibrosis should generally not be considered for a trial of de-prescribing.

Best Practice Advice 6
PPI users should be assessed for upper gastrointestinal bleeding risk using an evidence-based strategy before de-prescribing.

Best Practice Advice 7
Patients at high risk for upper gastrointestinal bleeding should not be considered for PPI de-prescribing.

Best Practice Advice 8
Patients who discontinue long-term PPI therapy should be advised that they may develop transient upper gastrointestinal symptoms due to rebound acid hypersecretion.

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Best Practice Advice 9
When de-prescribing PPIs, either dose tapering or abrupt discontinuation can be considered.

Best Practice Advice 10
The decision to discontinue PPIs should be based solely on the lack of an indication for PPI use, and not because of concern for PAAEs. The presence of a PAAE or a history of a PAAE in a current PPI user is not an independent indication for PPI withdrawal. Similarly, the presence of underlying risk factors for the development of an adverse event associated with PPI use should also not be an independent indication for PPI withdrawal.

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.[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. Torsade's 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.

Individual Proton Pump Inhibitors

Medication	Typical Dosing	Additional Information	AWP*
Dexlansoprazole (Dexilant®)	**Dyspepsia**: 30mg daily **Nonerosive GERD**: 30mg daily **Erosive esophagitis**: 60mg daily for 8 wks. 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.	$315
Esomeprazole (Nexium®)	**Heartburn:** 20mg daily for 14 days (OTC); can repeat again after 4 months if needed **Nonerosive GERD**: 20mg-40mg daily for 4-8 weeks; can repeat for additional 4 weeks if still symptomatic. **Erosive esophagitis:** 40mg daily for 4-8 weeks, then 20mg daily	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: $20 Tablet (Brand Only): $20
Lansoprazole (Prevacid®)	**Mild/Intermittent and Nonerosive GERD**: 15mg daily for 4-8 weeks; can increase to 30mg if still symptomatic. Discontinue once asymptomatic for 8 weeks. **Severe GERD**: 30mg daily. Discontinue once asymptomatic for 8 weeks. **Erosive Esophagitis:** 30mg daily	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, Ensure pudding, or strained pears and swallowed immediately.	Capsule: $360 Tablet: $946

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	Heartburn: 15mg daily for 14 days (OTC); can repeat every 4 months as needed	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.	
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. **Severe or Erosive GERD**: 20-40mg daily and for at least 8 weeks once symptoms are controlled. Can taper to lowest effective dose or to discontinue once asymptomatic for patients with non-erosive esophagitis. Patients with erosive esophagitis continue 20mg daily. **Heartburn**: 20mg 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 and swallowed immediately with a glass of water if unable to swallow whole. Oral suspension should be allowed to thicken for 2-3 minutes and administered within 30 minutes of reconstitution.	Capsule: $222 Tablet: $28
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.	Best given 30-60 minutes before breakfast Oral suspension may be sprinkled on 1 tsp of applesauce and swallowed within 10 minutes or	Tablet: $324

	Severe or Erosive GERD: 40mg daily and for at least 8 weeks once symptoms are controlled. Can taper to lowest effective dose or to discontinue once asymptomatic for patients with non-erosive esophagitis. Patients with erosive esophagitis continue 40mg daily.	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.	
Rabeprazole (Aciphex®)	**Mild/Intermittent and Nonerosive GERD**: 20mg daily Discontinue once asymptomatic for 8 weeks. **Severe or Erosive GERD**: 20mg daily and for at least 8 weeks once symptoms are controlled. Can taper to lowest effective dose or to discontinue once asymptomatic for patients with non-erosive esophagitis. Patients with erosive esophagitis continue 20mg daily.	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: $1490 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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