Stewardship of Proton Pump Inhibitors: Considerations for Use and Deprescribing

Key Messages

- **Proton pump inhibitors (PPIs) are approved by the Food and Drug Administration (FDA) for the management of multiple conditions. FDA-approved labeling and treatment guidelines provide information regarding appropriate dosage and duration of treatment for these drugs.**
- **Short-term use of PPIs is defined as ≤8 weeks, while long-term use is defined as >8 weeks. Prolonged use (≥1 year) has been associated with adverse events and safety concerns.**
- **Long-term use of PPIs without an ongoing indication or evidence of benefit contributes to increased pill burden, increased medication-related costs, and potential adverse effects. If an appropriate indication is not present, consider deprescribing the PPI.**

At the conclusion of this activity, participants will be able to:

- Identify the appropriate dosing and duration of PPIs based on FDA-approved indications and guideline recommendations;
- discuss considerations for long-term PPI therapy; and
- determine when deprescribing of PPIs is appropriate based on patient-specific factors.

Introduction

PPIs are one of the most commonly prescribed classes of medications in the United States.[1] PPIs irreversibly block the H+/K+ ATPase enzyme in the stomach leading to decreased production of acid. PPIs are used to treat a variety of conditions related to gastrointestinal acid production. Current FDA-approved uses for PPIs include gastroesophageal reflux disease (GERD), dyspepsia, erosive esophagitis, peptic ulcer disease, hypersecretory conditions (e.g., Zollinger-Ellison syndrome), non-steroidal anti-inflammatory drug (NSAID)-associated ulcers, and *Helicobacter pylori (H. pylori)*.[2-7]

Table 1 provides a detailed summary of the FDA-approved indications and dosing of PPIs including the recommended duration of treatment based on the approved product labeling. Notably, dosing, length of therapy, and treatment regimens differ based on the PPI and the condition being treated.

Table 1. FDA-approved indications and dosing of PPIs.[€, 2-7]

FDA-approved indications	Dexlansoprazole (Dexilant®)	Esomeprazole (Nexium®)	Lansoprazole (Prevacid®, Prevacid® SoluTab®)	Omeprazole (Prilosec®)	Pantoprazole (Protonix®)	Rabeprazole (Aciphex®)
EE - healing	60 mg once daily up to 8 weeks	20-40 mg once daily for 4-8 weeks*	30 mg once daily up to 8 weeks^	20 mg once daily for 4-8 weeks*	40 mg once daily up to 8 weeks^	20 mg once daily for 4-8 weeks^
EE - maintenance	30 mg once daily[+]	20 mg once daily**	15 mg once daily[@]	20 mg once daily[@]	40 mg once daily[@]	20 mg once daily[@]
GERD - nonerosive, symptomatic	30 mg once daily for 4 weeks	20 mg once daily for 4 weeks***	15 mg once daily up to 8 weeks	20 mg once daily up to 4 weeks		20 mg once daily up to 4 weeks*
Pathological hypersecretory conditions		40 mg twice daily; may titrate up to 240 mg (treat as long as clinically indicated)	60 mg once daily, may titrate up to 90 mg twice daily (dose is individualized)	60 mg once daily, may titrate up to 120 mg three times daily (dose is individualized)	40 mg twice daily, may titrate up to 240 mg once daily	60 mg once daily, may titrate up to 100 mg once daily or 60 mg twice daily
H. pylori eradication		Triple therapy: 40 mg once daily for 10 days (with amoxicillin and clarithromycin)	Triple therapy: 30 mg twice daily for 10-14 days (with amoxicillin and clarithromycin) Dual therapy: 30 mg three times daily for 14 days (with amoxicillin)	Triple therapy: 20 mg twice daily for 10 days (with amoxicillin and clarithromycin)[#] Dual therapy: 40 mg once daily for 14 days (with clarithromycin)[#]		Triple therapy: 20 mg twice daily for 7 days (with amoxicillin and clarithromycin)
Duodenal ulcer healing			15 mg once daily for 4 weeks	20 mg once daily for 4 weeks*		20 mg once daily up to 4 weeks*
Duodenal ulcer maintenance			15 mg once daily			
Benign gastric ulcer			30 mg once daily up to 8 weeks	40 mg once daily for 4-8 weeks		
Risk reduction of NSAID-associated gastric ulcer		20-40 mg once daily up to 6 months**	15 mg once daily up to 12 weeks			
Gastric ulcer - NSAID healing			30 mg once daily for 8 weeks			
Heartburn OTC treatment			15 mg once daily up to 14 days	20 mg once daily for 14 days, may repeat every 4 months		
GERD maintenance						20 mg once daily[@]

EE=erosive esophagitis; FDA=Food and Drug Administration; GERD=gastroesophageal reflux disease; *H. pylori*=*Helicobacter pylori*; NSAID=non-steroidal anti-inflammatory drug; OTC=over-the-counter.
[€]Table includes adult dosing only; [+]controlled studies did not extend beyond 6 months in adults and 16 weeks in patients 12-17 years of age; *additional 4-8 weeks may be necessary; **controlled studies did not extend beyond 6 months; ***additional 4 weeks may be necessary; ^additional 8 weeks may be necessary; [@]controlled studies did not extend beyond 12 months; [#]plus once daily for 18 days and 14 days if ulcer present for triple and dual therapy, respectively.

Indication-guided therapy

In a large observational study that assessed ambulatory visits, nearly two-thirds of PPI users lacked an indication for use.[8] In addition to identifying an appropriate indication, a key component of PPI therapy is evaluating an appropriate duration of use. Treatment guidelines and product labeling address duration which is dependent on the indication.[1,9-16] The American Gastroenterological Association (AGA) issued practice statements in 2022 regarding deprescribing of PPIs and defined short-term use as ≤8 weeks and long-term use as >8 weeks.[1] Other guidance does not specifically define short- and long-term use; recommendations for appropriate duration of treatment are based on the condition being treated (see Appendix).[10-16]

Conditions which typically require short-term use include dyspepsia, acute peptic ulcer disease, NSAID-related ulcer healing, nonerosive symptomatic GERD (not refractory GERD), *H. pylori* eradication, and stress ulcer prophylaxis (patients in intensive care unit with risk factors).[1-7,9-13,15] Discontinuation after symptom resolution in these conditions is usually appropriate. Long-term use is typically required for hypersecretory conditions (e.g., Zollinger-Ellison syndrome), maintenance treatment of erosive esophagitis (Los Angeles [LA] classification grades C/D), maintenance treatment of ulcers (including NSAID-related ulcers in higher risk patients), and gastroprotection in high-risk patients receiving aspirin/NSAIDs when the benefits outweigh the risks of continued therapy.[1-7,9,11,12,14,16,17] As part of a clinical practice update on deprescribing of PPIs, the AGA published guidance regarding appropriate PPI use; Figures 1 and 2 summarize this guidance.

Figure 1. Summary of indications for short- and long-term use of PPIs.[1]*

Indicated for short-term use (≤8 weeks)	Indicated for long-term use (>8 weeks)
• *H. pylori* eradication • Stress ulcer prophylaxis for ICU patients with risk factors • Uninvestigated GERD/dyspepsia • Treatment of NSAID-related gastric and duodenal peptic ulcers	• Barrett's esophagus • Clinically significant (LA grade C/D) erosive esophagitis • Esophageal strictures from GERD (i.e., peptic strictures) • Hypersecretory conditions (e.g., Zollinger-Ellison syndrome) • Gastroprotection in users of aspirin/NSAID at high risk for GI bleeding

GERD=gastroesophageal reflux disease; GI=gastrointestinal; *H. pylori=Helicobacter pylori*; ICU=intensive care unit; LA=Los Angeles; NSAID=non-steroidal anti-inflammatory drug; PPI=proton pump inhibitor.
*Note: additional definite and conditional indications for long- and short-term PPI use are listed in the 2022 AGA clinical practice update.

Figure 2. Summary of indications that **do not** support short- or long-term use of PPIs.[1]

Indications that do not support use of a PPI	Indications that do not support long-term use of a PPI
• Empiric treatment of laryngopharyngeal symptoms • Acute undifferentiated abdominal pain • Acute nausea and vomiting not believed to be related to GERD/esophagitis • Any isolated lower GI symptoms	• 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 aspirin/NSAID drug therapy • Prevention of recurrent upper GI bleeding from causes other than: peptic ulcer disease (including gastric and duodenal erosions), erosive esophagitis

GERD=gastroesophageal reflux disease; GI=gastrointestinal; NSAID=non-steroidal anti-inflammatory drug; PPI=proton pump inhibitor.

Deprescribing

Deprescribing refers to the practice of discontinuing or reducing the dose of medications when they cause harm or no longer provide benefit.[18] Continued use of a PPI without an ongoing indication or evidence of benefit contributes to increased pill burden, increased medication-related costs, and potential adverse effects.[1]

Long-term use of PPIs has raised safety concerns due to associations with conditions such as:[19-26]

- *Clostridium difficile* infection
- Pneumonia
- Fractures
- Dementia
- Chronic kidney disease
- Hypomagnesemia
- Vitamin B12 deficiency
- COVID-19

However, in a randomized controlled trial comparing PPIs with placebo, higher rates of adverse events among PPI users were not observed except for a possible increased risk of enteric infections.[27]

In addition to patient-specific factors, the decision to de-prescribe PPI therapy should consider whether patients have an appropriate indication rather than solely focusing on the concern for adverse events.[1]

Figure 3 summarizes statements developed by the AGA to provide guidance for deprescribing PPIs.

Figure 3. Guidance for deprescribing PPIs.[1,9,10]

Primary care providers should regularly review the ongoing indication for PPI use (prescription and over-the-counter) and document that indication. Reviews should also identify candidates for de-prescribing.

Conditions for which PPI continuation is indicated:

- Barrett's esophagus
- Erosive esophagitis (LA grade C or D)
- Esophageal ulcer
- Peptic stricture
- Elevated risk of upper GI bleed:
  - A history of upper GI bleed
  - Multiple antithrombotics (including both anticoagulant and antiplatelet agents)
  - Aspirin or NSAID therapy and 1 other risk factor:
    - older than 60 years
    - severe medical comorbidity
    - using second NSAID or aspirin
    - using an antithrombotic
    - using an oral corticosteroid

A trial of de-prescribing should be considered for all patients without a definitive indication for chronic PPI use.

Unintentional chronic PPI use is an area of concern (e.g., stress ulcer prophylaxis continued at discharge without an ongoing need).

Recommend de-prescribing

Base solely on the lack of an indication for PPI use, and not because of concern for PPI-associated adverse events.

Patients should be advised that they may develop transient upper GI symptoms due to RAHS.

Dose tapering regimen -or- **Discontinue abruptly**

Evidence does not support the superiority of any method.

Manage RAHS Symptoms

- Use as-needed over-the-counter antacids or histamine type-2 receptor antagonists.
- Alternatively, as-needed PPI therapy could be considered.

Lifestyle Modifications for GERD

- Sleep on left side.
- Sleep with head elevated.
- Eat smaller meals.
- Avoid trigger foods.
- If needed:
  - Weight loss
  - Smoking cessation

A step down to once-daily PPI dosing should be considered for most patients receiving twice-daily dosing for a chronic indication.

- Double-dose PPIs (either double-strength or twice daily) have not been studied in randomized controlled trials and are not FDA-approved (exception: Zollinger-Ellison syndrome).
- There is currently no evidence to support double-dose therapy over standard-dose PPIs for prevention of extension or progression to dysplasia or cancer in patients with Barrett's esophagus.
- For management of laryngopharyngeal symptoms, PPIs are ineffective at any dose.

Re-evaluate if severe persistent symptoms last for more than 2 months after stopping continuous PPI therapy.

FDA=Food and Drug Administration; GERD=gastroesophageal reflux disease; LA=Los Angeles; NSAID=non-steroidal anti-inflammatory drug; PPI=proton pump inhibitor; RAHS=rebound acid hypersecretion.

Symptoms of rebound acid hypersecretion (RAHS) may present a barrier to discontinuation of PPI therapy.[1] While the evidence does not support the superiority of any deprescribing method, a dose tapering regimen may be chosen to gradually reduce acid inhibition.

The dose tapering regimen may need to be adapted based on patient-specific factors, but as a general strategy:[28,29]

- Slowly taper off the PPI over 2-4 weeks.
- Reduce the dose by 50% with each step.
    - For example:
        - Twice daily → once daily
        - Once daily → every other day
        - Every other day → stop PPI
- Manage RAHS symptoms with as-needed antacids or histamine type-2 receptor antagonists.

Alternatively, the PPI may be discontinued abruptly.[1] As-needed antacids or histamine type-2 receptor antagonists may be used to manage RAHS symptoms with this method as well.

Conclusion

PPIs are effective for various indications, which should be routinely reviewed for evidence of benefit, appropriateness, and safety. The multidisciplinary team, including prescribers and pharmacists, plays an important role in the evidence-based use of PPIs.

Appendix: Guideline recommendations

Evidence-based guidelines have been published which address appropriate treatment for patients receiving PPI therapy. Guidelines from the American College of Gastroenterology (ACG), American Gastroenterological Association (AGA), and the Canadian Association of Gastroenterology (CAG) provide recommendations for the treatment of GERD,[10] dyspepsia,[13] Barrett's esophagus,[16] *H. pylori*,[13,15] NSAID-associated ulcers,[12] and upper gastrointestinal bleeding/ulcer bleeding.[11] Management of Zollinger-Ellison syndrome is discussed in the 2013 North American Neuroendocrine Tumor Society's (NANETS) consensus guidelines regarding management of neuroendocrine tumors.[14] Table A summarizes the guideline recommendations for these conditions including appropriate treatment and duration of use.

Table A. Guideline recommendations for PPIs.[10-16]

Indication	Drugs FDA-approved	Summary of guideline recommendations
GERD	Esomeprazole Dexlansoprazole Lansoprazole Omeprazole Rabeprazole	ACG guidelines (2022)[10] • Heartburn and regurgitation and no alarm symptoms: empiric 8-week trial of PPIs once daily before a meal (strong recommendation, moderate level of evidence); attempt discontinuation of PPI after trial unless patient has BE or EE (conditional recommendation, low level of evidence). If symptoms return, further evaluate patient (strong recommendation, low level of evidence) • Extraesophageal symptoms and typical GERD symptoms: twice-daily PPI therapy for 8-12 weeks (conditional recommendation, low level of evidence) • Refractory GERD: optimization of PPI therapy (strong recommendation, moderate level of evidence); patients who require maintenance treatment should be given the lowest effective dose (conditional recommendation, low quality of evidence) • LA Classification grades⁺ C or D esophagitis: indefinite maintenance treatment with a PPI or surgery is recommended (strong recommendation, moderate level of evidence)
Dyspepsia	Lansoprazole Omeprazole	ACG/CAG guidelines (2017)[13] • Asserts that PPI treatment should be discontinued if no longer providing a benefit and long-term use is not recommended without attempts to stop treatment every 6-12 months • Age <60 years with dyspepsia and *H. pylori* positive: empiric treatment of *H. pylori* is recommended (strong recommendation, high quality evidence) • Age <60 years with dyspepsia and *H. pylori* negative or remaining symptomatic after *H. pylori* eradication: empiric PPI treatment is recommended (strong recommendation, high quality evidence) • Age ≥60 years: an endoscopy is recommended to exclude upper GI neoplasia (conditional recommendation, very low quality of evidence) • Functional dyspepsia (no organic pathology) and *H. pylori* negative or symptomatic despite *H. pylori* eradication therapy: maintenance PPI therapy is recommended (strong recommendation, moderate quality of evidence)
Barrett's esophagus		ACG guidelines (2022)[16] • Esophagitis (LA Classification grades⁺ B, C, or D): 8-12 weeks of PPI therapy and a follow-up endoscopy to ensure healing (conditional recommendation, low level of evidence)* • Patients receiving chemoprevention with BE should receive once-daily PPI prevention, and twice-daily if necessitated by poor control of reflux symptoms or esophagitis (strong recommendation, moderate level of evidence)

Indication	Drugs FDA-approved	Summary of guideline recommendations
Peptic ulcer disease	Esomeprazole Lansoprazole	ACG upper GI and ulcer bleeding guidelines (2021)[11] • Bleeding ulcers treated with endoscopic hemostatic therapy: 3 days of high-dose continuous or intermittent PPI therapy (≥80 mg daily) (strong recommendation, moderate- to high-quality evidence); high-risk patients should continue twice-daily PPI treatment until 2 weeks after endoscopy (conditional recommendation, low quality of evidence) ACG NSAID-associated ulcer guidelines (2009)[12]: see NSAID-associated ulcers below AGA *H. pylori* guidelines (2021)[15] • Proper eradication is necessary to prevent PUD. Refer to guidelines below
Heliobacter pylori	Esomeprazole Lansoprazole Omeprazole Rabeprazole	AGA guidelines (2021)[15] • Standard dose PPI twice daily for 14 days along with any 1st or 2nd line therapy ACG/CAG guidelines (2017)[13] • In the event of 2 or greater treatment failures: PPI high-dose twice daily for 14 days may be used
NSAID-associated ulcers	Esomeprazole Lansoprazole	ACG NSAID-associated ulcer guidelines (2009)[12] • High-risk patients for NSAID GI toxicity (history of PUD and concurrent use of antiplatelets, anticoagulants, or corticosteroids) or >2 risk factors: co-therapy with a PPI or misoprostol is recommended (or treatment with a COX-2 inhibitor) • Moderate-risk patients (1-2 risk factors: age >65 years, high-dose NSAID, history of uncomplicated ulcer, concurrent use of aspirin, corticosteroids or anticoagulants): co-therapy with a PPI or misoprostol (or treatment with a COX-2 inhibitor) • Note: guidelines did not specify the duration of PPI therapy
Hypersecretory conditions (Zollinger-Ellison syndrome)	Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole	NANETS guidelines (2013)[14] • Excess gastrin secretions from gastrinoma: maintenance PPI 2-3 times daily • PPI product labeling does not specify a duration of treatment for this disorder, but consensus guidelines support chronic use due to the nature of the disease and possible complications when left untreated

AGA=American Gastroenterological Association; ACG=American College of Gastroenterology; BE=Barrett's esophagus; CAG=Canadian Association of Gastroenterology; COX-2=cyclooxygenase-2; EE=erosive esophagitis; GERD=gastroesophageal reflux disease; GI=gastrointestinal; *H. pylori*=*Helicobacter pylori*; LA=Los Angeles; NANETS=North American Neuroendocrine Tumor Society; NSAID=non-steroidal anti-inflammatory drug; PPI=proton pump inhibitor; PUD=peptic ulcer disease.
[+]LA Classification system of esophagitis: grade A: ≥1 mucosal break(s) no longer than 5 mm that does not extend between the tops of 2 mucosal folds; grade B: ≥1 mucosal break(s) >5 mm long that does not extend between the tops of 2 mucosal folds; grade C: ≥1 mucosal break(s) that is continuous between the tops of ≥2 mucosal folds but which involves <75% of the circumference; grade D: ≥1 mucosal break(s) which involves at least 75% of the esophageal circumference.[30]
*Double-dose PPI (twice standard dosing or twice daily dosing) can be used to decrease ongoing inflammation.
**Labeling for omeprazole states an additional 14 days of therapy when using dual therapy and an additional 18 days of therapy when using triple therapy for patients presenting with an ulcer.[5]

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