Neutralizing the Myths of Long-term PPIs
Neutralizing the Myths of Long-term PPIs
A VA Clinician’s Guide

VA Pharmacy Benefits Management Academic Detailing Service
Real Provider Resources
Real Patient Results
Your Partner in Enhancing Veteran Health Outcomes

This Educational Tool was developed for a pilot PPI Campaign

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Background

Proton pump inhibitors (PPIs) are often used beyond their original indication.

3% of Veterans with new diagnosis of gastroesophageal reflux disease (GERD) discontinued or de-escalated therapy after two years.¹

As many as half of PPI prescriptions written in primary care do not have an indication.²

41% of Veterans admitted for acute care did not have an indication for a PPI but the majority tolerated dose reduction or discontinuation.³

Clinical inertia drives many PPI prescription renewals.

As evidence emerges regarding the risks of long-term PPIs, careful evaluation of the need for continued PPI treatment is warranted.
Evidence of Harm in PPI Therapy

Table 1. Increased Risk Observed for Patients on PPI Therapy

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk vs. H2 Blocker Users</th>
<th>Risk vs. No PPI Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death – all cause(^4,5)</td>
<td>25%</td>
<td>15–68%</td>
</tr>
<tr>
<td>Death – cardiovascular(^6)</td>
<td>No difference</td>
<td>54%</td>
</tr>
<tr>
<td>Incident chronic kidney disease (CKD)(^7,8,9)</td>
<td>22–39%</td>
<td>36–76%</td>
</tr>
<tr>
<td>Death in CKD(^10)</td>
<td>--</td>
<td>39% all-cause mortality 51% cardiovascular-related mortality</td>
</tr>
<tr>
<td>Acute kidney injury (AKI)(^9)</td>
<td>--</td>
<td>44%</td>
</tr>
</tbody>
</table>

--- = not studied

**Infections** such as *Clostridium difficile* and pneumonia have been reported. Pneumonia has been associated with initiation of PPI. *C. difficile* diarrhea has been linked with recurrent infection.\(^11,12\)

**Micronutrient deficiencies**, especially for calcium, magnesium, iron, and vitamin B\(_{12}\), have been reported. No recommendations for supplementation have been established.\(^13\)

Despite previous reports of increased risk of **dementia** from PPI use, several large, national cohorts found no relationship between PPI use and dementia.\(^14,15,16,17\)

Recent cohort analysis from Kaiser and others have not found a positive association with long-term PPI use and hip **fracture**.\(^18\) Bone mineral density assessment in long-term PPI users (≥5 years) was no different than non-PPI users.\(^19\) However, the FDA Adverse Event Reporting System Data Mining Set, found PPIs are associated with fractures in multiple sites.\(^20\)

**Adverse outcomes in patients on PPIs** from observational studies raise concern of significant harm to Veterans prescribed PPIs. Despite concerns about research methods, experts recommend thoughtful evaluation regarding the need for continued therapy in patients prescribed long-term PPIs.
Benefits and Risks

Balancing the benefits and risks of PPI therapy in patients with gastroesophageal symptoms

Figure 1. Risks and Benefits of Long-term PPI Use

Table 2. Summary of Evidence Regarding the Risks of PPI Therapy

<table>
<thead>
<tr>
<th>Risk</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium difficile</em> diarrhea (recurrent)</td>
<td>X Probable</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>— Possible</td>
</tr>
<tr>
<td>Micronutrient deficiencies</td>
<td>— Possible</td>
</tr>
<tr>
<td>Chronic kidney disease (CKD)</td>
<td>— Possible</td>
</tr>
<tr>
<td>Death in CKD</td>
<td>— Possible</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>— Possible</td>
</tr>
<tr>
<td>Cardiovascular (CV) mortality</td>
<td>O Unclear</td>
</tr>
<tr>
<td>Dementia</td>
<td>O Unclear</td>
</tr>
<tr>
<td>Fracture</td>
<td>O Unclear</td>
</tr>
</tbody>
</table>

Red – Probable association with PPI therapy  Yellow – Possible association with PPI therapy  White – Unclear association
Identifying Veterans without Indications for Chronic PPI Use

*Who should continue a PPI long-term?*

Although most patients will not need long-term PPI, some patients may benefit due to underlying issues.

**Figure 2. Continuing Use of PPI's**

<table>
<thead>
<tr>
<th>Patients with a History of:</th>
<th>Patients Regularly Taking NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Eosinophilic esophagitis</td>
<td></td>
</tr>
<tr>
<td>- Erosive esophagitis</td>
<td></td>
</tr>
<tr>
<td>- Esophageal ulcer</td>
<td></td>
</tr>
<tr>
<td>- Esophageal stenosis/stricture</td>
<td></td>
</tr>
<tr>
<td>- Dysphagia (other than oropharyngeal)</td>
<td></td>
</tr>
<tr>
<td>- Pancreatic enzyme replacement</td>
<td></td>
</tr>
<tr>
<td>- Gastric or duodenal ulcer</td>
<td></td>
</tr>
<tr>
<td>- Barrett’s esophagus</td>
<td></td>
</tr>
<tr>
<td>- Zollinger-Ellison Syndrome</td>
<td></td>
</tr>
<tr>
<td>- Idiopathic pulmonary fibrosis</td>
<td></td>
</tr>
</tbody>
</table>

**OR**

**NSAID users meeting *any* of the following criteria:**
- >65 years of age
- Take a 2nd NSAID
- Take daily aspirin
- Take an anti-thrombotic drug
- Take an oral steroid

**Low-dose aspirin users meeting *any* of the following criteria:**
- ≥60 years of age
- Take NSAIDs regularly
- Take an anti-thrombotic drug
- Take an oral steroid

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If none of the above are met, taper and/or discontinue PPI use
Using PPIs for Chronic NSAIDs Users

Low Dose Aspirin Therapy

NSAID therapy, including low dose aspirin, is associated with increased risk of major bleeding events for many older adults.  

Co-prescribing a PPI in these patients can prevent a major GI bleed. In a prospective cohort of older adults taking low dose aspirin for secondary prevention of vascular events, 21 of the oldest adults had to be treated with a PPI to prevent one case of GI bleeding.  

PPI co-prescribing did not change the risk of major cardiovascular outcomes in patients on low dose aspirin compared to those not on concomitant PPIs.  

Re-evaluate the need for continued low dose aspirin or chronic NSAID therapy based on latest evidence before adding a PPI.  

In older adults on NSAIDs, including low dose aspirin, the benefits of co-prescribing PPIs outweigh the risks of adverse effects.
Discontinuing or Tapering PPI Therapy

Taper when possible and aim to discontinue the PPI

Figure 3. Recommended PPI Tapering Schedule

After decreasing a Veteran’s prescription from twice daily to once daily, work with the Veteran to decrease their dose further.

Consider keeping them on once daily dosing for 30 days before decreasing their dose to every other day.

After consultation with the patient, determine the best time to discontinue the PPI.

Alternative agents may be used in place of the PPI such as an H2 blocker.

If twice daily PPI use (except Zollinger Ellison Syndrome)
Reduce frequency to once daily. Progression to next taper step determined by provider.

If once daily PPI use
Reduce frequency to every other day for two to four weeks

Stop PPI use
Prescribe an H2 blocker (e.g., famotidine 10–20 mg twice daily prn) with refills

Patients should be cautioned that they may have rebound symptoms for a few weeks after discontinuation.

Short-course therapy, typically 4–12 weeks:

- Veterans completing a short-course of PPI at a daily dose should stop their PPI. Tapering is not required.
- If dose escalation was required to address symptoms, reduce the dose to daily for 4 weeks, then discontinue.

Only a minority of patients will require daily maintenance PPI therapy to provide acceptable symptom relief.
Interventions to Address GI Symptoms

Remind patients of the lifestyle modifications that can reduce symptoms

**Do**
- Lose weight, if overweight or recent weight gain.
- Elevate the head of the bed.
- Wait 2–3 hours after a meal before going to bed.

**Limit**
- Consuming alcohol.
- Smoking.
- Foods that trigger symptoms, e.g., caffeine, chocolate, spicy foods.

Keep in mind some medications worsen GI symptoms:
- Antibiotics, like tetracycline and clindamycin
- NSAIDs
- Dabigatran
- Potassium chloride
- Iron supplements
- Bisphosphonates
- Calcium channel blockers, e.g., nifedipine
- Opioids
- Assess indication for medication
- Instruct Veteran to follow administration instructions, taking with a full glass of water to reduce GI irritation.

**PPIs for Symptomatic Relief**
- Yes: Prescribe PPI once daily for 8 weeks. No one PPI is more effective than another.
- Yes: Instruct Veteran to take 30–60 minutes before the morning meal.
- Yes: If partial response, increase PPI frequency to twice daily.
**Acid Lowering Therapy Options:**

All Available without a Prescription

**Medication options**

Three main classes are used for acid suppression:

1. Antacids, such as calcium carbonate, aluminum and magnesium hydroxide
2. H2 blockers, such as famotidine
3. PPIs

*A key difference between acid suppression medications is the onset of symptom relief.*

**Figure 4. Time needed for acid suppressing drugs to provide symptom relief**

![Figure 4](image)

**Management after PPI de-prescribing**

Options for managing recurrence of symptoms include:

- Intermittent courses of once daily PPI for 4 weeks
- On-demand therapy, where patient takes PPIs as determined based on symptoms and response.

However, H2 blockers and antacids are an effective and short time-to-onset of symptom relief option for patients with infrequent (two times per week or less) symptoms.

Only a minority of patients with require daily maintenance PPI therapy to provide acceptable symptom relief.
Referring Veterans for Further Evaluation

Refer Veterans for further evaluation if they have:

✓ presence of any ‘red flag’ features at presentation or throughout treatment

   Red flag features include:
   • Hematemesis
   • Blood in stool
   • Anemia
   • Previous GI malignancy or ulcer
   • Recurrent vomiting
   • Anorexia or unexplained weight loss
   • Early satiety
   • Abdominal mass
   • Hepatomegaly

✓ inadequate symptom relief after a short-course of PPI therapy that included a dose escalation

✓ ongoing symptoms despite long-term PPI therapy that have not had an endoscopy.
Key Messages

- Proton pump inhibitors are often used beyond their recommended duration of therapy.

- Prolonged PPI use can lead to harm. The risks of adverse effects may outweigh the chance of benefit, especially if the prolonged reason for using a PPI is unknown.

- In older adults with an indication for low dose aspirin or chronic NSAID therapy, co-prescribing PPIs outweighs the risk of adverse effects.

- Lifestyle modifications are recommended to reduce or eliminate GI-related symptoms.

- Unless a patient is indicated for chronic PPI therapy, PPIs should be prescribed for short term use (4 to 12 weeks) to treat GERD related symptoms.

- For patients who have been taking PPIs for an extended duration and do not have a clear indication, deprescribing their dose utilizing a taper strategy has been successful.

- Management after PPI deprescribing may require on-demand therapy. Only a minority of GERD patients will require daily maintenance PPI therapy. Consider referral for further evaluation for refractory patients.


These are general recommendations only. For specific recommendations on policies and procedures, please identify and contact the facility point of contact for additional information.

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This reference guide was created as a tool for VA providers and is available from the Academic Detailing Service SharePoint.

These are general recommendations only. The treating provider should make clinical decisions based on an individual patient’s clinical condition.

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