Proton Pump Inhibitors: Appropriate Use and Safety Concerns

Proton pump inhibitors make up more than half of the gastrointestinal drug market, and are estimated to cost Americans 11 billion dollars each year. However, data suggest that only one-third of PPI use is appropriate. This misuse can have both negative financial and health-related consequences. Studies have shown there are risks associated with chronic use, and occasionally even short-term use, of PPIs. Treatment guidelines, such as those for gastroesophageal reflux disease, help tease out appropriate use of these drugs based on the latest evidence for their benefits and risks. This chart discusses the appropriate use of PPIs along with the safety concerns associated with them.

**Abbreviations:** ADMA = asymmetric dimethylarginine; BMD = bone mineral density; COX-2 = cyclooxygenase-2; CKD = chronic kidney disease; CV = cardiovascular; GERD = gastroesophageal reflux disease; GI = gastrointestinal; ICU = intensive care unit; IM = intramuscular; INR = international normalized ratio; MI = myocardial infarction; NSAID = non-steroidal anti-inflammatory drug; OTC = over-the-counter; PPI = proton pump inhibitor.

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| Which conditions are appropriate for short-term PPI use?| **GERD**  
  - Recommend an initial eight-week course of therapy with a PPI.  
  - For patients that require more long-term therapy, recommend a trial of a lower dose, on-demand therapy, or intermittent therapy to minimize exposure.  

  **Gastric and duodenal ulcers**  
  - Recommend FDA- and Health Canada-approved regimens for ulcer healing, these typically last four to eight weeks.  

  **H. pylori**  
  - Recommend first-line PPI-containing regimens, in the U.S. and Canada.  
  - See our PL Chart, *H. Pylori Treatment Regimens for Adults*, for more information on specific regimens.  

  **Stress ulcer prophylaxis**  
  - Reserve stress ulcer prophylaxis with PPIs for ICU patients with at least one of the following:  
    - Coagulopathy (platelet count <50,000 mm³, INR >1.5, or aPTT >2 times control)  
    - Mechanical ventilation for >48 hours  
    - History of GI ulceration or bleeding within one year of admission  
    - Glasgow Coma score ≤10 |

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| Short-term PPI use, continued                         | • Thermal injury to >35% of body surface area  
• Partial hepatectomy  
• Multiple trauma  
• Transplantation perioperatively in the ICU  
• Spinal cord injury  
• Hepatic failure  
• Two or more of the following risk factors:  
  • Sepsis  
  • ICU stay of more than one week  
  • Occult bleeding lasting at least six days  
  • High-dose corticosteroids (>250 mg/day of hydrocortisone)  
  • Recommend discontinuation at discharge, unless there is another indication for use.  

Which conditions may require long-term PPI therapy?  

Refractory GERD  
• Consider GERD refractory in patients not responding to PPI therapy after two to three months.  
• Suggest adding a bedtime dose of an H2-blocker, especially for nighttime symptoms.  
• Consider switching to another PPI, doubling the dose, or adding metoclopramide for non-responders.  

Erosive esophagitis  
• Consider maintenance PPI therapy with continued symptoms after an eight-week trial of PPI.  
• The dose and length of therapy is determined by the severity of disease and the specific PPI being used.  
• Recommend using the lowest effective dose, including on-demand or intermittent therapy during maintenance therapy.  

Zollinger-Ellison Syndrome  
• Higher doses are often necessary initially; recommend reducing the dose as gastric output decreases.  
• Suggest using symptom control (e.g., pain, diarrhea) to guide dosage titrations, when gastric output volumes are not an option.  
• Recommend using the lowest effective dose.  

NSAID-induced ulcers  
• Consider use in patients taking NSAIDs that have another risk factor for GI bleeding (e.g., older age; concomitant use of a corticosteroid, anticoagulant, or antiplatelet agent).  
• In patients with a previous ulcer, PPI use with an NSAID reduces the incidence of recurrent bleeding by 4% to 6% over a six-month period.  
• Recommend PPIs for patients with a history of an ulcer who also require an NSAID.  

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| Conditions requiring long-term PPI therapy, continued                            | • PPI use with COX-2 inhibitors decreases recurrent bleeds by almost 9% over one year, compared to COX-2 inhibitors alone.  
• Recommend PPIs with a COX-2 inhibitor instead of a traditional NSAID, for patients with a GI bleed history.  
**Chronic anticoagulation after a GI bleed**  
• Recommend PPIs for patients on anticoagulants after an upper GI bleed.  
**Barrett’s esophagus**  
• Recommend once-daily treatment with a PPI.  
• Reserve twice-daily dosing for patients with poor control on once-daily PPI therapy.                                                                                                                                                                                                                       |
| Should H2-blockers and PPIs be taken together?                                   | • Nighttime acid secretion is primarily mediated by histamine.  
• Nighttime acid breakthrough occurs in over 70% of patients taking twice-daily PPI therapy.  
• Consider adding a bedtime H2-blocker to PPI therapy, especially for nighttime control.  
• Data is lacking on any benefit of administering PPIs and H2-blockers at the same time.                                                                                                                                                                                                                  |
| What are significant drug interactions associated with PPIs?                      | • PPIs inhibit CYP2C19 in varying degrees (e.g., esomeprazole and omeprazole are moderate inhibitors).  
• Consider H2-blockers as an alternative to avoid CYP2C19 interactions when acid suppression is needed.  
  • H2-blockers are not as effective in preventing GI bleeding.  
  • Avoid changing to cimetidine, as it also inhibits CYP2C19.  
• PPIs can increase concentrations of some medications to toxic levels, by decreasing their metabolism. See our PL Chart, Cytochrome P450 Drug Interactions, for more information.  
• U.S. and Canadian product labeling recommend avoiding the use of clopidogrel with strong or moderate CYP2C19 inhibitors, such as omeprazole.  
• GERD guidelines state there is not an increase of CV events in patients using clopidogrel with a PPI.  
• For specifics, see PL Detail-Document, Proton Pump Inhibitor and Plavix Interaction: An Update.  
• PPIs can reduce effectiveness of medications requiring an acidic pH for absorption (e.g., atazanavir).  
  • Recommend screening for interactions if starting a PPI in a patient taking critical or narrow therapeutic index medications.  
• Absorption of calcium, iron, and vitamin B12 may be reduced during PPI therapy. Most patients will not require additional replacement, especially if PPI use is short-term.  
• If supplemental administration is needed:  
  • Recommend calcium citrate, as its absorption is less affected by GI pH.  
  • Consider administering vitamin B12 by intranasal or IM routes.  
  • Consider administering iron intravenously.                                                                                                                                                                                                                                                                  |
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| Is hypomagnesemia associated with PPI therapy? | • Magnesium absorption can also be reduced with PPI therapy, especially with long-term use.28  
   • Low magnesium levels can occur three months into PPI therapy, but risk is higher after a year.27,28  
   • Symptoms of low magnesium include muscle cramps, heart palpitations, dizziness, tremors, or seizures.28  
   • Normal serum magnesium levels vary by lab but are typically 1.8 to 2.3 mg/dL (1.5 to 1.9 mEq/L).31  
   • Recognize concomitant medications that can lower magnesium levels (e.g., thiazides, loop diuretics).  
   • Monitor with concomitant digoxin, as digoxin toxicity can occur with low magnesium levels.48  
   • Consider checking levels during long-term therapy, especially those taking digoxin or on diuretics.28  
   • ICD-10 code (E43.82) may be required for reimbursement, as magnesium isn’t included in standard electrolyte panels.29  
   • Consider checking a baseline magnesium level for patients requiring long-term PPI therapy.28  
   • Recommend OTC magnesium supplements (e.g., Slow-Mag, MagOx) to treat low levels.30  
   • Magnesium levels won’t always improve in patients taking a PPI. Consider replacing PPI with an H2-blocker if magnesium levels don’t improve with supplementation.30  
   • Recommend IV magnesium supplementation if magnesium is less than 1.2 mg/dL (1 mEq/L) or in symptomatic patients.30  
   • For more information on the management of hypomagnesemia, see our PL Detail-Document, Treating Magnesium Deficiency and our PL Chart, Comparison of Oral Magnesium Salts.                                                                                                                                 |
| Do PPIs cause rebound hypersecretion?        | • Rebound hypersecretion can occur in a significant number of patients taking PPIs for at least two months.  
   • Degree of rebound hypersecretion is directly related to gastrin levels and duration of PPI use.47  
   • Symptoms of rebound hypersecretion may last three months or more, and can lead to inappropriate continued use of PPIs.72  
   • Consider tapering PPIs to successfully discontinue and limit hypersecretion.46  
   • Recommend reducing the dose, if not at the minimum dose per day.  
   • Extend the dosing interval to every other day and possibly every third day for a week or longer.  
   • Recommend antacids or H2-blockers as needed for breakthrough symptoms after PPI discontinuation.17,46  
| What do you do with PPI therapy at transitions of care? | • PPIs are often used inappropriately in the hospitalized patient.55,56  
   • Recommend reevaluating PPI indications at transitions of care as an opportunity to eliminate unnecessary therapy.14,54  

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| Is there an association between PPI use and asthma?                  | • Asthma and gastroesophageal reflux disease often co-exist. 19  
• Patients with asthma may be prone to asymptomatic reflux disease. 19  
• PPIs have been shown to provide no benefit compared to placebo in managing asthma symptoms. 18  
• Avoid PPIs in patients with asthma, unless they have an appropriate indication. 19  |
| Is there an association between PPI use and pneumonia?               | • Even short-term use (under one week) may increase the incidence of infections. 32  
• Ensure PPIs have a clear indication in hospitalized patients, especially those at risk for pneumonia (e.g., elderly, chronic lung disease, patients taking immunosuppressants). 32  
  • Hospitalized patients on mechanical ventilators while taking a PPI are at greatest risk of developing hospital-acquired gram-negative pneumonia. 32  
  • One additional case of hospital-acquired pneumonia was seen for every 111 non-ICU patients treated with a PPI for at least three days. 33  
• The evidence is not as strong linking PPIs with community-acquired pneumonia. 58  
  • One extra case of community-acquired pneumonia for every 226 patients treated with a PPI for five months. 34  
  • Meta-analysis found that PPIs do not increase the risk of hospitalization for community-acquired pneumonia. 44  
  • Analysis of pooled patient data from 24 randomized controlled trials concluded that there was no causal association between treatment with esomeprazole and a higher risk of community-acquired pneumonia over 180 days. 45  |
| Is there an association between PPI use and *Clostridium difficile* infections? | • PPI use may also lead to an increase in *C. difficile* infections and diarrhea. 11  
• For every 533 patients receiving a daily PPI in the hospital, at least one will develop *C. difficile*. 35  
• Patients being treated for *C. difficile* while taking a PPI are at a 42% increased risk of having a recurrent infection within 90 days. 11,36  
• Per Health Canada, though a firm cause and effect relationship between PPIs and *C. difficile* has not been confirmed, the possibility is still there. 67  
• Ensure PPIs have a clear indication to limit risk of *C. difficile*. 11  
• Use H2-blockers as alternative to PPIs, as they increase the risk of *C. difficile* to a lesser extent. 37  |
| Is there an association between PPI use and fractures?                | • PPI use has been associated with a 25% increase in overall fractures and a 47% increase in spinal fractures in postmenopausal women [Evidence level B; epidemiologic study]. 5  
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| PPIs and fractures, continued | • Approximately 2000 Canadian females would need to be treated with a PPI for one year to cause one additional fracture.\(^{65}\)  
• Taking high doses and/or long-term therapy have been reported to increase the incidence of hip, wrist, or spine fractures.\(^{3,43}\)  
• PPIs probably don’t increase fracture risk when used short-term in low doses.\(^{20}\)  
• Data suggest that PPIs do not increase the risk of osteoporosis and that the risk of hip fracture is only increased in patients with at least one other risk factor for hip fracture.\(^{8}\)  
• PPIs have not been shown to have a conclusive relationship with BMD.\(^{6}\)  
• Recommend PPIs for approved indications without concern for impact on BMD or risk for fractures, unless patients have other risk factors for hip fracture.\(^{8}\)  
• Encourage calcium citrate and vitamin D supplementation in PPI patients at risk for osteoporosis.\(^{20}\)  
• Per the FDA and Health Canada, use the lowest effective dose, for the shortest time period to minimize fracture risk.\(^{20,66}\) |
| Is there an association between PPI use and gastric or colon cancer? | • Evidence does not support an increased incidence of cancer in patients on PPIs.\(^{21}\) |
| Is there an association between PPI use and cardiovascular events? | • In 2007, the FDA concluded that there was no relationship between PPIs and adverse cardiac events.\(^{38}\)  
• In 2015, a data mining study found there MAY be an association of PPI exposure with risk for MI in the general population.\(^{41}\)  
• A proposed mechanism is that PPIs might lead to increased plasma levels of ADMA and decreased levels of nitrous oxide.\(^{40}\)  
• Elevated ADMA is associated with an increased risk of CV disease.\(^{40}\)  
• Randomized clinical trials do NOT show an increased risk for MI with PPI use.\(^{42}\)  
• A causal relationship between PPIs and cardiovascular events has not been firmly established.\(^{42}\)  
• Recommend ensuring PPIs have a clear indication and using the lowest effective dose. |
| Is there an association between PPI use and dementia? | • PPI use may be associated with an increased risk of dementia [Evidence level B, clinical cohort study].\(^{59}\)  
• Additional studies are needed to evaluate this association, assess if there is a causal relationship, and identify the mechanism.\(^{60}\)  
• Possible mechanisms proposed for this association include effects on amyloid and neurologic damage secondary to vitamin B12 deficiency, since PPIs may reduce vitamin B12 absorption.\(^{59,60}\)  
• Recommend H2-blockers, if these effectively control patient symptoms.  
• If PPIs are required, recommend ensuring they have a clear indication and using the lowest effective dose. |
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<td>Is there an association between PPIs and CKD?</td>
<td>• PPI use may be associated with a slight increased risk of CKD. Additional studies are needed to evaluate this association, assess if PPIs have a causal relationship, and identify the mechanism. H2-blockers have not been shown to have an association with CKD. Recommend H2-blockers, if these effectively control patient symptoms. If PPIs are required, recommend ensuring they have a clear indication and using the lowest effective dose.</td>
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<td>Is there evidence to support on-demand dosing with PPIs?</td>
<td>• On-demand dosing involves starting therapy when symptoms begin and stopping therapy when symptoms resolve. PPIs are not approved for on-demand dosing, but patients still use them this way with good results. Patient satisfaction is sometimes improved with on-demand dosing compared to daily regimens. Consider on-demand dosing for non-erosive GERD and mild erosive esophagitis.</td>
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<td>How should self-medication with OTC PPIs be addressed?</td>
<td>• PPIs are heavily advertised and readily available OTC. Encourage the following non-pharmacologic/lifestyle management first-line for GERD symptoms: Elevating head of the bed six inches Avoiding meals two to three hours before bedtime Weight loss, if appropriate Smoking cessation Psychological stress reduction, if necessary Ensure adequate sleep (limited data exists) Recommend limiting duration of self-medication to 14 days per treatment, and no more than three treatments per year. Encourage patients to contact their prescriber if longer therapy is necessary. Provide our PL Patient Education Handout, What You Should Know About Proton Pump Inhibitors, to teach patients how to take their PPIs correctly.</td>
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Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.
Levels of Evidence
In accordance with the trend towards Evidence-Based Medicine, we are citing the LEVEL OF EVIDENCE for the statements we publish.

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<td>High-quality meta-analysis (quantitative systematic review)</td>
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<td>Nonrandomized clinical trial</td>
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Project Leader in preparation of this PL Detail-Document: Beth Bryant, PharmD, BCPS

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