



**Outpatient use of Proton Pump Inhibitors
Clinical Practice Guideline
December 2017**

“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 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, including:^{1, 2, 3,4,5,6, 8}

- increased risk of fracture*
- increased risk for community-acquired pneumonia*
- increased risk for re-infarction or re-hospitalization in patients with CAD taking clopidogrel and a PPI¹⁰ concomitantly. Controversial per UptoDate.
- increased risk for iron deficiency
- increased risk for enteric infections, specifically *Clostridium difficile* colitis*
- kidney disease*
- vitamin B-12 deficiency*
- hypomagnesemia*
- cardiovascular risk*
- fundic gland polyps**
- gastric cancer***
- colon cancer*
- dementia*
- mortality

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Eusebi, et. al.⁸, reviewed the evidence for many of these associated risks noted by the * on the list above 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.

A recent edition of the Medical Letter⁹ also 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 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 March 2017, the American Gastroenterological Association 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.

Ten recommendations for Best Practice were made in the article for the long term use of PPIs:

Best Practice Advice 1: Patients with GERD and acid-related complications (ie, 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

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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 (eg, 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.

In addition, patients with Zollinger Ellison Syndrome should be on long term PPI’s.

UpToDate is by and large in agreement with the AGA and the Eusebi et al review article except that UpToDate recommends laboratory screening for magnesium where testing is suggested for patients with additional risks, eg, on diuretics. UpToDate also suggests annual B-12 levels be done.

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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.

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