



## A Patient Guide to Proton Pump Inhibitors

Learn the facts about PPIs and find out why they are among the safest of all acid-suppressive medications.

### PPI Safety: The Short Answers

- PPIs are among the safest of all medications, both prescription and non-prescription, with millions of people having taken PPIs, often for decades, without ill effects.
- Only a very small minority of long-term PPI users may develop vitamin, mineral or electrolyte deficiencies, and these deficiencies are easily correctable.
- There is no evidence that PPI use accelerates bone mineral loss.
- There is no link between chronic PPI use and cancer.
- Recent data suggesting a link between PPI use and diseases such as dementia or chronic kidney disease are weak and inconclusive. Further prospective clinical trials are required to investigate these hypotheses.
- PPI use does not increase the risk of cardiac death in patients taking Plavix for severe coronary artery disease, but PPIs do lower the risk for upper gastrointestinal bleeding if taken with aspirin and Plavix.
- If you have been prescribed PPIs for any reason, ask your gastroenterologist if the medication is necessary, and, if so, if you need to take it daily.
- Help yourself. Remember: losing weight, improving your diet and eating habits and avoiding nicotine products may cure or at least substantially improve your acid reflux, making acid-suppressive medications unnecessary.

### PPIs: Known Benefits, Possible Risks

Proton pump inhibitors (PPIs) are an important class of acid-suppressive medications and are one of the most commonly prescribed medications in the United States. PPIs have earned a reputation worldwide in the medical community as safe and effective drugs, even when used over the long term, which, for many patients, has meant years or even decades of uninterrupted use. Omeprazole, the first PPI, was introduced in human clinical trials in the U.S. in 1982 and was released in Europe in 1989 and in the U.S. in 1990. Hence, given the widespread use of PPIs for decades, physicians and the scientific community in general have observed the effects of these potent acid-blockers over many billions of patient-years of experience.

The depth and breadth of this experience has created a well-deserved sense of safety among physicians and the general public in prescribing and using PPIs, so much so that the FDA made Prilosec (omeprazole) available OTC in 2003 and other PPIs have since followed suit.

For a number of years, PPIs have been known to be associated in a relatively small subset of patients with minor, easily correctable side effects such as mild iron or Vitamin B12 deficiency or, more recently, magnesium deficiency. In the past decade, the question was raised by the results of observational (retrospective) studies as to whether PPIs may cause lowered bone mineral density (osteoporosis) and an increased risk of low trauma bony fractures, particularly of the hip and spine. As well, similar “look back” studies suggested a modestly increased risk of *C. difficile* colitis, a common intestinal infection, in PPI users. Similarly, results of initial studies suggesting that PPI users have a higher risk of both community-acquired and hospital- or healthcare-associated pneumonia could not be corroborated by subsequent studies.

Upon review of all available safety data in 2008, the American Gastroenterology Association Institute (AGAI) found insufficient evidence to either recommend or discourage routine bone densitometry, calcium supplementation, *H. pylori* screening, or any other routine precaution in long-term PPI users. That said, pending updated recommendations from the AGAI, your physician may make individualized recommendations for monitoring or supplementation. For instance, iron and Vitamin B12 absorption may be diminished in some, albeit usually to a mild degree, but your doctor may recommend periodic monitoring, perhaps annually in some cases, and prescribe supplementation if warranted. As well, low magnesium levels may occur in some individuals, particularly after five or more years of continuous PPI use. Your physician may recommend checking your magnesium level if you have taken PPIs for many years or if you already take medications known to cause hypomagnesemia, such as diuretics or certain anti-rejection medications in organ transplant recipients or if you take digoxin for a cardiac arrhythmia.

The FDA recognizes that there may be an association between long-term PPI use and an increased risk for low trauma bony fractures, such as fractures of the hip and spine, and suggests that the lowest effective dose be used only as long as necessary. However, there is no evidence that long-term PPI use accelerates bone mineral density loss (osteopenia or osteoporosis). Clinical studies suggest that bone fractures in PPI users primarily occur in persons already at risk, such as cigarette smokers. If you have risk factors for osteoporosis, such as a strong family history, chronic cigarette use, low body weight, long-term prednisone usage, a history of a previous low trauma fracture or excessive alcohol use, your primary doctor may wish to monitor your bone density periodically and recommend preventative calcium and Vitamin D supplements or other appropriate therapies if bone mineral loss is discovered. Remember that stopping smoking, drinking alcohol in moderation and performing regular weight-bearing exercises will both strengthen your bones and reduce your acid reflux.

There is no scientific evidence suggesting that long-term PPI use causes cancer of any type in humans. *H. pylori*, a bacteria that lives in the lining of the stomach, is the most common chronic bacterial infection in humans with conservative estimates suggesting that half the world’s population is infected including many in the United States. *H. pylori* infection remains asymptomatic in the vast majority of people, occasionally causes peptic ulcers (particularly in those who take chronic aspirin or NSAID therapy), usually has no impact on acid reflux symptoms or GERD treatment and is only rarely associated with the development of cancer in the stomach. Thus, most experts do not believe that testing for *H. pylori* is essential in all long-term PPI users.

Recently, results of a few observational studies on PPI side effects have been widely reported in the popular media. The results suggest that long-term PPI use may cause serious diseases, specifically chronic kidney disease, dementia and cardiovascular events like heart attacks. Great care must be taken in interpreting the results of these studies by virtue of their intrinsic design limitations. Retrospective studies “look back” at previous study results or population data bases and, by definition, have inherent weaknesses that do not allow scientists and clinicians to determine cause and effect between the medical intervention examined (for example, a surgical procedure or a specific medication) and a specific outcome like a symptom, side effect, disease state or even death. Observational studies often contain unknown or unrecorded confounding factors within the population of patients being studied that may introduce “residual bias,” even after careful statistical adjustment by the researchers and statisticians, that can weaken or even invalidate the studies’ conclusions. Moreover, the size of the effects demonstrated in the recent studies in question are small (the “Odds Ratio” or “Hazard Ratio” is less than 1.5 in the dementia and kidney disease studies), making it even more difficult to determine whether the association is real or, in fact, due to a residual bias. That said, even a small effect can be important, particularly when the medication in question is so widely used both in prescription and non-prescription form. Definitive randomized and prospective clinical trials are clearly necessary to accurately answer these important questions.

An important prospective study in people with symptomatic coronary artery disease who also take PPIs reassures us that PPIs not only do not counteract the benefit of strong blood-thinning anti-platelet medications like clopidogrel (Plavix), but PPIs also decrease the risk of dangerous upper gastrointestinal bleeding in those taking both aspirin and prescription anti-platelet medications like Effient, Brilinta or Plavix.

Nonetheless, it is well established that PPIs can cause an acute kidney disease known as AIN (acute interstitial nephritis). AIN, however, is rare. A large Mayo Clinic study found, over almost 20 years, only seven cases per year of AIN and only one case per year attributable to PPIs. The majority of cases were caused by other medications, particularly antibiotics and NSAIDs. In most cases, AIN causes acute symptoms that prompt people to seek medical attention, such as malaise, bilateral flank pain, vomiting and lowered urine output. Moreover, AIN is treatable with prompt drug discontinuation and is most often reversible. Currently the American College of Gastroenterology and the American Gastroenterology Association do not advocate for or against routine monitoring of kidney function in PPI users. Nevertheless, if you have risk factors for kidney disease such as hypertension, diabetes, use of diuretics or ACEIs, cardiovascular disease or advanced age, your physician may recommend periodic monitoring of renal function.

These studies remind us of the importance, as with any medication, of making certain that it has been prescribed for an appropriate indication and at the lowest effective dose. Studies reveal that almost one third of PPI users do not have an appropriate medical indication and three quarters of patients continued on PPIs after prescription in a hospital do not need them. Certain conditions, like GERD or dyspepsia, if uncomplicated by esophageal strictures (scar tissue) or Barrett’s Esophagus with dysplasia (an uncommon condition which may lead to esophageal cancer) and if well-controlled on daily PPI therapy, may be amenable to intermittent, two-to-four-week courses of PPIs or even “on demand” therapy with OTC H<sub>2</sub>-blockers (e.g., ranitidine or famotidine) or PPIs. For infrequent reflux, occurring once a week or less, OTC antacids containing calcium, magnesium or aluminum may suffice. In uncomplicated GERD, the risk of developing clinically important esophageal erosions, strictures or Barrett’s Esophagus with non-daily or episodic PPI use is minimal according to studies. Patients with Barrett’s who do not experience daily reflux

symptoms may wish to discuss with their gastroenterologist whether continuing daily PPI use is necessary, as the benefit in risk reduction for esophageal cancer over decades of PPI therapy is relatively low (about 1% - 2%) as is the risk of developing a serious PPI side effect.

However, it is critical that people at "high risk" for peptic ulcers or any gastrointestinal bleeding continue with daily PPI therapy as prescribed. "High risk" individuals are those on antiplatelet medications (like Plavix/ clopidogrel, Effient, Brilinta or aspirin at any dose) or NSAIDs (prescription or non-prescription) who have a history of ulcers or GI bleeding, who also take Coumadin/warfarin or corticosteroids (like prednisone), or who are over 60 years of age. As well, people with coronary artery disease who take two antiplatelet drugs (most commonly aspirin and clopidogrel) but do not have any "high risk" factors may also benefit from daily PPI use though at their doctor's discretion.

If you take daily PPIs and your doctor determines that daily therapy is not required, he or she will recommend a tapering schedule to allow you to achieve the lowest effective dose or even to discontinue scheduled PPI use, if appropriate. Tapering is necessary in order to avoid a common phenomenon known as "rebound hyperacidity," which commonly occurs in people who take either PPIs or H2-blockers for long periods, usually months or longer, and then abruptly discontinue the medication. The "rebound" phenomenon may cause an unpleasant but temporary worsening of reflux symptoms that can last for as long as two weeks.

Importantly, after discussion with your physician, should you decide to decrease or discontinue your PPI use yet still experience acid reflux symptoms, better adherence to anti-reflux lifestyle modifications may provide added symptom relief. These measures include weight loss (if overweight), elevation of the head of the bed with 6" blocks or placement of a wedge-pillow under the mattress and avoidance of eating within three hours of retiring (if experiencing nocturnal reflux or irritative throat symptoms due to GERD), smoking/ nicotine cessation and avoidance of identifiable triggers (such as caffeine, alcohol, chocolate and spicy or fatty foods, to name a few).

We at Austin Gastroenterology strive to provide our patients with safe, effective and up-to-date care for their digestive disorders. We pledge to keep our patients abreast of definitive future study results regarding PPI safety when they become available.

*- Dr. Glenn Robinson, Austin Gastroenterology*