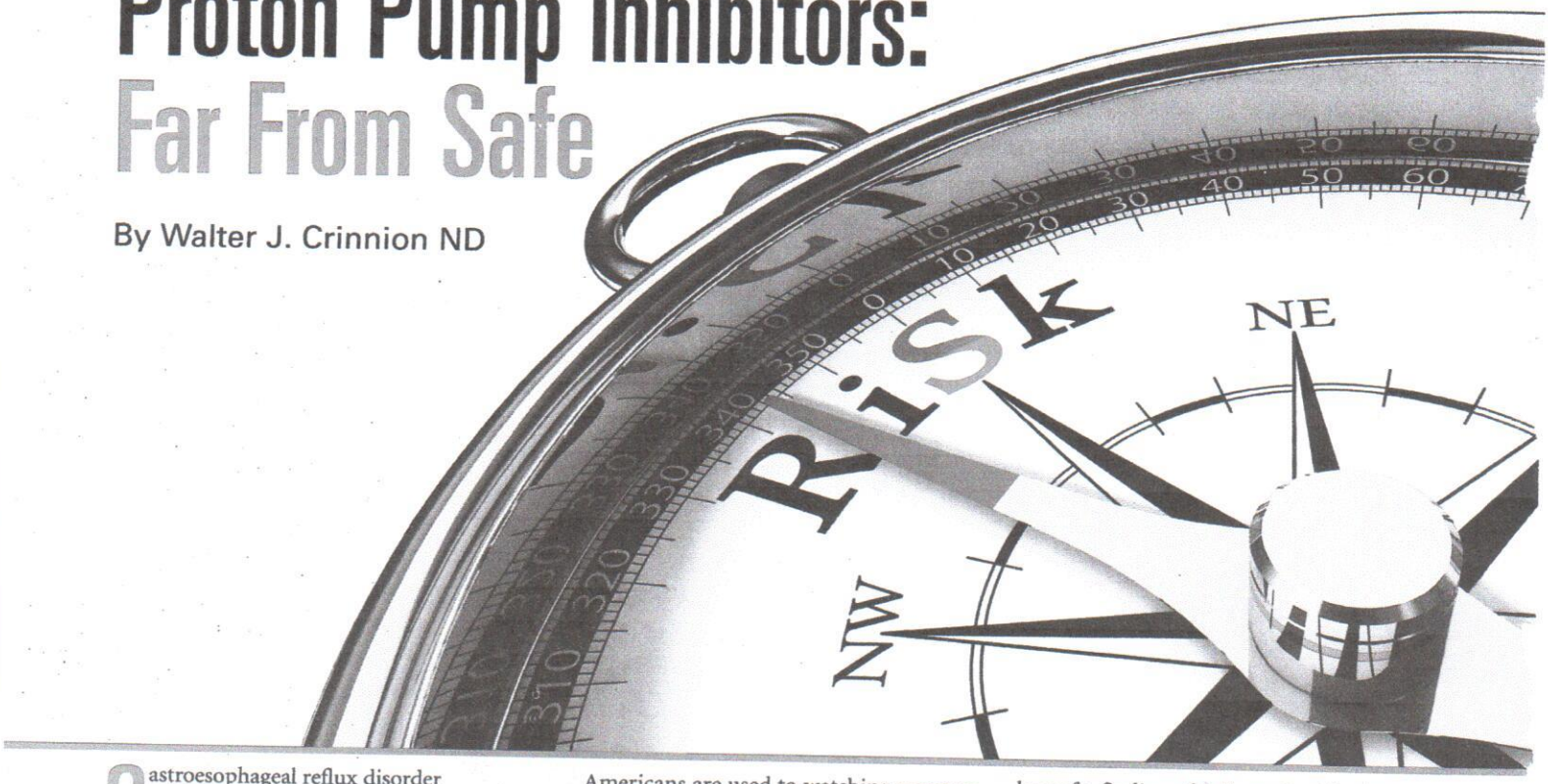
Proton Pump Inhibitors: Far From Safe

By Walter J. Crinnion ND



Gastroesophageal reflux disorder (GERD), or heartburn, is the most common digestive disorder in our society. It resulted in more than 157 million prescriptions being written for proton pump inhibitors (PPIs) in 2012 alone. PPIs act on the parietal cells in the stomach preventing the production of both hydrochloric acid (HCL) and intrinsic factor. In addition to those millions of persons who sought (and paid for) medical care for this problem, others simply purchased PPIs, or their histamine 2 blocker cousins, over-the-counter (OTC) without having a doctor's visit. Total sales of PPI/H2 blockers to reduce stomach acid production totaled $9.5 billion in 2012, with Nexium accounting for $6 billion of those sales.[1]

PPIs were originally approved for short-term use in cases of GERD. Now, they are being recommended for long-term treatment in persons of all ages who have or are at risk for heartburn. They are also recommended for the treatment of acute upper gastrointestinal bleeding, Barrett's esophagitis, dyspepsia (ironic, since this is often due to insufficient stomach acid production), eosinophilic esophagitis, *Helicobacter pylori* infections, peptic esophageal strictures, peptic ulcer disease and Zollinger-Ellison syndrome.[2]

Americans are used to watching commercials for pharmaceutical drugs that contain warnings listing the various problems that could befall them. Yet, we don't even need to see our doctor to get a prescription, so surely these PPI medications must be totally safe, right? The truth is they are frighteningly far from safe.

Warnings

The U.S. Food and Drug Administration (FDA) has a webpage devoted to notices on the adverse effects of PPIs.[3] Amongst the warnings, it states the increased risk for PPI users of acquiring a *Clostridium difficile* overgrowth while also taking broad-spectrum antibiotics (especially in the elderly) that results in chronic, watery diarrhea and can lead to death. The FDA also warns that PPI use (for a minimum of three months) will result in overt magnesium deficiency manifesting as: seizures, tetany, tremors, spasm, atrial fibrillation, supraventricular tachycardia, abnormal QT intervals and parathyroid dysfunction resulting in low calcium levels.[4] [It should be noted that these are not the typical cases of magnesium deficiency that naturopathic physicians and nutritionists work with all the time. This is an MD-recognized, insurance-reimbursed state of magnesium depletion (the equivalent of a finding of pellagra, beri-beri or scurvy) requiring intravenous replacement of magnesium and hospitalization.] Another FDA warning is about the increased risk of hip, wrist and spine fractures after taking PPIs for a year.[5] Further, the FDA noted that persons taking clopidogrel bisulfate (marketed as Plavix) to prevent clot formation would have the effect of this medication negated by PPIs.[6,7]

In addition to these FDA warnings, several other serious health problems have been linked to PPI use in the medical literature. Persons using PPIs had a 39 percent greater risk of developing community-acquired pneumonia than those not on PPIs.[8] Those persons using "high dose" PPIs had a 50 percent greater risk of getting pneumonia, the most common killer of hospitalized individuals over the age of 50.

Another study showed that persons over the age of 65 who were released from acute care hospitals were 50 percent more likely to die within a year if they were on PPI therapy[9], and those on high dose PPI therapy they were 159 percent more likely to die in that year. This study was published in *JAMA Internal Medicine* in 2013 and included the following statement: "... physicians need to use caution and balance benefits and harms in long-term prescrip-

tion of high-dose PPIs."

Another study looked at almost 20,000 patients who survived their first heart attack and were put on aspirin therapy to prevent a recurrence. At the end of a year, only 17 percent had experienced another heart attack, stroke or cardiovascular death. But those who were on aspirin and PPIs had a 46-61 percent greater risk for being one of the ones who died! Unfortunately, the concurrent use of aspirin and PPI is not a coincidence—PPIs are regularly prescribed to persons using daily aspirin to prevent aspirin-induced peptic ulcer disease. Those who did not die while taking PPIs typically did experience increases in morbidity; one common complaint being an increase in weight gain among PPI users.[10]

More alarmingly, two studies on animal models have suggested that PPIs increase the production of amyloid (beta peptides in the brain), the hallmark sign of Alzheimer's disease.[11,12]

Disturbing Deficiency

Another far-reaching effect of PPI use is the development of vitamin B12 deficiency, what was once viewed as a problem solely for long-term vegetarians.

The proper functioning of parietal cells is critical for the absorption of vitamin B12. The secretion of gastric HCL is necessary for the cleavage of B12 from dietary protein, while the intrinsic factor is critical for B12 absorption. According to Guyton's *Textbook of Medical Physiology*, without HCL, only 1/50 of the available B12 is absorbed. As a person ages, their HCL secretion diminishes and with it, their appetite, meal portion size and ability to both release and absorb protein-bound B12. Atrophic gastritis, typically associated with achlorhydria, is commonly found in persons over the age of 65. These classic age-related declines in HCL production, along with the presence of *H. pylori* (that also causes hypochlorhydria), are already noted to lead to B12 deficiency.[13]

Depending upon the amount of vitamin B12 stored in the liver, deficiency symptoms may be masked for a period of months to years. In 2004, a study of individuals over the age of 65 showed that those who took PPIs for more than two years were 345 percent more likely to be deficient in vitamin B12.[14] In this study actual blood levels of B12 were measured in the participants, with a serum B12 level of <130pg/mL being considered low. Persons with B12 levels between 130-300 pg/mL were also considered low if they also showed the functional B12 deficiency markers of elevated methylmalonic acid or homocysteine.

A recent study in *JAMA* also found that PPI use was associated with B12 deficiency.[15] This was a much larger study of almost 26,000 patients in the Kaiser Permanente insurance group. Unfortunately, B12 deficiency was defined in this patient records review study by having a prescription for supplemental B12. No blood tests were used to actually measure B12 levels (or functional deficiency markers) as in the previous study, which naturally biases the study toward fewer cases of B12 deficiency, typically the most blatant. But even so, those Kaiser Pemanente members who were on PPIs for two or more years were 65 percent more likely to have overt B12 deficiency. Interestingly, the Kaiser study, which looked at anyone over the age of 18, noted that younger persons who had been on PPIs for at least two years were 712 percent more likely than their peers to have B12 deficiency.

The problem is that while some B12 deficiencies are fixed by taking more B12, some of the most serious complications appear to be irreversible[16], such as the neurologic problems. The neurologic syndrome of B12 deficiency includes behavior, mood, cognitive functional and structural changes.[17] Irreversible spinal cord abnormalities are detectible in a high percentage of these cases, along with changes in the brain and optic nerve. Paresthesias, cognitive defects, depression, anxiety, obsessive behaviors are also seen along with muscular weakness and spasticity.[18] Further, memory impairment is common, as is the diagnosis of dementia, especially in elderly. One must always keep B12 deficiency in mind in any older patient with these manifestations, but especially if they are on PPIs.

Conclusion

Indeed, "… physicians need to use caution and balance benefits and harms in long-term prescription of high-dose PPIs."[9]

While PPIs could reduce the symptoms of GERD, even this benefit comes with a caveat: all PPIs do not appear to reduce the potential incidence of esophageal carcinoma that can occur because of GERD.[19]

Compare this to the potential harms:

- B12 deficiency
- Magnesium deficiency
- Inability to use Plavix
- Increased risk of Clostridia infection
- Increased risk of pneumonia
- Increased risk of death after hospitalization
- Increased weight gain
- Increased risk for Alzheimer's

How does this weigh out?

The truth is, GERD/heartburn are easily reversed by avoiding alcohol, reducing weight, reducing meal portion size and even walking after dinner.[20-22] For those who do not want to make these simple changes, a variety of digestive supplements are available that work quite nicely to reverse and prevent the signs and symptoms of GERD.

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