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Long Term PPI Use and Associated Complications

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Do I take a Proton Pump Inhibitor (PPI)?

Currently, physicians are prescribing proton pump inhibitors (PPIs) to treat patients for a variety of diseases or symptoms. PPIs are commonly used to treat heartburn, ulcers or gastroesophageal reflux disease (GERD). GERD is a condition where stomach contents leak back into the esophagus causing

irritation, heartburn and other symptoms. PPIs work by inhibiting the proton pump in parietal cells (the cells that create stomach acid). As a result of this inhibition, the amount of stomach acid produced is decreased. PPIs are available in both prescription and over the counter (OTC) formulations, mak-

ing them increasingly accessible and commonly misused. For many people, the use of a PPI, especially long term use, is not necessary and may promote unwanted side effects. For other patients, such as those with Scleroderma, the utility of PPI therapy vastly outweighs the side effect associated risks.

| Available as Prescription Only | |
|--------------------------------|---------------------------|
| Brand Name | Generic Name |
| Protonix® | Pantoprazole |
| Nexium® | Esomeprazole |
| Vimovo® | Esomeprazole and Naproxen |
| Dexilant® | Dexlansoprazole |
| Aciphex® | Rabeprazole |

| Available Over the Counter | |
|----------------------------|-----------------------------------|
| Brand Name | Generic Name |
| Prilosec® | Omeprazole |
| Zegerid® | Omeprazole and Sodium Bicarbonate |
| Prevacid® | Lansoprazole |

What is Long-Term Use?

– PPIs have a variety of Food and Drug Administration (FDA) labeled indications, most of which call for a short course of therapy. Self-treatment for Gastroesophageal Reflux Disease (GERD) with over the counter (OTC) PPI therapy is only recommended for 2 weeks. Conversely, when prescribed by a physician, PPIs may be utilized for long-term use if the benefit outweighs the risk. Although there is no definitive answer as to what qualifies as long-term therapy, multiple sources have identified 1 year as the cut off between short and long-term therapy. For certain disease states, such as scleroderma, long term PPI therapy is recommended in order to avoid the complications associated with gastric reflux.

Common Side Effects of PPIs

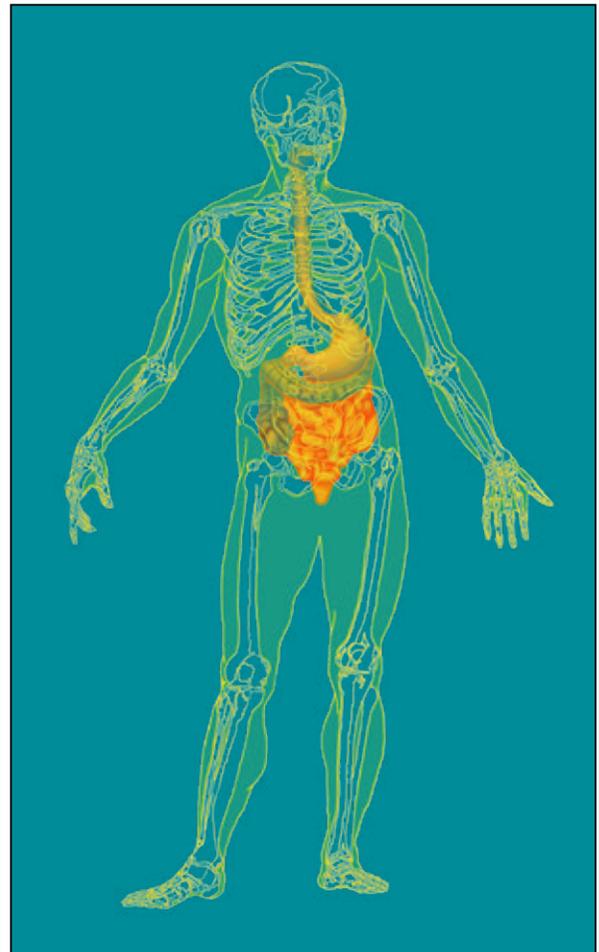
– Side effects most commonly associated with PPI use include headache, nausea, vomiting, diarrhea, dizziness, rash, anemia and arthralgias; but are generally well tolerated.

– Side effects less commonly seen include alopecia, upper respiratory tract infection, increased liver enzymes, abnormal vision and hypomagnesemia (low magnesium levels).

What are Potential Conditions PPIs can Effect?

– Recently, PPIs have gained negative publicity for the risks associated with their long-term use. Through years of clinical experience, drug studies and increased awareness to the possibility of side effects, PPIs have been associated with effects on: vitamin/mineral absorption, increased risk of bone fractures, pneumonia, enteric infections, *Clostridium difficile* associated diarrhea and the formation of gastric polyps. **The goal of disclosing these possible side effects is not to deter patients**

from using these products, but to better educate individuals on the safety and appropriate use of these medications.



Decreased Absorption of Important Vitamins/Minerals

- **Calcium.** PPIs affect the body's ability to absorb calcium from the diet, as well as from calcium supplements. By lowering the stomach acid levels, the ability to digest the calcium and adequately absorb it into the body is decreased. Once your blood calcium levels are low, the body will attempt to correct this imbalance in the only way it can, by taking it from the bones. The longer the body is low on calcium, the more calcium will be removed from the bone. This chain of events can lead to osteoporosis and bone fractures. Studies have found a link between long term PPI use and the risk of hip fractures. Studies also show a correlation between higher dosages, and longer duration of use towards overall increased fracture risk.^{1,2,3}
 - Calcium Citrate is the best option for calcium supplementation for patients currently on a PPI. Calcium citrate does not require an acidic environment to absorb the calcium in the digestive tract, while calcium carbonate does require stomach acid.
- **Vitamin B12** is necessary for proper red blood cell formation, neurological function, and DNA synthesis. It is also an essential factor in metabolism of fats and proteins. In order for the body to absorb vitamin B12, gastric acid is needed to release the B12 from food. There is also an association of decreased absorption in elderly populations. Therefore, patients utilizing long-term PPIs and/or elderly populations will have decreased absorption of B12 from food sources.^{1,3,4} To reduce the likelihood of low levels of B12, it is recommended to take B12 supplements or ingest B12 fortified foods to counteract malabsorption. Side effects associated with low

It is very important to read product labels. From this Citrical® label it can be seen that each serving (2 tablets) is only 500 mg of elemental calcium. Therefore to get the recommended daily amount of calcium, at least 4 tablets should be taken every day.

Supplement Foods

Serving Size: 2 tablets

Servings Per Container: (Net Qty Contents/Serving Size [# tablets])

| | Amount Per Serving | % Daily Value |
|---------------------|--------------------|---------------|
| Vitamin D | 400 IU | 100% |
| Calcium (elemental) | 500 mg | 50% |
| Sodium | 5 mg | < 1% |

vitamin B12 levels include anemia, fatigue, weakness, constipation, loss of appetite and weight loss.⁶ To prevent the development of these side effects, it is important to have B12 levels monitored when on long term PPI therapy.

- Low B12 levels may require supplementation with oral tablets, sublingual tablets or fortified foods. If B12 levels do not normalize with oral supplementation, vitamin B12 is available as a monthly injection that bypasses gastrointestinal absorption.
- **Iron** is an important part of many proteins and enzymes that maintain good health. In addition it is an essential component of oxygen transport in the blood. Iron digestion and absorption can be affected by PPI usage. Like other vitamins and minerals, iron (specifically non-heme iron, 66% of iron found in food), has markedly decreased absorption in the

absence of gastric acid. The terms heme and non-heme, describe if the iron is derived from hemoglobin (the protein involved in oxygen transport). Heme iron is found in animal foods that originally contained hemoglobin, while non-heme iron comes from plant foods. Patients undergoing long term suppression of gastric acid may be at risk for low iron levels so it is important to have your iron levels monitored.^{1,3}

- According to studies, the absorption of iron bis-glycine is not associated with decreased absorption with changes in gastric pH.⁴ Iron-bisglycine is available in products known as Ferrochels, and Hemagenics. Also, the possibility of iron by injection is available for patients not able to tolerate oral supplementation. Always consult with your doctor or pharmacist before starting a new medication.



– **Magnesium** is an important mineral in the body used to maintain normal muscle and nerve function, and heart rhythm. In addition, magnesium supports the immune system and improves bone stability. Although rare, PPIs have been linked with states of hypomagnesemia (low magnesium levels), but the mechanism is unknown at this time. Theories suggest that PPI-induced hypomagnesemia is likely due to gastrointestinal magnesium loss. Symptoms of hypomagnesemia include fatigue, unsteadiness, paresthesia, tetany, cardiac arrhythmias, so it is important to monitor patients' magnesium level with prolonged use of PPIs.³

- If you are experiencing low magnesium levels, your physician may advise you to take a magnesium supplement in order to counteract the magnesium loss in the stomach. Always consult with your doctor or pharmacist before starting a new medication.

PPI Associated Pneumonia

– Pneumonia is a breathing condition caused by a bacterial infection of the lung. It is an unpleasant condition that affects millions of people each year and includes symptoms of cough, fever, shaking chills and shortness of breath. Patients who use PPIs are at an increased risk for pneumonia and other upper respiratory tract infections.¹ PPI use can lead to an increase in bacterial colonization of the stomach due to a less acidic environment. In addition, PPI use may be associated with pulmonary micro-aspiration and lung colonization. In other words, during ventilation, materials from the gastrointestinal tract can enter the lungs and be deposited. Therefore, patients using PPIs have more bacterial colonization leading to an increased risk of bacteria entering the respiratory tract.

- To prevent bacteria from entering the lungs, prop the bed up at night or sleep with multiple pillows to elevate the upper portion of your body. This will prevent both heartburn and gastric acid from entering the lungs. Also, there are multiple ways to prevent pneumonia including washing your hands before eating and preparing foods, smoking cessation, and being vaccinated. Always consult with your doctor or pharmacist about the need for a vaccination.

Enteric Infections

- Enteric infections are defined as an infection of the intestinal tract and present with diarrhea, abdominal discomfort, nausea, vomiting and anorexia. Patients may be more susceptible to cholera and species of *Shigella* and *Salmonella* while under PPI therapy due to small bowel bacterial overgrowth. This increased risk can be attributed to the gastric acid suppression due to PPI therapy. Normally, gastric acid would destroy the majority of ingested bacteria and prevent infection. Only a few cases of infections in patients taking PPIs have been reported and a variety of case studies argue against this risk.¹
 - Even with conflicting evidence there are still recommendations to avoid such infections. Taking extra care in making sure food is not spoiled or contaminated. Practicing not only proper hygiene, but proper kitchen hygiene (cleaning surfaces and utensils after contact with raw meats). Avoiding sick or infected individuals and frequent hand washing are all ways to avoid enteric infections.

Growth of Gastric Bacteria

- *Clostridium difficile* (*C.diff*) can cause life-threatening cases of diarrhea and conditions like colitis and inflammation of the lining of the colon. PPIs can decrease the

stomach acid and thus increase the growth of bacteria. By making the stomach less acidic, PPIs may leave the door open for infections that may not have taken hold if the acid levels had been “normal.”² Recently in February 2012, the FDA added a special alert to the drug monographs of PPIs to include a possible increased risk of *C. diff*-associated diarrhea. It is reported that there is an estimated 1.4 to 2.75 fold increased risk of developing *C.diff*-associated diarrhea. Risk factors and most reported cases include elderly patients, chronic or underlying conditions, simultaneous use of broad-spectrum antibiotics (amoxicillin, ciprofloxacin, levofloxacin).⁷

- It is recommended to contact your physician if patients experience persistent watery stools, bloody diarrhea, abdominal pain/tenderness, nausea, loss of appetite, or fever while taking PPIs. It is also advised to use the lowest dose for the shortest duration.⁷

Gastric Polyps

- Gastric polyps are masses of cells that form on the inside lining of the stomach and are considered rare. Gastric polyps are typically asymptomatic and very rarely progress to cancerous tissue. One risk factor for developing gastric polyps is the long term use of PPIs; as there has been an increased incidence of polyps in recent years due to increased usage of PPIs. This is because when parietal cells (acid producing cells) are suppressed by PPIs, hyperplasia (increase in the number of cells) can occur in a time dependent manner. In other words, the body will create more cells because the previous cells are not producing acid. Majority of polyps may not require treatment; treatment is usually indicated only if polyps are cancerous or larger than 1cm. Antral polyposis is often attributed to

Helicobacter pylori (*H. pylori*) infection, which has a decreased incidence since the widespread use of PPIs. However, it is not guaranteed that antral polyposis and *H. pylori* are seen together. PPI usage has been associated with a 4 fold increased risk of developing benign gastric polyps. Typically when PPIs are stopped for a period of months, gastric polyps will dissipate.⁵

Drug Interactions

- PPIs, like any other drug, can interact with other drug therapies you may be taking. Although an interaction may exist, it may still be safe for you to take the combination together. Talk to your pharmacist about the risk of combining these therapies.
 - PPIs may increase the effects of: amphetamines (Adderall), aripiprazole (Abilify), benzodiazepines (Xanax, Valium, Ativan), carvedilol (Coreg), cilostazol (Pletal), citalopram (Celexa), escitalopram (Lexapro), cyclosporine (Neoral, SandIMMUNE), dexamethylphenidate (Focalin), fluconazole (Diflucan), phenytoin (Dilantin), methotrexate (Rheumatrex), pimozide (Orap), raltegravir (Isentress), saquinavir (Invirase), tacrolimus (Prograf), vitamin K antagonists (Coumadin, warfarin), voriconazole (VFEND).
 - PPIs may decrease the effects of: atazanavir (Reyataz), bisphosphonates (Fosamax, Boniva, Actonel), cefditoren (Spectracef), clopidogrel (Plavix), clozapine (Clozaril), dabigatran (Pradaxa), dasatinib (Sprycel), delavirdine (Rescriptor), erlotinib (Tarceva), gefitinib (Iressa), indinavir (Crixivan), iron salts (ferrous sulfate, ferrous gluconate, ferrous fumarate, Iron), itraconazole (Sporanox), mesalamine (Asacol), mycophenolate (CellCept), nelfinavir (Viracept), posaconazole (Noxafil), rilpivirine (Edurant), tipranavir (Aptivus), vismodegib (Erivedge).



Are Other Antacids/Acid Suppressants Safe?

- Other over the counter products work to lower the amount of acid produced by the body to fight GERD, heartburn, ulcers, etc. These antacid products include Tums, Maalox, Gaviscon, Mylanta, Pepto-Bismol and Roloids. Another class of acid suppressing drugs are Histamine H₂-receptor antagonists (H₂RA) which include Pepcid (famotidine), Zantac (ranitidine), Tagamet (cimetidine) and Axid (nizatidine). In contrast to PPIs, antacids only temporarily neutralize stomach acid and similarly H₂RAs limit acid secretion to a lesser degree than PPIs. Due to their lower degree of acid suppression or neutralizing, these drugs do not show the same long term effects as PPIs when considering osteoporosis, decreased mineral bioavailability or gastric polyps.

What should I do?

- Discuss with your doctor your symptoms and overall need for a PPI instead of alternative treatments with over the counter antacids and acid suppressants. Although there are issues with long term use, PPIs are an effective and beneficial treatment for a variety of indications. Patients and prescribers must always weigh the risk vs. benefit of medication use, as with all medications. Increased awareness of the possible side effects and precautions is important to help

minimize these unwanted effects. Your healthcare professionals are aware of these conditions and under their supervision, undesired side effects can be avoided. If patients are indicated for the long term use of PPIs, following the above advice can help reduce possible adverse effects associated with this class of medication.

Why am I taking a PPI for the treatment of Scleroderma?

- In Scleroderma, esophageal dysfunction can lead to severe complications if not treated effectively. Normally, the lower esophageal sphincter, or valve, acts as a gate between the stomach and esophagus which opens to allow food to enter the stomach and then closes promptly to prevent food from coming back up. In systemic scleroderma, the gate does not close properly and the result is a backwash of acid and a burning sensation (heartburn) as food and acid return into the esophagus. The acid may also injure the lining of the lower portion of the esophagus, causing scarring and a narrowing (stricture) of the tube. The addition of PPI therapy can decrease the risk of scarring and stricture formation. The benefit of using PPIs outweighs the risks associated with PPI use. In general, the side effects associated with long-term PPI therapy can be prevented with proper monitoring by your provider.

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The Scleroderma Foundation's mission is three-fold:

- ☞ To help patients and their families cope with scleroderma through mutual support programs, peer counseling, physician referrals, and educational information.
- ☞ To promote public awareness and education through patient and health professional seminars, literature, and publicity campaigns.
- ☞ To stimulate and support research to improve treatment and ultimately find the cause and cure of scleroderma and related diseases.



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