CONNECTICUT MEDICAL ASSISTANCE PROGRAM DEPARTMENT OF SOCIAL SERVICES & HEALTH INFORMATION DESIGNS

Connecticut Medical Assistance Program Quarterly Newsletter

Proton pump inhibitors (PPIs) are the most potent inhibitors of gastric acid secretion on the market today. They are a class of medications used to treat disorders such as erosive esophagitis (EE), symptomatic gastroesophageal reflux disorder (GERD), duodenal and gastric ulcers, eradication of *Helicobacter pylori (H. pylori)* infection, pathological hypersecretory conditions such as Zollinger-Ellison syndrome (ZES), and prevention of NSAID related GI ulcers.[1] Most FDA approved indications recommend short term use of PPIs, generally 4-8 weeks of treatment, however, many Americans go on to receive chronic PPI therapy without an appropriate diagnosis. Off label use and inappropriate treatment length is pervasive in the US with more than half of patients receiving PPI therapy without an appropriate indication.[2]

Indications for short term (4-8 weeks) PPI use include but may not be limited to:[1]

- Healing of erosive esophagitis (EE)
- Treatment of gastroesophageal reflux disease (GERD)
- *Helicobacter pylori (H. pylori)* eradication (in combination with antibiotics)
- Short-term treatment of duodenal ulcers
- Short-term treatment of gastric ulcers

Indications for long term (> 12 week) PPI use include but may not be limited to:[3]

- Severe esophagitis (LA grade C or D)
- Barrett's esophagus
- Documented history of bleeding GI ulcer
- Chronic NSAID use with bleeding risk factors
- Zollinger-Ellison syndrome

Not all PPIs are approved for the same indications. The dose and length of therapy depend on the indication and the PPI being prescribed. For more information regarding indication, dosing, and length of therapy, the Centers for Medicare and Medicaid (CMS) has provided a reference document and links to prescribing guidelines.

PPIs are a widely used class of medication at the national and state level. During 2019, PPIs were the 7th most used class of medications within the Connecticut Medical Assistance Program population, accounting for 250,459 prescriptions filled for 65,709 unique recipients, resulting in approximately 9% of the CT Medicaid population receiving a PPI at some point during 2019. It is estimated that 1 in 10 ambulatory care patients within the US have documented use of a PPI.[4] Additional estimates show that 40-55% of primary care patients and up to 65% of hospitalized patients have no documented indication for PPI use.[2,5,6,7] Taking a closer look at the Connecticut Medical Assistance Program population, of the 65,709 patients who received a PPI during 2019, 23,622 patients (36%) had no diagnosis to support use.

There are 6 PPIs approved for use in the US (table 1), 3 of which are available OTC (over-the-counter).[8] Omeprazole was the first PPI to become available in the US in 1989, followed by 5 additional medications in the class. All PPIs currently on the US market have similar chemical structures, containing both a pyridine and benzimidazole ring, and have similar half-lives of approximately 1-2 hours.[8]

Because of their short half-life, it is recommended that PPIs are dosed preprandial. PPIs pass through the upper and mid GI tract and are absorbed in the proximal small bowel. After absorption, they circulate to activated gastric parietal cells. A single dose of a PPI can inhibit about two-thirds of H+/K+ ATPase (proton pumps) which in turn inhibits acid secretion. To counteract the inhibition of the active H+/K+ ATPase pumps, the body attempts to produce more pumps, which can take up to 36 hours. PPIs are effective at inhibiting the remaining one-third uninhibited pumps and other newly generated pumps when multiday treatment is used.[8]

Table 1 Proton Pump Inhibitors Available in the United States[8]

Drug	Dosages (mg)	IV	Liquid or suspension	Generic	Over the counter
Omeprazole	10, 20, 40	Yes	No	Yes	Yes
Esomeprazole	20, 40	Yes	Yes	Yes	Yes
Lansoprazole	15, 30	Yes	Yes	Yes	Yes
Dexlansoprazole	30, 60	No	No	No	No
Pantoprazole	20, 40	Yes	Yes	Yes	No
Rabeprazole	20	No	No	Yes	No

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PPIs are metabolized primarily through the hepatic P450 cytochrome system. Omeprazole and esomeprazole (stereoisomer of omeprazole) are almost exclusively metabolized by CYP2C19, therefore having the most drug-drug interactions when compared to other medications in the class. The FDA recommends avoiding the concurrent use of omeprazole and clopidogrel due to inhibition of clopidogrel activation from its prodrug form, potentially decreasing its antiplatelet effect.[9,10] Rabeprazole, lansoprazole, and dexlansoprazole (stereoisomer of lansoprazole) are metabolized by CYP2C19 and CYP3A4, having less drug-drug interactions due to multiple metabolic pathways. Pantoprazole, which has the least potential for drug-drug interactions, is metabolized via 2C19 O-demethylation and sulfate conjugation.[8]

PPIs are associated with a phenomenon known as Rebound Acid Hypersecretion (RAHS). RAHS has been shown to occur after just 8 weeks of PPI therapy and occurs when the medication is discontinued. RAHS can prompt a restart of the PPI in order to treat rebound symptoms, even if the underlying need for the PPI (GERD, ulcer) has been resolved. This can perpetuate inappropriate use of PPIs. Therefore, if RAHS is suspected, it is not recommended to restart PPI therapy.[11,12]

Generally, PPIs are considered safe with relatively few side effects. This, in part, may have prompted the widespread use of PPIs seen today. The initial safety profile observed has been questioned with more chronic and long term use now being practiced. The drug class effect of blocking acid secretion and creating a hypoacidic environment is integral to treating indicated disease. In the short term, this effect can help heal damage to the stomach or esophageal lining, but when used long term , PPI induced chronic hypoacidic environment is not natural and consequences of this state are not yet completely understood. Most studies reviewing long term effects of chronic acid suppression are observational epidemiological studies that are too short to capture the magnitude of consequences that may take decades to develop. Using epidemiological studies to show consequence can also be weak because of potential confounding variables.[13] While the gold standard for studies has remained randomized controlled trials (RCTs), studying long term, often rare side effects of medications can be a difficult with RCT. This would require a large number of patients to be enrolled and followed for an extended time period which is often better evaluated from an observational or retrospective study.[14]

Although rare and not fully understood, there are associated risks with chronic long term use of PPIs, some of which are detailed below.

Impaired Absorption of Micronutrients

Reports show that daily PPI therapy for greater than 3 years can impact the absorption of cyanocobalamin (Vitamin B_{12}). Side effects from this deficiency can include peripheral neuropathy and cognitive impairment. The proposed mechanism is that the hypoacidic environment causes a decrease in absorption of dietary B_{12}.[15] It is not currently recommended to obtain B_{12} levels or supplement intake for patients receiving chronic PPI therapy.[16]

Magnesium is the fourth most abundant intracellular ion in the human body. Normal magnesium levels fall between 1.7 – 2.2 mg/dL. Normal magnesium levels help to decrease inflammation, platelet aggregation and cardiac arrhythmias but when levels fall below 1.7 mg/dL, patients can risk experiencing arrhythmias, seizures, and tetany.[17,18] The first reported case of PPI associated hypomagnesemia occurred in 2006 with other case reports to follow.[19] This prompted the FDA (Food and Drug Administrations) to release a warning in 2011 regarding the potential of PPIs to increase the risk of hypomagnesemia when used long term (longer than 1 year) and recommends a magnesium level be obtained prior to initiating long term PPI therapy.[15,20] Additionally, the risk of hypomagnesemia from PPIs is increased when used concurrently with diuretics.[14] The proposed mechanism for PPI induced hypomagnesemia is that when the pH of the intestinal lumen increases, there is a decrease in activity of TRPM6 channels, which are responsible for magnesium absorption. If the pH of the intestinal lumen is high, there is a decrease in magnesium absorption, and thus, low magnesium levels.[21]

Magnesium deficiency can also be destructive to bone, decreasing bone stiffness and osteoblast activity, while increasing the number of osteoclasts.[22]

Bone Fractures

Long term PPI therapy has been associated with decreased bone mineral density (BMD),[22] and in 2010, the FDA released a safety alert regarding the potential for PPIs to increase the risk of fracture in the hip, wrist, and spine with high dose or chronic use of these medications.[15,23] The FDA warning regarding risk of fracture with OTC PPI use was removed in 2011 due to lack of data surrounding short term low dose use of PPIs and effect on BMD.[9] There are a few proposed mechanisms attempting to explain why PPIs increase the risk of fracture which include malabsorption of calcium due to hypochlorhydria, gastrin induced parathyroid hyperplasia, and osteoclastic vacuolar proton pump inhibition.[16] It is not currently recommended to obtain calcium levels or supple-

Box 1. Adverse Events Associated With PPI Use

Adverse nonkidney events
- Atrophic gastritis
- Vitamin B_{12} malabsorption
- Cardiovascular disease
- *Clostridioides difficile* infection
- Community-acquired pneumonia
- Dementia
- Gastric cancer
- Osteoporotic fractures

Adverse kidney outcomes
- Hypomagnesemia
- Acute kidney injury
- Acute interstitial nephritis
- Incident chronic kidney disease
- Kidney failure

Causes of death associated with PPI use
- All-cause mortality
- Death due to cardiovascular disease
- Death due to chronic kidney disease
- Death due upper gastrointestinal cancer

ment intake for patients receiving chronic PPI therapy.[16]

Acute Kidney Injury (AKI), Acute Interstitial Nephritis (AIN) and Chronic Interstitial Nephritis

PPI use has been linked to AKI and AIN[14] with more recent studies suggesting a link between PPI use and an increase in risk of CKD, CKD progression, and kidney failure.[24,25] The first reported case of PPI induced AIN occurred in 1992 and was due to omeprazole.[26] PPIs are now considered one of the most common medication related causes of AIN, and in instances where patients present with hypomagnesemia, AKI or AIN, the PPI should be considered as a cause.[14,27] A population based cohort study looking at almost 600,000 patients found that those who received PPI treatment had a twofold greater risk of developing AIN than patients who did not receive PPI treatment.[28] Because PPIs are generally used short term, it is not recommended to monitor eGFR. However, in the event long term therapy is used, it is reasonable to monitor eGFR once a year along with a magnesium level.[14] The mechanism by which PPIs cause kidney damage is not completely understood, however, proposed mechanisms include hypersensitivity reaction to PPIs causing a decline in glomerular filtration rate or inhibition of the lysosomal proton pump.[29]

Increased Risk of Infection

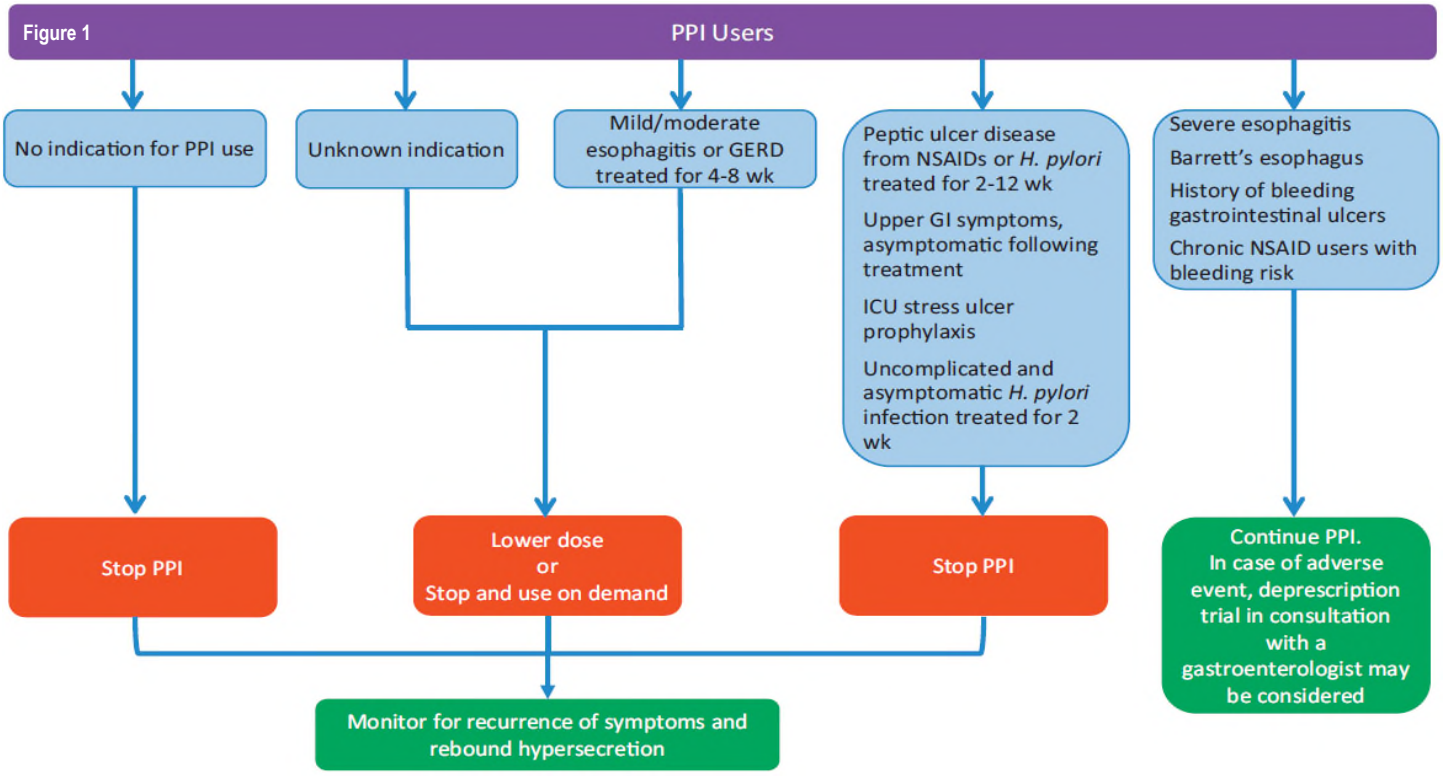
In early 2012, the FDA released a statement regarding PPI use and the increased risk of *Clostridium difficile*-associated diarrhea (CDAD).[30] They recommend that patients be on the lowest dose and shortest duration needed of a PPI, and if they develop diarrhea that does not improve, CDAD should be considered. The mechanism by which PPI use is thought to contribute to the risk of CDAD is that the decrease in gastric acid caused by the PPI can disrupt the microbiome of the GI tract, allowing for bacteria to colonize in an area where they wouldn't normally survive under acidic conditions.[31,32]

While the FDA has not released statements regarding the risk of pneumonia with PPIs, a large cohort study looking at older adults found that PPI use was associated with an increased risk of pneumonia during the 2nd year of PPI treatment.[33] Gastric acid kills bacteria and when PPIs are used, acidity decreases and bacterial colonization of the stomach can occur, increasing the risk of micro-aspiration pneumonia and bacterial colonization outside of the GI tract.[33]

It is not currently recommended to promote probiotic use in patients to prevent infection.[16]

Gastric Neoplasia

Gastric cancer is the third leading cancer-associated cause of death in the US.[34] Risk factors for gastric cancer include: male gender, age, *H. pylori* infection, diet, smoking, and family history. Atrophic gastritis and intestinal metaplasia are precancerous gastric factors associated with risk of developing gastric cancer.[35] PPIs are thought to contribute to the risk of gastric cancer through a pathway starting with a hypoacidic environment. Gastric hypoacidity (due to PPIs) causes the release and elevation of gastrin (hypergastrinemia) levels. This excess gastrin targets enterochromaffin-like (ECL) cells to produce more acid to correct the hypoacidic environment. In situations where gastrin levels are elevated due to hypoacidic gastric environments, ECL cells are constantly targeted by gastrin



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and can go on to develop gastric ECL neuroendocrine tumors (NETs) and carcinomas.[13] This pathway of blocking acid secretion to chronic gastric hypoacidity to hypergastrinemia causes changes to the gastric mucosa, chronic inflammation, intestinal metaplasia, and gastric atrophy (the latter two being risk factors for gastric cancer).[36-38]

The risk of gastric cancer in patients with hypergastrinemia (elevated gastrin levels) was documented decades before PPIs came to market.[39] Additionally, it has been proven that inhibition of gastric acid secretion in rodents leads to hypergastrinemia, ECL cell hyperplasia, and induction of gastric tumors.[40-42] Studies are limited and often observational or retrospective with multiple confounding variables, or other causes of cancer. There is a need for more well designed prospective studies to illustrate the potential link between long term PPI use and risk of gastric cancer.[35]

While micronutrient malabsorption, kidney damage, increased risk of infection, bone fractures, and gastric neoplasia are not a complete list (Box 1)[14] of associated risks of chronic PPI use, these topics of consideration serve as an opportunity to address appropriate use of this class of medication and when to determine if deprescribing is appropriate.

In the clinical practice guideline for deprescribing proton pump inhibitors (PPIs), Farrell, et al defines 5 categories of patients and provides recommendations for each category regarding PPI use: (1) those who have no indication for PPI use, (2) those for whom the indication is unknown, (3) those with mild or moderate esophagitis or GERD, (4) those who were treated with PPIs for a well-defined indication (e.g., peptic ulcer disease due to NSAID use, or H pylori infection, or upper gastrointestinal symptoms) but remained on PPI treatment beyond the indicated period and well after resolution of symptoms, or (5) those with conditions that require long-term use of PPIs, including Barrett's esophagus, bleeding ulcers, severe esophagitis, and long-term NSAID users with bleeding risk. (Fig.1.)[14,43] These guidelines have been published in order to help guide clinicians in discontinuing inappropriate PPI therapy, specifically in patients who do not have an indication for use.

Medical reviews and OTC screening can help to identify patients who may meet criteria for deprescribing. Keep in mind that appropriate indications for long term therapy should be limited to prevention of nonsteroidal anti-inflammatory drug–induced ulcers, severe esophagitis, Barrett's esophagus, idiopathic chronic ulcer, refractory gastroesophageal reflux disease, pathologic hypersecretory conditions (e.g., Zollinger-Ellison syndrome), and certain patients with a history of gastrointestinal ulcer with bleeding.[43] Deprescribing opportunities include patients with a history of *Helicobacter pylori* infection, peptic ulcer disease, heartburn, dyspepsia, or gastroesophageal reflux disease.[43]

Although PPIs are the most effective blockers of gastric acid secretion, limiting PPI use to patients who have an appropriate indication and judiciously reassessing long-term use is fundamental. Always balance the risk versus benefit in patients who have a documented indication for use, ensuring the lowest effective dose and shortest duration possible. The risk of side effects with long term use should not be a deterrent in patients who truly require PPI treatment. When considering deprescribing in appropriate cases, abrupt discontinuation can cause RAHS, tapering doses, applying a step-down approach, or using PRN (as needed) H_2RAs (H-2 receptor antagonists) or PPIs can all be more effective strategies to discontinuing a PPI versus abrupt discontinuation.[11] Applying pharmacovigilance and engaging all stakeholders: pharmacists, prescribers, and patients, can aide in the deprescribing process. Additionally, healthcare systems should implore stewardship programs to monitor this class of medication for appropriate use and disseminate information to appropriate parties.

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