# Proton pump inhibitors: balancing the benefits and risks of long-term use

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This is to acknowledge that Chenlu Tian, M.D. has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Tian will be discussing off-label uses in her presentation.

Dr. Chenlu Tian is an assistant professor in the Department of Digestive and Liver Diseases at UT Southwestern Medical Center. In addition to housestaff teaching, Dr. Tian has a clinical interest in quality improvement and promoting patient health education. In 2016, she implemented an electronic consultation platform for the Department of Digestive and Liver Diseases within the electronic medical records system of Parkland Health Systems to improve primary provider access to specialist input. She continues to be a provider for e-consultation. Through her practice, she has noticed increased primary care provider concern regarding use of PPIs in recent years as this class of medication has come under closer scrutiny for reports of various adverse effects. However, PPIs are also highly effective in the treatment of various acid-related upper GI disorders. The purpose of this presentation is to address the benefits of long-term PPI use in a defined set of indications, examine the evidence behind reported potential risks, and finally discuss how to mitigate the risks including an approach to de-escalation of therapy.

At the end of this lecture, the audience should be able to:

1. Know the mechanism of action and pharmacokinetics of PPI therapy
2. List the indications for long-term PPI use
3. Know which reported adverse effects have likely causality versus those with weak association, unproven causality.
4. Know the common reasons for PPI misuse
5. Understand a general approach to PPI de-escalation

Twenty-nine years ago, in 1989, omeprazole became the first proton pump inhibitor (PPI) to be introduced for the management of acid-related disorders. Currently, seven PPIs are approved for use by the U.S. Food and Drug Administration. Omeprazole, omeprazole-sodium bicarbonate, esomeprazole, and lansoprazole are currently available over the counter. By 2015, PPIs ranked in the top 10 national health-related drug expenditures list with an estimated $11 billion cost-expenditure in the US annually [1]. As utilization grew, so did the concern for potential side effects. This review will address the benefits of long-term PPI use in a defined set of indications, examine the evidence behind reported potential risks, and finally discuss how to mitigate the risks including an approach to de-escalation of therapy.

**Mechanism of action and pharmacokinetics**

The parietal cell in the fundus and body of the stomach produces acid when receptors on the cell surface bind histamine, acetylcholine, or gastrin. Downstream signaling culminates in the activation of the hydrogen-potassium ATPase, which is the final step of acid secretion. This ATPase is commonly known as "the proton pump". This pump actively secretes hydrogen which combines with chloride in the gland lumen to produce hydrochloric acid. Proton pump inhibitors bind and irreversibly inactivate this pump to prevent gastric acid production (Figure 1).

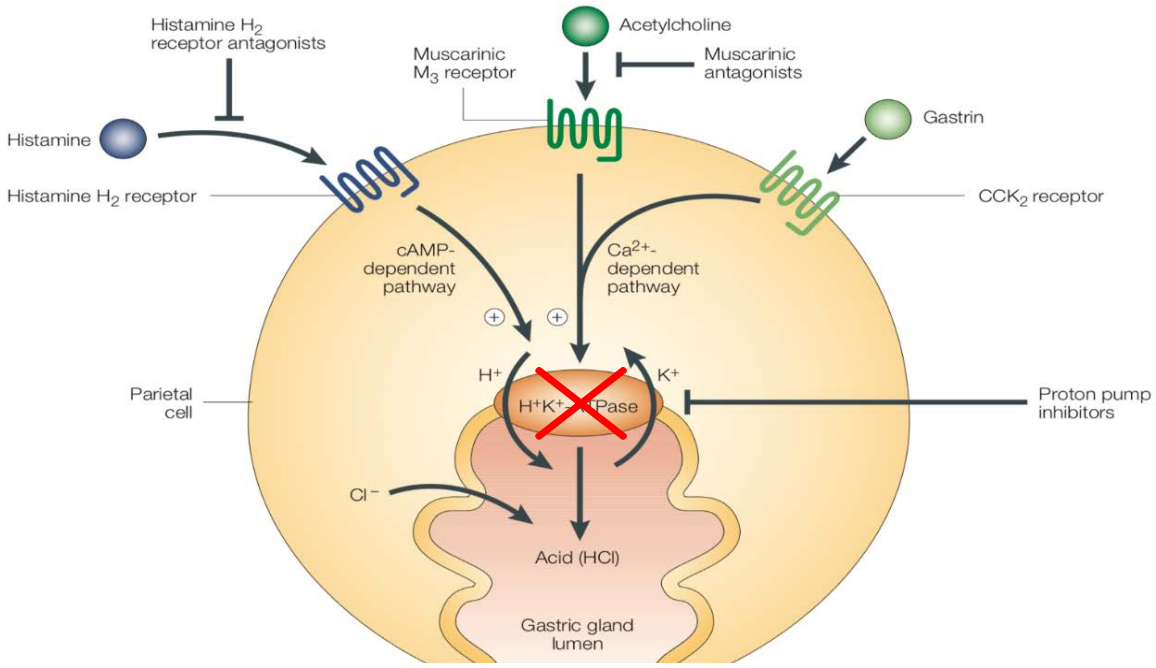

Figure 1. Proton pump inhibitors and the acid secretion pathway.

PPIs are prodrugs and weak bases. Various packaging such as enteric coating, gelatin capsules, or coated granules, prevent premature activation and degradation by luminal gastric acid. They are absorbed in the proximal small bowel and have high bioavailability of 60-80%. Due to being weak bases, the prodrugs accumulate in the acidic environment of the secretory canaliculi of the parietal cell and are activated when the regional pH falls below their pKa. They have an extremely short half-life of 1-2 hours but long duration of action due to irreversible covalent binding to the proton pump [2, 3]. Their ability to suppress acid production requires active canaliculi expression of H/K ATPases. Since proton pumps are not all recruited to the cell

surface during a PPI's short half-life, only 2/3 of proton pumps are inhibited by a single dose. The time of highest pump expression is typically after a prolonged fast, in the morning. Thus, for maximal efficacy, all traditional delayed-release PPIs should be taken 30-60 minutes before meals. A steady-state is reached after multiday treatment. Restoration of acid secretion after discontinuing PPIs depends on proton pump turnover. Maximal acid secretion capacity may not be restored for 24 to 48 hours [4].

Prior studies have shown that maintaining an intragastric pH >4 helps with healing of acid-related disorders of the upper GI tract. PPIs are very effective at raising intragastric pH [5]. In a randomized study of thirty-four GERD patients, PPIs were able to control pH >4 anywhere from 11 to 15 hours. Up to 65% of patients achieved >12 hours of control on a single daily dose. Increasing dosage and frequency to twice daily can increase duration of action to 15 to 20 hours [6]. Compared to H2 receptor antagonists (H2RAs), PPIs are more effective at maintaining intragastric pH >4 and this effect is sustained over time; whereas tachyphylaxis is seen with H2RAs after several days of use [7].

**Benefits of long-term PPI use**

The current FDA approved indications of PPI use are listed in Table 1. Other off-label but commonly accepted uses include chemoprevention of esophageal cancer in Barrett's, treatment of PPI responsive esophageal eosinophilia, and functional dyspepsia. The use of PPIs in GERD and related complications, NSAID-ulcer prophylaxis, and Barrett's esophagus will be further reviewed as these indications may entail longer duration of use.

Table 1. Food and Drug Administration Indications for PPI Use

| |
|---|
| - GERD |
| - Erosive esophagitis: acute healing and long-term maintenance |
| - Peptic ulcer disease: acute healing and prevention in high risk individuals |
| - *Helicobacter pylori* eradication |
| - Zollinger-Ellison syndrome |
| - Stress ulcer prophylaxis |

Treatment of GERD and GERD-related complications

A Cochran meta-analysis from 2013 compared treatment of GERD-like symptoms with PPIs and H2RAs [8]. Seven trials evaluating empiric treatment of GERD with PPI versus H2RAs demonstrated superiority of PPIs over H2RAs in achieving symptom control (RR 0.66, 95% CI 0.60 to 0.73). For endoscopy-negative reflux disease, or non-erosive reflux disease (NERD), PPIs were still superior, but the difference seen was smaller (RR 0.78, 95% CI 0.62 to 0.97). PPIs were also superior to H2RAs in the treatment of reflux esophagitis across all grades of severity, and achieved healing rates of 80% by 8 weeks versus 50% with H2RAs [9]. Furthermore, a prospective study of patients with history of healed reflux esophagitis demonstrated significantly higher rates of remission on maintenance therapy with a PPI compared to H2RA (80% vs 49%, P = 0.03) (figure 2) [10]. Erosive esophagitis can lead to

secondary fibrosis and scarring resulting in esophageal stricture. Patients with history of peptic strictures placed on PPI therapy also require fewer redilations at 12-month follow-up than those on H2RA (30% versus 46%, p<0.01) [11]. In patients with peptic strictures, PPI users also reported fewer dysphagia symptoms and were more likely to be asymptomatic and eating a normal diet on follow-up. Thus, PPIs are not only effective for controlling GERD symptoms but also effective in healing of GERD-related complications.

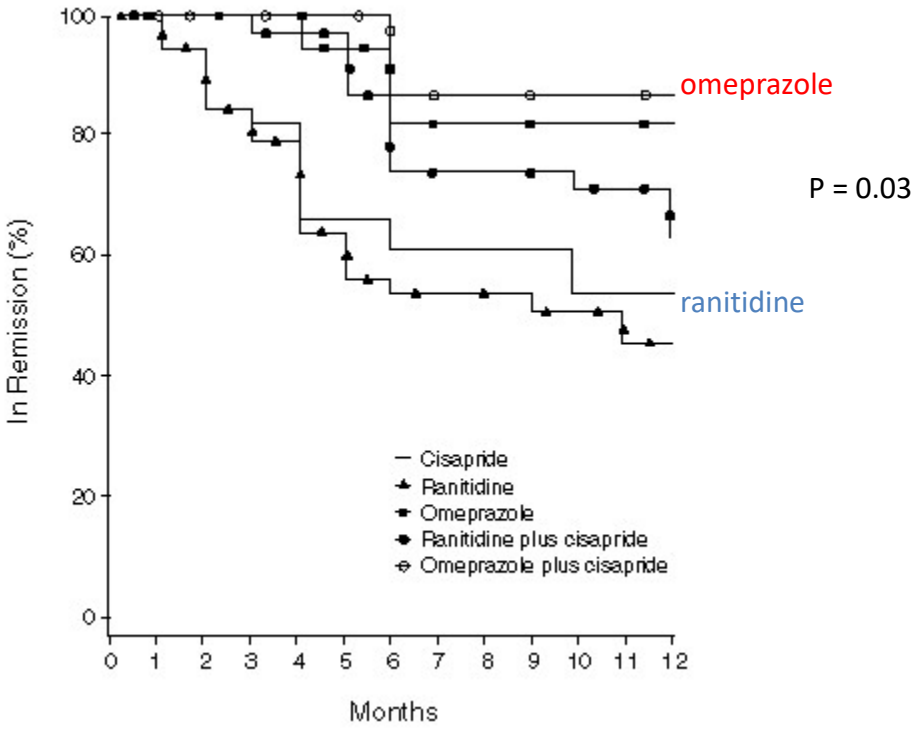


Figure 2. Omeprazole is more effective than ranitidine for maintenance of healed esophagitis.

Peptic ulcer disease healing and prevention

PPIs are also effective in the healing and prevention of peptic ulcer disease. A recent meta-analysis compared the effects of various gastroprotectants on ulcer healing [12]. Summarized rates of ulcer healing from 204 trials showed that PPIs are superior to other types of gastroprotectants, namely H2RAs and prostaglandin analogues. PPIs are also superior at decreasing rates of rebleeding, need for endoscopic intervention, need for transfusion and surgery. However, no mortality benefit was seen. The same meta-analysis also reviewed prevention studies. Overall, PPIs are the most effective agent for ulcer prevention compared to prostaglandin analogues and H2RAs. The superiority appears to be strongest for duodenal ulcers rather than gastric ulcers. This finding may be partially due to the fact that older studies did not determine the incidence of *H.pylori* infection prior to inclusion of patients and *H.pylori* is the most common cause of duodenal ulcers in certain parts of the world. On post-hoc analysis of older studies, the added protection of PPI was seen to occur among those with *H.pylori* infection.

In NSAID-related ulcer prevention, PPIs confer an absolute risk reduction of 10-15% for both non-selective and selective NSAID users [13]. Similarly, for long-term aspirin users, the use of PPIs led to an absolute risk reduction of around 6% compared to placebo [14]. Risk factors for NSAID-related ulcers are: history of ulcer, age greater than 65 years of age, high NSAID dose, or concomitant use of aspirin, steroids, or anticoagulants. Patients with these risk factors who are unable to stop NSAID therapy benefit from long-term PPI prophylaxis [15, 16].

Chemoprevention in Barrett's esophagus

Chronic inflammation in the esophagus in the setting of GERD may give rise to Barrett's esophagus, where the lining of the esophagus changes from squamous to a metaplastic columnar epithelium with gastric and intestinal features. Barrett's has been detected in roughly 10-15% of patients with chronic GERD and the risk of cancer progression in nondysplastic Barrett's is roughly 0.2-0.5% per year. PPI's proposed effects on chemoprevention include reducing esophageal acid exposure and reducing inflammation. Specifically, acid damages the mucosa through production of reactive oxygen species, leading to DNA breaks. Reflux also increases proinflammatory cytokines in the esophagus [17]. Due to the relative low rate of progression from Barrett's to adenocarcinoma, there is currently no randomized control trial data on chemoprevention with PPIs. However, a recent meta-analysis of seven observational studies totaling 2813 patients with Barrett's esophagus and 317 cases of esophageal adenocarcinoma or high-grade dysplasia showed a 71% risk reduction for advanced dysplasia or neoplasm in patients taking PPI therapy. Additionally, PPI use for greater than two to three years appeared to lower risk. Conversely, this protective effect was not seen with H2RAs [18].

**Potential risks of PPI therapy**

The current evidence is predominantly based on observational studies. While reviewing these studies, it is important to remember that observational studies are prone to various biases and thus difficult to establish causality. Protopathic bias, also known as reverse causality, occurs when a drug is initiated in response to the first symptoms of a disease that remains undiagnosed up til that point. For example, PPIs may be initiated for various GI symptoms resulting from a yet to be diagnosed disease and this gives the false appearance that PPIs caused the disease. PPIs are also known to be prescribed more in the elderly with multiple comorbidities. Adjusting for comorbidity status still may not capture disease severity and result in confounded PPI-adverse effect association. Adopting a systematic approach will help determine the plausible versus spurious associations. Questions to ask are: Is there a biological explanation for a reported association. Are the findings reproducible. Is there a direct relationship between dose or duration of PPI use and stated outcome? And finally, how strong is the association? Odds ratios between 0.33 and 3, also known as the zone of potential bias, should also be interpreted with caution. The evidence for most reported adverse effects is weak (Figure 3). It is also important to put numbers in perspective. The relative risk may sound high (e.g. 2-fold to 6-fold increase), but the estimated absolute risks for individual patients are exceedingly low (Table 2) [19]. The evidence for some of these adverse effects is further discussed below.

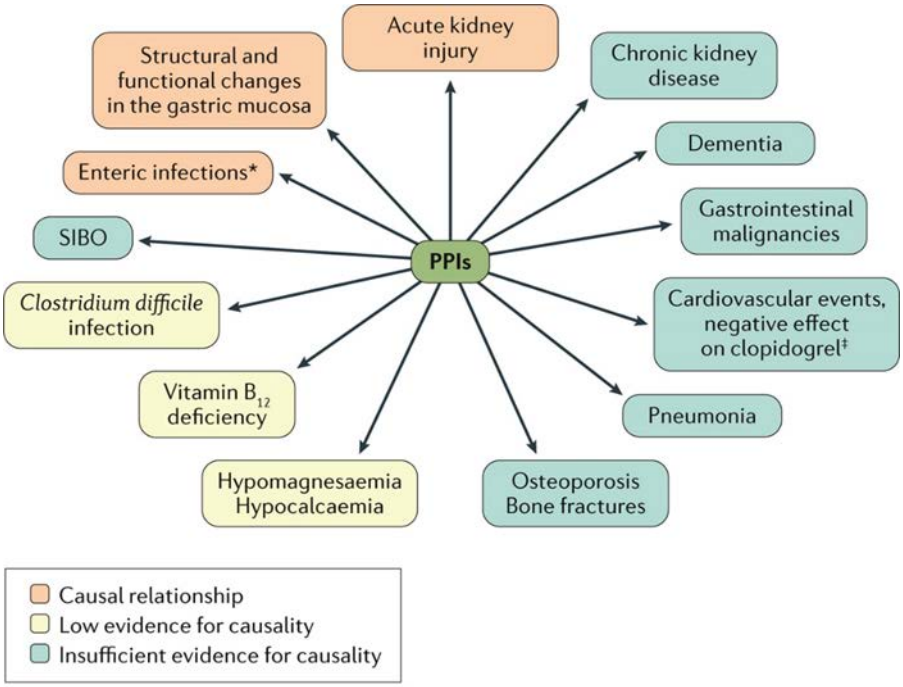


Figure 3. PPIs and reported adverse effects with proven and unproven causality.

Table 2. Estimated absolute excess risks of potential adverse effects.

| Potential Adverse Effect | Relative Risk | Absolute Excess Risk |
|---|---|---|
| Chronic kidney disease | 10% to 20% increase | 0.1% to 0.3% per patient/y |
| Dementia | 4% to 80% increase | 0.07% to 1.5% per patient/y |
| Bone fracture | 30% to 4-fold increase | 0.1% to 0.5% per patient/y |
| Myocardial infarction | No association in RCTs | -- |
| Campylobacter or Salmonella infection | 2-fold to 6-fold increase | 0.03% to 0.2% per patient/y |
| Clostridium difficile infection | No risk to 3-fold increase | 0% to 0.09% per patient/y |
| Pneumonia | No association in RCTs | -- |
| Micronutrient deficiencies | 60% to 70% increase | 0.3% to 0.4% per patient/y |

Acute kidney injury

Multiple case series and case-control studies have shown a potential risk of developing acute interstitial nephritis with patients on PPIs. This is thought to be an idiosyncratic reaction. In a series of 133 patients with biopsy-proven AIN, 12% were thought to be PPI-induced [20].

Two large population-based studies found a fivefold increased risk in patients older than 60 and increased risk when PPIs were taken within 120 days before developing acute kidney injury [21, 22]. Based on the current evidence, the association between AIN and PPIs appear moderate and consistent.

Chronic kidney injury

Chronic kidney disease is thought to arise from recurrent acute interstitial nephritis. Current evidence comes from cohort studies. One study of 10,482 patients from the Atherosclerosis Risk in Communities study showed an increased risk in self-reported PPI users compared to those on H2RAs (HR 1.5) [23]. Another larger cohort study utilizing the VA national database found a similar risk in new PPI users (HR 1.2) [24]. Overall, the association of CKD and PPIs appear to be of very low magnitude. This brings into question whether there are uncaptured baseline differences between PPI users and non-users.

Dementia

Studies in mice suggest PPIs may interact with brain enzymes leading to increased b-amyloid levels. The finding of increased risk in PPI users (HR 1.44) was first reported in a German study of 73,679 patients who were 75 years or older with no baseline dementia and followed for 7 years [25]. However, subsequent studies have had conflicting results. A large case-control study of patients with dementia found a mildly reduced risk with PPI use [26]. More recently, a Danish study published in 2018 used survey results from the Danish Twin Registry and found no association between PPI use and cognitive decline [27]. Thus, the association between dementia and PPI use appear weak and inconsistent.

Bone fracture

The biological explanation for bone fracture is thought to be from decreased gastric acidity leading to decreased absorption of calcium. The first studies evaluating fracture risk with PPI therapy came from observational studies in Denmark. Those studies reported hip fracture risk in older patients >65 years of age on PPIs for greater than a year [28]. A subsequent Canadian study reported no risk of osteoporotic fracture if PPIs were used for 6 years or less [29]. Two meta-analyses of 7 and 10 observational studies showed marginal increased risk with OR 1.24 and 1.25 respectively [30, 31]. On subgroup analysis, no duration effect was seen. Effects on osteoporosis and bone mineral density have also been mixed [32, 33]. Given these data, the association between bone fracture and PPIs appear weak and inconsistent.

Cardiovascular

The concern for cardiovascular events and specifically myocardial infarction arises from the fact that PPIs are metabolized by an isozyme of the cytochrome P450 gene called CYP2C19. Because the anti-platelet drug clopidogrel is activated by CYP2C19, there was worry that PPIs may decrease activated metabolites of clopidogrel. Additionally, nitrous oxide is released by endothelium to prevent platelet adhesion to the vessel wall. PPIs may reduce endothelial nitrous oxide resulting in thrombosis. While most data come from systematic reviews of cohort studies, there are also randomized control trial data. A 2015 meta-analysis of 39 studies, predominantly observational, evaluated the risk of cardiovascular events for patients on PPI and clopidogrel [34]. When the authors only analyzed the observational studies, they found a mild to moderate

increased risk for cardiovascular events such as myocardial infarction, stent thrombosis, and stroke as well as all-cause mortality. Odds ratios ranged from 1.39 to 1.90. However, no increased risk in mortality or ischemic events was seen when they analyzed the data from 8 randomized controlled trials and propensity-matched studies. A recent 2018 meta-analysis of 22 studies also addressed the impact of PPIs on cardiovascular risk in the absence of clopidogrel [35]. The authors found a marginal increased risk on data from 7 observational studies. However, no increased risk was seen on data from 8 RCTs. Taken together, the association of cardiovascular events and PPIs appear weak and not supported by randomized control trial data.

Pneumonia

The biological explanation for pneumonia is decreased gastric acidity allowing bacterial colonization and transfer to the lung. Back in 2011, a meta-analysis of 8 observational studies (including both community and hospital settings) demonstrated mild risk of pneumonia in PPI users, odds ratio 1.22 [36]. A later meta-analysis of 19 randomized control trials evaluating the safety of PPIs for stress ulcer prophylaxis in critically ill patients showed no significant risk for hospital-acquired pneumonia or mortality [37]. Another retrospective analysis of 24 randomized control trials did not show an association between PPI and community-acquired pneumonia [38]. Thus, the association of pneumonia and PPIs appear weak and inconsistent.

Enteric infections

The biological explanation for enteric infections stems from decreased gastric acidity allowing bacterial colonization as well as a change in the gut flora. Two meta-analyses evaluating the risk of *c.difficile* included 42 and 51 case-control and cohort studies, respectively [39, 40]. They showed a mild risk increase ORs 1.74 and 1.65. Noted limitations of these studies include the observational nature, no adjustment for comorbidities, and no report on the duration of PPI exposure or antibiotic intake. Thus, the association between *c.difficile* and PPIs appears weak. A systematic review from 2011 evaluating the risk of other enteric infections demonstrated a relative risk of 4.2 to 8.3 for salmonella and 3.5 to 11.7 for campylobacter [41]. Though an increased risk was seen, the magnitude was heterogeneous and has been estimated to be closer to 3-fold. The association between salmonella and campylobacter infections and PPIs appears moderate and consistent.

Micronutrient deficiencies

Hypomagnesemia is very rare and possibly an idiosyncratic reaction leading to decreased intestinal absorption. Evidence from case series and case-control studies suggest an increased risk for PPI-associated hypomagnesemia in patients with chronic renal insufficiency or diuretic use [42-45]. However, no significant association has been found in the absence of renal disease or diuretic use. Thus, based on current data, monitoring for magnesium can be considered if patient has concurrent chronic renal disease or diuretic use. B12 deficiency may stem from the need for gastric acid to release B12 from nutrients. A case control study within the Northern California Kaiser population comparing 25,956 patients with vitamin B12 deficiency and 184,199 patients without B12 deficiency demonstrated an increased risk in patients who used PPIs for 2 or more years (OR 1.65) [46]. Though the level of evidence is low, checking vitamin B12 can be considered for long-term PPI users with dietary restrictions.

**Misuse and de-escalation**

It is important to understand that baseline differences between PPI users and non-users make it difficult to study potential adverse effects retrospectively. While many reported associations remain weak with low level evidence, the number of studies has led to increasing vigilance and concerns of misuse. Modest risks may become important when PPIs are inappropriately prescribed due to a lack of potential benefit. Thus, an assessment of PPI indication and an attempt at reduction when possible can mitigate risks. Misuse is not only a disservice to patients but also costly to the healthcare system. A study of 946 patients in the Michigan VA system quoted a yearly excess cost of $1.5 million based on average wholesale price costs [47]. What are some of the common causes of misuse? Studies cite a lack of documented appropriate indication, lack of documented reevaluation of symptoms or assessment of continued need, use of PPIs for extraesophageal symptoms, and inappropriate continuation of PPIs posthospitalization for stress ulcer prophylaxis [1, 47]. Besides iatrogenic causes of overuse, the self-prescribing patient adds another layer of complexity. But even in these instances, providers can educate patients on appropriate PPI usage, when to seek additional medical help, and how-to step-down PPI use.

There is sparse literature on PPI reduction; the available data is almost entirely limited to patients with uncomplicated GERD. In a 2003 study examining the feasibility of step-down therapy from multiple to single-dose proton pump inhibitor use, a 6 month follow-up showed that 79.5% of patients were successfully weaned to daily dosing without symptom recurrence; though, a longer duration of PPI use was associated with greater chances of symptom recurrence [48]. Young age and a dominant symptom of heartburn are other predictors of unsuccessful PPI step-down [49]. The efficacy of on-demand therapy has been evaluated in patients with non-erosive reflux disease. One multi-center study from Europe enrolled 721 patients with nonerosive reflux symptoms controlled on PPI therapy to on-demand PPI or placebo [50]. During a 6-month follow-up, the authors found that patients taking a PPI were more willing to continue with the study as compared to placebo and had better control of heartburn symptoms. The mean PPI usage translated to roughly once every three days. Conversely, on-demand therapy in complicated GERD patients has been unsuccessful. When 539 patients with endoscopically-confirmed healed erosive esophagitis were randomized to maintenance with daily therapy or on-demand therapy, rates of remission were 81% for daily PPI users and only 58% for on-demand users ($p<0.0001$) [51]. The protectiveness of daily maintenance therapy was seen across all grades of esophagitis, and the difference was more pronounced in severe disease.

Weaning PPIs is also challenging when potentially modifiable risk factors have not been addressed. The association between GERD symptoms and weight gain has been well documented in literature and an increasing BMI associated with increasing risk. Data from a large case-control study of 10,545 patients from the Nurses Health Cohort showed a 40% reduction in frequent GERD symptoms for women who reduced their BMI by 3.5 or more compared with controls [52].

In summary, PPIs are very effective in treating acid-related disorders. For a well-defined set of indications, current evidence supports long-term PPI use as the benefits greatly outweigh risks. The evidence for the majority of reported adverse effects appear weak, and the magnitudes of absolute risk are low for individual patients. However, in the setting of misuse, these potential risks become magnified. The general approach for patients with uncomplicated GERD is to

periodically reassess and document symptom response to achieve the lowest effective dose. Figure 4 is a suggested algorithm for PPI de-escalation.

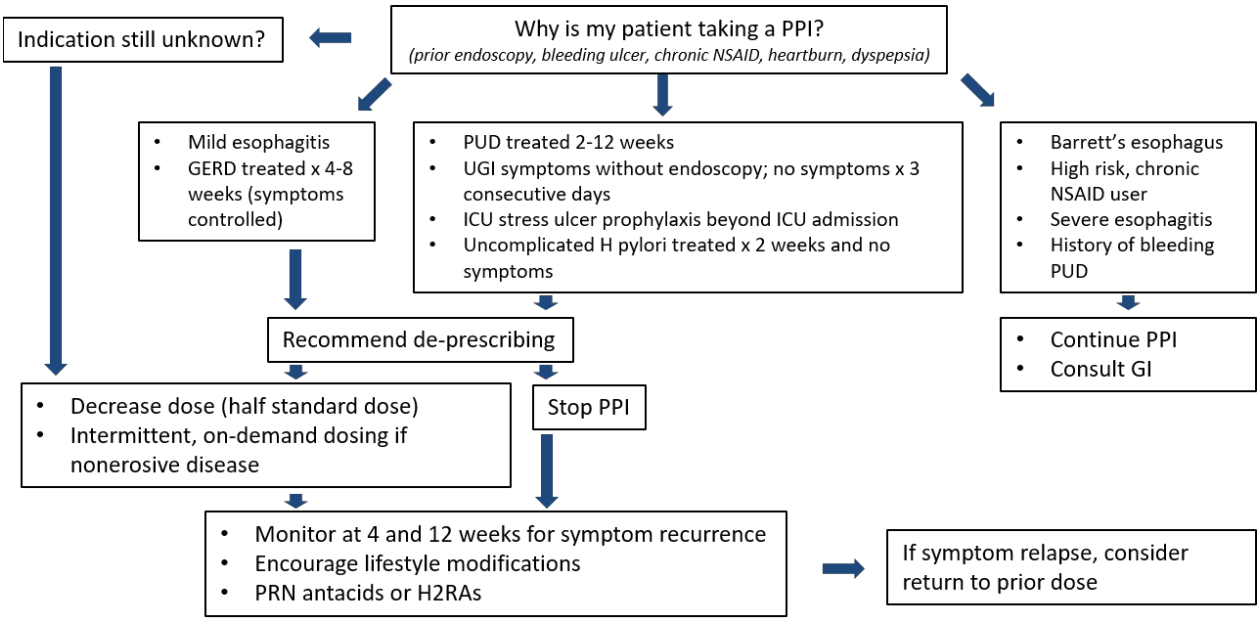


Figure 4. Algorithm for de-escalation of PPI therapy.

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