Prevalent Prescribing of Proton Pump Inhibitors: Prudent or Pernicious?

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ABSTRACT

In recent years, the “user-friendly” profile of proton pump inhibitors (PPIs) has resulted in their increased use for a variety of gastrointestinal conditions. Indeed, this trend has been spurred by the profound ability of these agents to decrease gastric acid as well as by their perceived lack of drug interactions and adverse effects. However, recent data suggest possible negative ramifications of the widespread and long-term use of PPIs in larger and sicker groups of patients.

In this article, we attempt to place in context the possible risks associated with the use of PPIs. Our concerns and caveats to temper their overuse are extrapolated from rare but possibly harmful adverse effects noted in certain subgroups in the older literature as well as more recently published case-control studies implying increased infection risks. We recommend further research using more robust study designs to clarify the true risks of long-term use of these agents.

Key words: proton pump inhibitors, PPIs, adverse effects, infection, interactions, polypharmacy

INTRODUCTION

Proton pump inhibitors (PPIs) elicit the reduction of gastric acid secretion via the selective and irreversible inhibition of proton-activated and potassium-activated adenosine triphosphatase (H/K-ATPase), an enzyme within the gastric parietal cells. Although the serum half-lives of PPIs are relatively short, the ability of these drugs to suppress gastric acid secretion for longer than 24 hours is a result of the long half-life of the enzyme they inhibit. The half-life of this enzyme, H/K-ATPase, is about 50 hours.1

This pharmacological feature of bringing about profound reduction in acid secretion has rendered PPIs highly effective in the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), Barrett’s esophagus, Zollinger–Ellison syndrome, and as one component of combination therapy in the eradication of Helicobacter pylori–related PUD.2 Moreover, the direct suppression of gastric acid by PPIs has proved beneficial in stress-related mucosal bleeding (SRMB) in critically ill patients.3

Evidence also suggests protection from PUD for patients receiving long-term therapy with nonsteroidal anti-inflammatory drugs (NSAIDs).4 Even though there is a paucity of well-designed research to justify this practice, PPIs are also used as ulcer prophylaxis for patients taking corticosteroids and anticoagulants. Unfortunately, through their unprecedented efficacy and relative lack of toxicity, these frequently prescribed medications have become yet another contributor to the ever-proliferating problem of polypharmacy.

This article discusses the possible risks associated with the long-term use of PPIs and provides a cautionary perspective on curbing the unnecessary use of these agents.

HISTORICAL BACKGROUND: PERCEIVED RISKS AND BENEFITS

The first PPI on the U.S. market, omeprazole (Prilosec, AstraZeneca), appeared in 1988.5 This approval paved the way for the sequential introduction of other PPI congeners: pantoprazole (Protonix, Wyeth),6 lansoprazole (Prevacid, TAP),7 rabeprazole (Aciphex, Esai/Jansen),8 and esomeprazole magnesium (Nexium, AstraZeneca), the $-isomer of omeprazole.9

All PPIs have a similar mechanism of action, but they differ somewhat in how they bind to sites adjacent to the cysteine residues on the proton pumps.10 Table 1 delineates the characteristics of PPIs currently on the market.

The popularity of prescribing PPIs may be attributed to their improved efficacy in acid suppression over their progenitor agents, the histamine H2-receptor antagonists (H2RAs) and the antacids, and their aforementioned relative lack of serious adverse drug effects (ADEs) or drug interactions.

In general, H2RAs possess some pharmacological shortcomings. For instance, they suppress gastric acid from parietal cells inadequately and block only the H2-related stimulation of acid secretion, which is just one of the three main pathways from which gastric acid is produced and secreted. As a result of collateral up-regulation of the unblocked gastrin and cholinergic pathways to stimulate acid secretion, tachyphylaxis may occur with H2RAs, beginning as early as 48 to 72 hours into therapy, which gastric acid is produced and secreted. As a result of collateral up-regulation of the unblocked gastrin and cholinergic pathways to stimulate acid secretion, tachyphylaxis may occur with H2RAs, beginning as early as 48 to 72 hours into therapy.
thereby preventing significant reductions in gastric pH for any significant period of time.

Antacids provide a relatively rapid onset of action, but their ability to neutralize gastric acid often lasts only minutes; they provide only a transient gastric acid pH above 4, a level that is needed for the effective treatment of many gastric acid-related conditions.

To achieve effective therapeutic doses of antacids, it is often necessary to administer them at least four times daily; however, this practice limits patient compliance. Moreover, antacids are not devoid of ADEs, which often include either diarrhea from the magnesium salts or constipation from the aluminium or calcium salts. These problems tend to be dose-related and often result in a low rate of patient acceptance and subsequently increase the likelihood of poor patient compliance.3

The enthusiasm for prescribing PPIs to humans was at first somewhat attenuated by animal studies that raised questions about hypergastrinemia, argyrophil cell hyperplasia, fundic gland atrophy, and even neoplasms after long-term therapy.11–13 Indeed, in one study, lifelong treatment with PPIs was associated with enterochromaffin-like cell carcinoids in 20% of female rats.14 Fortunately, the same progression to tumor cells in humans does not occur without specific gene mutations and conditions.15–17

Although it has recently been written that some experts feel that a rise in esophageal cancers may be attributed to the overuse of PPIs, these sentiments have not been borne out in any well-designed trials to date.18 Concerns about gastric cancer have not become manifested in people, but long-term PPI therapy may be associated with the progression of atrophic gastritis. These studies demonstrate a small increase (less than 1.5%) in the incidence of this condition in association with PPIs.19

Aside from these concerns, PPIs have generally been considered well-tolerated medications. Most commonly, patients have reported headache, constipation, diarrhea, and abdominal pain. Less frequently attributed intolerances have included allergic reactions, rashes, dizziness, joint and muscle pain, visual disturbances, depression, and dry mouth.20 For the most part, these ADEs have been deemed mild and self-limiting and have seldom resulted in the discontinuation of PPI therapy.

That being said, the long-term effects of PPIs, although seemingly rare, have been well defined. Isolated case reports have provided some information regarding ADEs not reported by the manufacturer. For instance, an interesting case report by Bong et al.20 described a lichenoid drug reaction that occurred nine months following omeprazole therapy. This reaction was rechallenged twice, once with lansoprazole and again with pantoprazole. Both courses demonstrated the same lichenoid eruption. Another case report with esomeprazole was related to rhabdomyolysis.21 Symptoms arose six weeks after esomeprazole therapy was initiated. Rarely, lymphocytic colitis has been seen and confirmed upon rechallenge.22,23

Naturally, safety is always a concern when pregnant women use medications that alleviate some of the discomforts related to acid reflux. Although safety data for PPIs remain relatively sparse, a meta-analysis did not reveal any significant risk of major fetal malformations with use of these agents.24 At present, PPIs are listed as pregnancy category B drugs, except for omeprazole, which is a category C agent. PPIs are not currently recommended for breastfeeding mothers.5–9

THE MAGNITUDE OF OVERUSE OF PPIs: REPORTS FROM THE LITERATURE

Several studies have confirmed the overuse of acid-lowering agents in both inpatient and outpatient settings.25–27 Acid-lowering therapy with an acceptable indication in these studies included a diagnosis of current GERD, non-erosive reflux disease (NERD), peptic ulcer disease (PUD), active upper gastrointestinal (GI) bleeding, prophylactic usage with NSAIDs, and H. pylori eradication. Conversely, PPI usage without an acceptable indication in these studies included a history of PUD or GERD without a current diagnosis or documented active disease within 90 days before admission. Other questionable indications included anemia, ulcer prophylaxis for low-risk patients, and no identifiable diagnosis.

In one analysis by Nardin et al., 54% of hospitalized patients in a general medicine service received acid-suppressive therapy consisting of either H2RAs or PPIs.25 Based on their criteria, 65% of patients did not possess any discernible indications for inpatient therapy. Even more troubling, from the standpoint of polyphasma and pharmacoeconomics, was the fact that 55% of those inappropriately given these agents for ulcer prophylaxis as inpatients were continued on these medications as outpatients. The gravity of this issue was reiterated in a study by Naunton et al. in which PPIs were prescribed without an appropriate indication more than 60% of the time.26

Data from one of our studies corroborate these findings.27 At the University of Michigan Hospital, 71% of patients admitted to the general medicine service were prescribed acid-suppressive therapy during their hospital stay. According to the criteria discussed earlier, only 10% of these inpatients were receiving appropriate acid-suppressive therapy. This figure included only patients under the fairly rigorous criteria of having active GI bleeding, taking NSAIDs, or having PUD or GERD with documented exacerbations within 90 days of admission. However, a higher number of 31% would have been achieved if anyone with a listed diagnosis of GERD, no matter how remote, was deemed to have an appropriate indication.

This perspective is an important one, because experience gained in the long-term treatment of GERD tells us that after the initial one to three months of therapy, up to 50% of patients have frequent symptomatic relapses, thereby earning a “PPI-for-life” status.28 Thus, the number of patients with clinically justifiable indications for acid-lowering therapy in our study probably fell to somewhere between those two extremes of 10% and 31%. Nonetheless, this would still imply that most of our patients received this therapy without an evidence-based indication.

Our study also found that this inappropriate prescribing within the hospital contributed to the superfluous use of these agents in the community. Overall, 54% of these inpatients were prescribed outpatient acid-suppressive therapy as well. Again, depending on how we determined the status of GERD as an approved indication, only from 10% to 27% of patients prescribed these medications upon discharge were found to have an appropriate long-term indication.

These studies underscore the proclivity for indiscriminate prescribing of PPIs by practitioners in the hospital setting and the continuance of these agents over the long term without a bona fide indication. Certainly, clinical pharmacists could be instrumental in screening for excessive use both upon admission to the
hospital and before or after hospital discharge. In these cases, subsequent intervention could greatly contribute to curbing the unnecessary use of acid-lowering agents.

NEGATIVE RAMIFICATIONS OF PPI USE
Drug–Drug and Drug–Nutrient Interactions

Except for esomeprazole (Nexium), PPIs are marketed as racemic mixtures of S- and R-enantiomers. In general, they are metabolized by the cytochrome isoenzymes CYP450 2C19 and 3A4. The isozyme CYP 2C19 demonstrates polymorphic variation within the population. This enzyme is deficient in 3% of whites and blacks and in 13% to 22% of Asians.

The stereoselectivity of PPIs in the S- and R-enantiomers varies in the rate of metabolism; the R-enantiomer is cleared via the liver more rapidly than the S-enantiomer. Therefore, drugs that affect CYP450 enzymes may ultimately affect efficacy and tolerance to PPI therapy. Conversely, the effect of PPIs on CYP450 isoenzymes may potentiate ADEs with interacting drugs (see Table 1).1–3,28

Li and associates investigated the inhibitory effects of five PPIs on four human CYP450 enzymes (2C9, 2C19, 2D6, and 3A4).29 This study was the first to analyze all five PPIs together under identical experimental conditions.

Despite the variations between PPIs and CYP450 inhibition, the clinical relevance of the findings remains to be determined. More studies are needed to ascertain the extent of the real-world problem of polypharmacy and drug interactions with PPIs. At present, little information is available to show that isozyme inhibition or induction is a major issue with PPIs in the milieu of polypharmacy. It has been demonstrated in the past, however, that clinically significant drug interactions in elderly, frail patients often go undetected in studies enrolling healthier, younger volunteers.

Through their inhibition of active proton pumps, PPIs create a gastric environment with a pH above 4 for a significant portion of the dose interval.3 Decreased gastric acidity is not without consequences. Drugs that are pH-dependent for absorption may potentially be affected by PPIs. Such agents include acid/alkaline-labile drugs, pH-dependent formulations, and drugs that are weak acids or bases, such as ketoconazole (Nizoral, Janssen), digoxin, nifedipine (Procardia, Pfizer), indinavir sulfate (Crixivan, Merck), and aspirin.

PPIs may produce premature dissolution of enteric-coated formulations, such as bisacodyl tablets (e.g., Dulcolax, Boehringer Ingelheim), destined for release in the duodenum. Increased absorption of digoxin, nifedipine, aspirin, midazolam (Versed, Roche), didanosine (Videx, Bristol-Myers Squibb Oncology), or methadone (Dolophine, Roxane) may be associated with PPIs. Because these other drugs (not PPIs) possess properties as weak bases that require an acid medium for absorption,

<table>
<thead>
<tr>
<th>PPI</th>
<th>Structure</th>
<th>Bioavailability</th>
<th>Half-Life</th>
<th>Renal/Hepatic Dosing</th>
<th>Drug Interactions</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td><img src="https://example.com/omeprazole.png" alt="Structure" /></td>
<td>30%-40% (increases slightly with repeated dosing)</td>
<td>0.1-1 hour</td>
<td>Reduce in hepatic impairment</td>
<td>Inhibits CYP 2C19, increasing levels of phenytoin, diazepam, warfarin</td>
<td>Headache, diarrhea (2.4%), nausea (1.9%), rash</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td><img src="https://example.com/esomeprazole.png" alt="Structure" /></td>
<td>64% (single dose); &gt;90% (repeated dosing)</td>
<td>1-1.5 hours</td>
<td>Max. dose = 20 mg in severe hepatic impairment</td>
<td>Potentiates atorvastatin via possible CYP 2C19</td>
<td>NA</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td><img src="https://example.com/pantoprazole.png" alt="Structure" /></td>
<td>77%</td>
<td>3.5-10 hours</td>
<td>None</td>
<td>Has less CYP450 effect than omeprazole</td>
<td>Headache, diarrhea, nausea, rash</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td><img src="https://example.com/lansoprazole.png" alt="Structure" /></td>
<td>&gt;80%</td>
<td>2 hours</td>
<td>Reduce in severe hepatic impairment</td>
<td>Induces CYP 1A2, decreasing theophylline levels; inhibits CYP 2D6</td>
<td>Headache (2.9%), diarrhea (4.1%), nausea (2.6%), rash</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td><img src="https://example.com/rabeprazole.png" alt="Structure" /></td>
<td>52%</td>
<td>1-2 hours</td>
<td>Use caution in severe hepatic impairment</td>
<td>NA</td>
<td>Headache (2.4%), diarrhea, rash</td>
</tr>
</tbody>
</table>

CYP = cytochrome; NA = not available.
Prevalent Prescribing of PPIs

decreased bioavailability has been noted with agents such as ketoconazole, itraconazole (Sporonox, Janssen), and indinavir.\textsuperscript{1,30–32} Despite the validation of these drug–drug interactions with PPIs in the studies cited earlier, definitive prospective dose adjustments have yet to be established.

Proper absorption of some nutrients may also be diminished in a state of low gastric acid. For example, vitamin B\textsubscript{12} absorption may be deficient in patients receiving long-term PPI therapy, especially when patients are taking higher doses of these medications for diseases such as Zollinger–Ellison syndrome.\textsuperscript{33}

Even though a deficiency in vitamin B\textsubscript{12} may lead to macrocytic, megaloblastic anemia with gastric mucosal atrophy\textsuperscript{34} and neurological symptoms of paresthesias and ataxia,\textsuperscript{34,35} PPIs have not yet been implicated as the sole causative agent related to vitamin B\textsubscript{12} deficiency anemia.\textsuperscript{1,30–32,34–36}

Calcium absorption of the carbonate salt (but not the citrate salt) is also impaired substantially in the environment of non-acidic gastric pH. A study of omeprazole published in 2005 demonstrated a significant decrease in calcium absorption from the carbonate salt in elderly women.\textsuperscript{37} Given this information, it would seem advisable to use calcium citrate instead of calcium carbonate for osteoporosis treatment and prevention in most patients for whom long-term PPI therapy is indicated.

Finally, lowering of the gastric acid output can result in decreased iron bioavailability. More research is required to explore the effects on other minerals and nutrients.\textsuperscript{1,30–32}

Do PPIs Increase the Risk of Infection?

Concerns have arisen surrounding the association of PPIs with the risks of acquiring GI and respiratory tract infections. Gastric acidity is a nonspecific immune defense against ingested pathogens, and it is thought that this acid forms an important barrier to the colonization of potentially pathogenic organisms. However, when the gastric pH exceeds 4, this innate barrier is extinguished and pathogens are no longer effectively killed.\textsuperscript{35,36} Ultimately, this condition of hypochlorhydria, when induced by PPIs, may result in the iatrogenic overgrowth of opportunistic microbes. Some trials have demonstrated the association of infection with the use of PPIs.\textsuperscript{38–40}

Dial et al.\textsuperscript{38}

Dial et al. examined a pharmacy database of 1,187 hospital patients in a retrospective cohort study over a nine-month period. To further investigate the relationship between PPIs and the severity of illness and the risk of Clostridium difficile (C. difficile) infection, the authors conducted a case-control study of an additional 94 patients. They noted a link between PPI use and the development of C. difficile disease (adjusted odds ratio [OR], 2.1; 95% confidence interval [CI], 1.2–3.5) in 6.8% of the sample (81 of 1,187 patients). The case-control study also revealed a similar association (adjusted OR, 2.7; 95% CI, 1.4–5.2).

Overall, patients receiving PPIs had a greater risk of C. difficile disease (9.3%) than those not taking PPIs (4.4%) (unadjusted OR, 2.1; 95% CI, 1.4–3.4). This translates to a risk of C. difficile acquisition of one case per 21 patients treated with PPIs in the hospital (number needed to harm [NNH] = 21).

The difference in the development of C. difficile in patients in medical wards and in surgical wards is also worth noting, at 10.9% vs. 2.9%, respectively (P < .001). This study indicated that the medical ward patients who were taking PPIs were at an increased risk of infection with C. difficile.

These findings are congruent with data showing that decreased gastric acidity is a risk for other infectious conditions such as traveler’s diarrhea, salmonellosis, and cholera.\textsuperscript{41}

Once again, the etiologic mechanism of these GI superinfections is thought to originate from the disruption of the normal intestinal flora precipitated by gastric acid suppression.\textsuperscript{42}

Laheij et al.\textsuperscript{39}

A trial was conducted in a nested-case-control format of a large database of general practitioners in The Netherlands. The aim was to study an association between acid-suppressant therapy and the development of community-acquired pneumonia (CAP).

Despite some of the study’s methodological limitations and confounders, Laheij and associates identified a relationship between current users of PPIs and the development of CAP (OR, 1.7; 95% CI, 1.3–2.2) and between those using combination PPIs plus H\textsubscript{2}RAs and CAP (OR, 1.76; 95% CI, 1.18–2.61). The risk of CAP was estimated to be one case per 226 patients using PPIs for 0.42 years (NNH = 226). Patients using H\textsubscript{2}RAs demonstrated a similar risk of CAP—one case per 508 patients using H\textsubscript{2}RAs over 0.23 years (NNH = 508).

Dial et al.\textsuperscript{40}

A more recent study by Dial and coauthors assessed the risk of acid-suppressive therapy and the risk of community-acquired C. difficile infections. The United Kingdom General Practice Research Database was used to conduct a two-population–based, case-control study.

The incidence of C. difficile infection, as diagnosed by general practitioners, increased from 1 per 100,000 cases in 1994 to 22 per 100,000 cases in 2004. The use of PPIs associated with community-acquired C. difficile diarrhea was an adjusted OR of 2.9 (95% CI, 2.4–3.4). The use of H\textsubscript{2}RAs associated with C. difficile was an adjusted OR of 2.0 (95% CI, 1.6–2.7).

This study underscored the risk of acid-suppressive therapy and infection and further cautions against the excessive use of PPIs and H\textsubscript{2}RAs among patients in the community.

Donskey et al.,\textsuperscript{42} Kyne et al.\textsuperscript{43}

Other investigators have provided positive correlations between PPIs and the colonization and infection with gram-negative bacilli, methicillin-susceptible Staphylococcus aureus (MSSA), methicillin-resistant S. aureus (MRSA), and vancomycin-resistant enterococci (VRE). Although further scrutiny is needed to confirm these data, they reveal long-term concerns for the inappropriate usage of PPIs within the current literature.

Cook et al.\textsuperscript{44,45}

Of course, concerns about pneumonia and acid suppression have been studied in the critically ill. Acid-suppressant therapy has become a cornerstone in the prophylaxis of stress-related mucosal bleeding (SRMB) in this patient population. Although few critically ill patients are truly at risk of clinically significant bleeding that would lead to death, Cook et al.\textsuperscript{44} identified two independent risk factors of concern: respiratory failure and...
coagulopathy. Therefore, critically ill patients with these risk factors should receive prophylaxis for SRMB.

The choice of acid-suppressant therapy has been controversial because of concerns about the risk of pneumonia. Comparing ranitidine (Zantac, GlaxoSmithKline) and sucralfate (Carafate, Aventis), Cook et al., in another study, did not find any significant differences in rates of pneumonia in either group \(P = .19\), confirming that \(H_2\)RAs might be safely used in patients with SRMB.\(^4\) However, with the recent FDA approval of omeprazole for this condition,\(^3\) the risk of pneumonia from PPIs becomes an important consideration.

Kantorova et al.\(^4\)

Kantorova and colleagues found no differences in rates of nosocomial pneumonia in patients taking omeprazole, famotidine (Pepcid, Merck), or sucralfate \(P > .34\). Even so, as PPI usage increases in patients with SRMB, we must consider the possible increased risk of opportunistic infections. At this time, there is no evidence-based literature that supports the routine use of acid-suppressant agents for SRMB in patients not situated in intensive care units (ICUs), such as those in the previously mentioned studies of Nardino, Naunton, and Pham et al.\(^25–27\)

**Overall Findings**

The results of these aforementioned case-control studies indicate a seemingly small but statistically significant risk of infection associated with the long-term use of PPIs; therefore, this concern cannot be summarily dismissed. More prospective controlled studies in this arena are required to elucidate the causal relationships between PPI use and \(C.\) difficile disease and pneumonias.

**INVESTIGATIONAL INDICATIONS FOR PPIs**

The therapeutic benefits of PPIs appear obvious for all of their current FDA-approved indications, and many other interesting off-label treatment regimens are under study. For instance, a PPI/\(H_2\)RA combination has been prescribed for GERD patients with nocturnal symptoms or presentations refractory to once-daily PPI therapy.\(^4\)

At first glance, a PPI/\(H_2\)RA combination seems contradictory, because \(H_2\)RAs limit the number of active pumps available for PPIs to inactivate. In addition, up-regulation of parietal cells by \(H_2\)RAs appears to further limit the effectiveness of PPIs. However, some data do justify the addition for short-term benefit or acute symptoms of GERD.\(^31,32,34–37\) However, long-term combination therapy with these agents (for more than seven days) has been linked to decreased maintenance of gastric pH and thus should be avoided.\(^4\)

The practice of switching from a once-daily PPI regimen to a twice-daily schedule in many cases has stemmed from data demonstrating a shorter time frame for ulcer healing\(^5\) as well as improved control of refractory GERD symptoms\(^5\) with the higher dose. Despite data supporting the efficacy and safety of long-term once-daily PPIs,\(^54,55\) none of the data extend to define the added benefits or risks of twice-daily dosing of chronic PPI therapy to the general patient population with other indications.
Another regimen, called “on-demand therapy” (ODT), is surfacing. Patients are allowed to initiate as-needed (p.r.n.) PPI therapy for variable durations according to their own GERD symptoms. This ODT regimen provides questionable benefits and seems contrary to the pharmacological properties possessed by these agents. PPIs suppress active proton pumps and are likely to be suboptimally effective on an as-needed basis.

Most recently, a review by Zacy et al. indicated that intermittent PPI or H2RA therapy was not beneficial in maintaining control of esophagitis but was effective for the acute relief of heartburn. Interestingly, on-demand therapy with PPIs may be beneficial in non-erosive GERD (NERD); patients with NERD make up a considerable proportion of the patient population. Certainly, patient education and careful selection are essential for the success of this PPI modality.

A more pervasive and relevant issue for hospital-based practitioners is the widespread practice of prescribing acid-suppressive agents to prevent SRMB in the general medicine services. However, this topic has not been thoroughly studied in any of the current literature, and most general medicine patients do not meet the criteria for independent risks of ventilatory support or coagulopathies, as outlined by Cook et al. Therefore, until definitive data showing benefits are available, the practice of using PPIs for SRMB prophylaxis in these non-ICU patients is not advisable.

**CONCLUSION**

The increased usage of PPIs in both inpatient and outpatient settings needs to be more critically questioned. Certainly, many patients with GI diagnoses have legitimate needs for these drugs to enhance their quality of life; in these cases, PPIs should not be withheld. However, the preponderance of data suggests that the prolific use of PPIs is often accompanied by medically unjustified indications, including the emerging tendency to prescribe them for preventing stress ulcers in low-risk patients.

Practitioners should consider the high cost of these medications in the already fiscally overloaded health care system, the potential for significant drug–drug and drug–nutrient interactions, and the possible increased risk of infection. Vigilant health care professionals should assess the appropriate use of PPIs for all patients upon admission, on discharge from inpatient care, and during routine visits to outpatient settings.

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