INTRODUCTION

Acid-peptic disorders comprise conditions whose pathogenesis involves the effects of gastric acid and peptic activity on the tissue, although other factors may also contribute to the condition.\(^1\) Included among these disorders are gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), gastroduodenal injury and resultant bleeding caused by medications (e.g., aspirin and other nonsteroidal anti-inflammatory drugs [NSAIDs]), and such acid-hypersecretory conditions as Zollinger–Ellison syndrome.

With an estimated prevalence of 25% to 35% in the general population, acid-peptic disorders are among the most common conditions diagnosed and treated by primary care physicians, internists, and gastroenterologists.\(^2\) Rheumatologists, orthopedic surgeons, otolaryngologists, surgeons, and intensivists are also major prescribers of these drugs for preventing and treating acid-peptic disorders.

The medical impact of these disorders and their treatment is substantial, as is their effect on patients’ quality of life. In addition, their burden on society is enormous. Indeed, it is estimated that acid-peptic disorders account for more than $20 billion in health care expenditures in the U.S. annually.\(^2\)

The pathophysiology of acid-peptic disorders involves an imbalance between the secretion of acid (and pepsin) and the mucosal defenses of the exposed tissue. Treatment is centered on correcting this imbalance and is detailed in numerous guidelines. For decades, the primary means of therapy was to neutralize gastric acid with antacids. The advent of cimetidine (Tagamet\textsuperscript{®}, GlaxoSmithKline), the first marketed histamine-2 receptor antagonist (H\(_2\)RA), in 1977 represented an important advance in the management of patients with acid-peptic disorders, achieving the reduction of gastric acid secretion while avoiding the inconvenience of large, multiple daily doses of antacids.

Today, proton pump inhibitors (PPIs) have largely supplanted the H\(_2\)RAs. Compared with H\(_2\)RAs, PPIs are more effective suppressors of gastric acid secretion. Moreover, they can be administered once daily in many patients, they are well tolerated, and they are not associated with the development of pharmacological tolerance or refractoriness. Omeprazole (Prilosec\textsuperscript{®}, AstraZeneca), the first drug of this class, was approved by the FDA in 1989, followed by lansoprazole (Prevacid\textsuperscript{®}, TAP) in 1995, rabeprazole (Aciphex\textsuperscript{®}, Janssen/Esai) in 1999, pantoprazole (Protonix\textsuperscript{®}, Wyeth) in 2000, and esomeprazole magnesium (Nexium\textsuperscript{®}, AstraZeneca) in 2001.\(^3\)

The indications approved for these agents vary, but they include the most prevalent and clinically important acid-peptic disorders (Table 1).

This article summarizes the pertinent data on the efficacy and safety of PPIs in the treatment of acid-peptic disorders and describes important considerations in selecting among these agents and between intravenous (IV) and oral preparations.

PHARMACOLOGY AND PHARMACOKINETICS

All PPIs are substituted benzimidazoles that suppress the final step in gastric acid secretion by binding to the proton pump (H\(^+\)/K\(^+\)-ATPase enzyme system) on the gastric parietal cell.\(^4\) When administered, PPIs are prodrugs that require conversion to an active moiety. This conversion occurs when the prodrug reaches a suitably acidic environment and is protonated, mainly within the secretory canalicular space of the parietal cell.

After conversion, the active species binds to cysteine residues, generally resulting in variable but slowly reversible

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**Table 1  Currently Approved Indications for the Use of Proton Pump Inhibitors**

- Treating symptomatic GERD
- Healing erosive esophagitis
- Maintaining healing of erosive esophagitis
- Treating hypersecretory conditions, including Zollinger–Ellison disease
- Healing duodenal ulcer
- Maintaining healing of duodenal ulcer
- Healing gastric ulcer
- Eradicating *Helicobacter pylori*
- Treating NSAID-induced ulceration
- Preventing NSAID-induced ulceration

GERD = gastroesophageal reflux disease; NSAID = non-steroidal anti-inflammatory drug.

Data from package inserts for Protonix\textsuperscript{®}, Nexium\textsuperscript{®}, Prevacid\textsuperscript{®}, Prilosec\textsuperscript{®}, and Aciphex\textsuperscript{®}\(^6,56–59\)

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inhibition of acid secretion by the proton pump. Some minor differences exist among the PPIs with respect to their mechanisms of action within the parietal cell. For example, rabeprazole forms a partially reversible bond with the proton pump, whereas pantoprazole preferentially binds avidly to an additional acid-inhibiting cysteine residue located deep within the membrane, which greatly impairs the reversibility of binding and prolongs duration of action. The clinical significance of these differences is unknown.

Because PPIs inhibit only actively secreting proton pumps, they should be administered when the maximum number of pumps is activated. Accordingly, patients should be instructed to take these medications about 30 minutes before a major meal, not at bedtime. Ideally, meals should be high in protein and low in fat to maximize stimulation of secretion (pump activity) and, hence, drug efficacy.

The suppression of gastric acid secretion associated with the IV administration of PPIs is rapid and profound. When these agents are administered orally, the onset of activity of the first dose is slower than that of antacids or H₂RAs. However, with repeated dosing and a long duration of action, no significant start-up delay is observed. For instance, in healthy volunteers, an initial oral dose of pantoprazole 40 mg inhibited acid secretion by an average of 51% within 2.5 hours. After seven days of once-daily dosing, however, acid secretion was inhibited by an average of 85% around the clock in most subjects.

In contrast to H₂RAs, there is no evidence of the development of pharmacological tolerance to PPIs in terms of their ability to raise gastric pH. This was shown in an early double-blind, crossover study by Merki and Wilder-Smith. In this study, 12 healthy subjects each received individually titrated 72-hour IV infusions of omeprazole, ranitidine (Zantac®, GlaxoSmithKline), or placebo, during which time gastric pH and dosing requirements were monitored. Whereas omeprazole consistently maintained a gastric pH above 4, the investigators recorded marked and statistically significant (P < .001) tolerance to the antisecretory effect of ranitidine infusion.

The pharmacokinetic profiles of the PPIs are summarized in Table 2. Despite the relatively short elimination half-lives of these products, their minimally irreversible binding to the proton pump allows for a long duration of acid suppression and once-daily dosing in most patients.

### EFFICACY

#### Gastroesophageal Reflux Disease

GERD is a clinical manifestation of excessive reflux of acidic gastric contents into the esophagus, resulting in irritation or injury to the esophageal mucosa. It is increasingly recognized that, in some cases, reflux extends beyond the esophagus into the pharynx, from where the refluxate may disperse to cause injury in the throat, larynx, lungs, teeth, ears, or sinuses. The reflux is caused by an impairment of the normal antireflux barrier between the stomach and the esophagus. Primary factors in its development are lower esophageal sphincter (LES) incompetence, transient LES relaxation, hiatal hernia, and faulty neutralization and clearance of refluxate.

The cardinal symptoms of GERD include acid regurgitation and heartburn.

GERD is among the most prevalent of gastrointestinal (GI) disorders. In a population-based study by Locke et al., nearly 20% of subjects experienced heartburn or acid regurgitation at least once weekly. By some estimates, however, the overall U.S. prevalence of GERD may be as high as 42%.

In well-controlled clinical trials, PPIs have been shown to be the most effective available option in the acute treatment of GERD and in maintenance therapy. A careful meta-analysis by Chiba et al. showed that PPIs achieve both more rapid and ultimately superior healing and symptom relief than H₂RAs or placebo (Figure 1).

#### Acute Treatment

In randomized, controlled, clinical trials conducted during the past decade in patients with erosive esophagitis, healing rates achieved with the available PPIs have been similar.

Most recently, Gillessen et al. randomly assigned patients with endoscopically proven GERD to double-blind, once-daily treatment with either pantoprazole 40 mg (n = 113) or esomeprazole 40 mg (n = 114). Healing was assessed via endoscopy, and the effect of treatment on GERD-related symptoms was evaluated by direct questioning of patients. Overall healing rates in the populations were identical on intent-to-treat (ITT) analysis and were 95% with pantoprazole and 90% with esomeprazole on per-protocol analysis (Figure 2). Overall relief of GERD symptoms was reported by 50% of ITT patients receiving pantoprazole and by 47% receiving esomeprazole. In the per-protocol population, 55% of the pantoprazole subjects and 51% of those receiving esomeprazole reported sympto-

### Table 2 Key Pharmacokinetic Characteristics of Available Proton Pump Inhibitors

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<tbody>
<tr>
<td>Bioavailability (%)</td>
<td>90</td>
<td>&gt;80</td>
<td>30–40</td>
<td>77</td>
<td>52</td>
</tr>
<tr>
<td>Time to peak concentration (h)</td>
<td>1.5</td>
<td>1.7</td>
<td>0.5–3.5</td>
<td>2.5</td>
<td>2–5</td>
</tr>
<tr>
<td>Elimination half-life (hours)</td>
<td>1.2–1.5</td>
<td>1.5</td>
<td>0.5–1</td>
<td>1</td>
<td>1–2</td>
</tr>
<tr>
<td>Primary route of excretion</td>
<td>Renal</td>
<td>Biliary</td>
<td>Renal</td>
<td>Renal</td>
<td>Renal</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>97</td>
<td>97</td>
<td>95</td>
<td>98</td>
<td>96</td>
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</tbody>
</table>

matic relief. This difference was not statistically significant.17

Symptomatic relief is typically the primary goal of the patient, and the speed at which symptoms resolve with PPI treatment appears to be dose-related. For example, Castell et al. showed that, based on patient diaries, lansoprazole 30 mg produced better symptomatic relief early in treatment than lansoprazole 15 mg or omeprazole 20 mg in patients with erosive GERD.14 Presumably, the higher dosages of other PPIs that are available by prescription only, likewise, would be more effective than the lower dosage of omeprazole that is obtainable without prescription—particularly in patients with moderate-to-severe disease.

**Maintenance Therapy**

Because of the high potential for recurrence of disease, maintenance therapy is an important component in the management of many patients with GERD.18 Indeed, most patients with severe symptoms, erosive esophagitis, or complications associated with GERD require continuous maintenance therapy after healing has been achieved. As in acute therapy, the superiority of PPIs over H2RAs in maintaining esophageal healing and symptom control is well established.19–21

In their study, Vigneri et al. randomly assigned 175 adults with newly healed esophagitis to 12 months of treatment with one of five regimens: (1) cisapride (Propulsid®, Janssen) 10 mg three times daily, (2) ranitidine 150 mg three times daily, (3) omeprazole 20 mg once daily, (4) ranitidine plus cisapride, or (5) omeprazole plus cisapride.21 (Cisapride is no longer available in the U.S.)

Endoscopy was performed after six and 12 months of treatment. Omeprazole monotherapy was significantly more effective than cisapride (P = .02) or ranitidine (P = .003). Combination therapy with omeprazole plus cisapride was significantly more effective than cisapride alone (P = .003), ranitidine alone (P < .001), or ranitidine plus cisapride (P = .03). Ranitidine plus cisapride was significantly better than ranitidine alone (P = .05). PPI-based regimens were also superior with respect to heartburn, pain, and regurgitation scores.21

**Time of Dosing**

Because PPIs bind only to activated proton pumps, they should be administered before meals.22 Pehlivanov et al. performed a study to compare the effect of morning and evening pre-meal administration of rabeprazole.23 In a double-blind fashion, 20 subjects with GERD received either rabeprazole 20 mg or placebo 30 minutes before a standardized breakfast or dinner for seven days. After a seven-day washout period, the regimens were reversed. Combined esophageal and gastric 24-hour pH monitoring was performed before and on day seven of each treatment. Although both regimens significantly increased gastric pH, the evening dosing of the PPI was associated with significantly better control of nocturnal gastroesophageal reflux than morning dosing.23

This small study with one PPI suggests that
administration of the drug before dinner may be preferable to administration before breakfast for patients with nocturnal GERD. This may differ in the case of larger doses of the longer-acting PPIs. Regardless of timing, however, some patients require twice-daily dosing from the outset of treatment in order to obtain satisfactory control of symptoms.

Intermittent and As-Needed (p.r.n.) Therapy
For some patients, intermittent or on-demand therapy with a PPI may be more appropriate, equally satisfactory, and less expensive than maintenance therapy. Talley et al. randomly assigned 721 patients who had achieved complete heartburn relief with short-term PPI therapy to on-demand esomeprazole, 20 mg or 40 mg, or placebo (maximum one dose per day) for six months. Compared with placebo, significantly fewer patients discontinued treatment with on-demand esomeprazole. The higher dose of esomeprazole provided no additional benefit over the lower dose.

In another study, Bytzer et al. found that on-demand therapy with rabeprazole 10 mg daily was highly effective in the maintenance treatment of nonerosive reflux disease.

Empirical and Diagnostic Use of PPIs
In patients with symptoms suggestive of uncomplicated GERD, a two-week trial of a PPI is a cost-effective means of confirming the diagnosis. In the individual patient, symptomatic response to such a trial is diagnostically as sensitive and specific in predicting GERD as the cause of symptoms as is 24-hour intrasophageal pH monitoring. Similarly, a lack of response to a PPI (given in adequate dosage) is strongly predictive that the patient does not have GERD and indicates the need for further diagnostic assessment.

Peptic Ulcer Disease
Peptic ulcers (gastric and duodenal) are lesions in the gastric or duodenal mucosa that reach or extend through the muscularis mucosa. In the general population, the lifetime prevalence of PUD ranges from approximately 5% to 10%. It is the most frequent cause of acute bleeding in the upper GI tract and is associated with approximately 50% of cases. The societal burden of PUD is substantial; it is estimated that peptic ulcers result in 2.7 million office visits and 470,000 hospital admissions yearly. Estimates of the annual direct medical costs associated with PUD range from $3 billion to $6 billion; costs attributed to lost work time are nearly $200 million annually.

Peptic ulcers usually occur in patients who have normal acid secretion but whose GI mucosal defenses have been disrupted because of *Helicobacter pylori* infection or therapy with aspirin or other NSAIDs or other newer drugs, such as clopidogrel (Plavix®, Bristol-Myers Squibb/Sanofi) or alendronate (Fosamax®, Merck). They may also occur in patients with other acid-secretory disorders.

Controlled studies of PPIs in the treatment of PUD have demonstrated superior healing rates, a shorter time to healing, and more effective symptomatic relief than those associated with H₂RAs. Salas et al. performed a meta-analysis of 16 trials of PPIs in the treatment of patients with gastric ulcer. Four of these compared a PPI with placebo, nine compared a PPI with ranitidine, and three compared a newer PPI (lansoprazole, pantoprazole, or rabeprazole) with omeprazole. Healing rate ratios relative to ranitidine and omeprazole are shown in Figure 3. Compared with the H₂RA, the pooled healing rate ratio (RR) of lansoprazole, omeprazole, and pantoprazole was increased at both four and eight weeks. The healing risk ratio in each trial of the newer PPIs was found to be at least com-
In the treatment of PUD, acid-suppression therapy should be accompanied by eradication of *H. pylori*-infected patients. Several effective PPI-based regimens in this setting are shown in Table 3.

Gisbert et al. performed a meta-analysis of studies evaluating pantoprazole as part of an eradication regimen for *H. pylori*. In three studies of pantoprazole plus one antibiotic, the mean eradication rate was 60%. In 80 studies of pantoprazole plus two antibiotics, the rate ranged from 69% to 85%. Twelve studies in the analysis were direct comparisons of pantoprazole-based regimens (n = 534) with regimens utilizing other PPIs (n = 603). The mean rates for eradication of *H. pylori* were 83% with pantoprazole plus antibiotics and 81% with other PPIs. This difference was not statistically significant.

### Acute Bleeding

Bleeding peptic ulcers are a common cause of emergency hospitalization and are associated with substantial morbidity, mortality, and health care expense. Despite current treatment approaches—fluid replacement, acid suppression, endoscopic hemostasis, and surgery—mortality rates as high as 30% are recorded in elderly patients. Data on the efficacy of H2RAs in the treatment of bleeding peptic ulcers are conflicting. Indeed, meta-analyses of IV H2RA therapy have found virtually no important difference between this approach and placebo in patients with bleeding duodenal ulcer and only small benefits in those with bleeding gastric ulcer. In contrast, the data support the role of PPIs in the acute and preventive treatment of bleeding peptic ulcers.

In a double-blind study involving patients who had undergone successful endoscopic hemostasis, Lau et al. randomly assigned subjects to receive IV omeprazole (a bolus injection of 80 mg, followed by a 72-hour infusion of 8 mg/hour) or placebo (n = 120). After the infusion, all subjects received oral omeprazole 20 mg once daily for eight weeks. The primary endpoint, recurrence of bleeding within 30 days after endoscopy, occurred in 6.7% of subjects in the IV omeprazole group and in 22.5% of those in the IV placebo group (P < .001).

Andriulli et al. analyzed data from 35 randomized trials comparing PPIs with H2RAs and/or placebo in patients (n = 4,843) with high-risk bleeding peptic ulcers. The key findings were as follows:

- **PPI monotherapy**, administered either orally or by bolus injection, was superior to H2RAs and to placebo in reducing recurrent bleeding rates in patients with or without active bleeding at the time of endoscopic assessment. The need for surgery was also lower in the PPI patients than in the H2RA patients.
- In patients without active bleeding, the efficacy of PPI monotherapy was similar to that of endoscopic hemostasis plus H2RA.
- PPI plus endoscopic hemostasis was superior to PPI alone with respect to reducing recurrent bleeding and surgery rates, and was superior to endoscopic therapy alone in reducing the recurrence of bleeding.
- The benefit of PPI therapy appeared to be independent of the route of administration or dosage.

In other meta-analyses, continuous IV infusions of PPIs at high doses were shown to reduce rates of recurrent bleeding, repeated endoscopy, blood transfusion, and surgical intervention, although the mortality rate (which is frequently a result of causes other than recurrent bleeding) was not significantly affected.

### Prevention and Healing of NSAID-Induced Ulceration

There is a clear association between the use of NSAIDs and PUD. Symptomatic ulcers occur in approximately 1% of patients taking non-salicylate NSAIDs after three to six months of chronic use and in 2% to 4% of these patients after one year, resulting in more than 100,000 hospitalizations and 15,000 deaths annually. Even the low doses of aspirin used for prophylaxis of cardiac events puts patients at risk for GI bleeding.

Strategies to reduce NSAID-induced mucosal injury and platelet dysfunction are as follows:

1. Patients should avoid NSAIDs or minimize their dosage; however, this may be impractical for patients with chronic inflammatory conditions.
2. As an alternative, physicians may select newer NSAIDs, such as cyclooxygenase-2 (COX-2) inhibitors, which may be less likely to cause bleeding than older NSAIDs; however, these drugs may be associated with an increased risk of cardiovascular events.
3. A cytoprotective agent such as misoprostol (e.g., Cytocept®, Pfizer) or an acid-suppressing drug might be administered together with an NSAID. A growing body of data suggests that PPIs are more effective than either H2RAs or misoprostol in preventing NSAID-induced ulcers and are better tolerated than the latter.

Yeomans et al. randomly assigned 541 patients who required continuous treatment with NSAIDs and who had ulcers to double-blind treatment with omeprazole, 20 mg or 40 mg daily or ranitidine 150 mg twice daily. After eight weeks, ulcers

<table>
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<tr>
<th>Regimen</th>
<th>Efficacy</th>
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<tr>
<td><strong>Two-Drug</strong></td>
<td></td>
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<tr>
<td>Amoxicillin + PPI</td>
<td>+</td>
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<tr>
<td>Clarithromycin + PPI</td>
<td>++</td>
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<tr>
<td><strong>Three-Drug</strong></td>
<td></td>
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<tr>
<td>Clarithromycin + metronidazole + PPI</td>
<td>+++</td>
</tr>
<tr>
<td>Clarithromycin + amoxicillin + PPI</td>
<td>+++</td>
</tr>
<tr>
<td>Amoxicillin + metronidazole + PPI</td>
<td>+++</td>
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<tr>
<td><strong>Four-Drug</strong></td>
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<tr>
<td>BSS + metronidazole + tetracycline + PPI</td>
<td>+++</td>
</tr>
<tr>
<td>BSS + metronidazole + clarithromycin + PPI</td>
<td>+++</td>
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*BSS = bismuth subsalicylate.*
resolved in 80% of the subjects receiving omeprazole 20 mg, 79% of those taking omeprazole 40 mg, and 63% of those given ranitidine ($P < .001$ compared with both doses of omeprazole).

In a similar study, Hawkey et al. compared two doses of once-daily omeprazole with misoprostol 200 mcg four times daily. The success rate with omeprazole 20 mg was 76%; with omeprazole 40 mg, it was 75%; and with misoprostol, it was 71%.

In their randomized, double-blind trial, Stupnicki et al. compared the efficacy and tolerability of pantoprazole 20 mg once daily with misoprostol 200 mcg twice daily in 515 arthritis patients receiving long-term NSAID therapy. Endoscopy was performed at the baseline evaluation and after three and six months of therapy. Efficacy endpoints included three criteria for remission: “therapeutic failure,” “endoscopic failure,” and “symptomatic failure.” Results are shown in Figure 4. Pantoprazole was significantly superior ($P \leq .005$) to misoprostol with respect to each of these endpoints.

**Table 4** Potential Drug Interactions Reported in the Prescribing Information for Proton Pump Inhibitors

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<tr>
<td>Drug dependent on gastric pH for absorption</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Diazepam</td>
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<td>X</td>
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<td>Phenytoin</td>
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<td>Propranolol</td>
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<td>Theophylline</td>
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<tr>
<td>Warfarin</td>
<td>X</td>
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Data from package inserts.

**Other Acid-Related Disorders**

Other disorders in which PPIs today play a prominent therapeutic role include Zollinger–Ellison syndrome and stress-related mucosal damage. PPIs also play a role in the prevention of aspiration pneumonitis.

**Zollinger–Ellison Syndrome**

A rare disorder associated with the presence of gastrin-secreting tumors, Zollinger–Ellison syndrome is characterized by chronic acid hypersecretion and severe PUD. By virtue of their profound, long-lasting acid suppression, PPIs are considered the therapy of choice for the long-term treatment of this disorder. Omeprazole, lansoprazole, and pantoprazole have all demonstrated efficacy in clinical studies of this syndrome.

**Stress-Related Mucosal Damage**

Most critically ill patients experience stress-related mucosal damage of the upper GI tract. The likelihood that mucosal damage and subsequent bleeding will develop is directly related to the severity of the patient’s underlying disease. The most widely used drugs for the prevention of stress-related mucosal injury have been IV H$_2$RAs. It has been suggested, though, that intermittent dosing with an IV PPI might be an effective alternative to high-dose continuous infusions of an H$_2$RA in critically ill patients.

**Prevention of Aspiration Pneumonitis**

Aspiration of gastric contents is a potentially fatal complication of general anesthesia; this complication can lead to chemical (aspiration) pneumonitis, airway obstruction, or bacterial pneumonia. Another potential cause of the pneumonia seen in patients using acid-suppressing drugs is bacterial colonization of the stomach resulting from hypochlorhydria, followed by translocation of the bacteria into the bloodstream and the lungs.

The severity of lung injury associated with aspiration is determined by the pH and volume of the aspirate. Omeprazole, lansoprazole, and pantoprazole, although not approved for use in this setting by the FDA, have been shown to effectively increase gastric pH and reduce gastric fluid volume in surgical patients who are at risk for aspiration pneumonitis.

**SAFETY AND TOLERABILITY**

PPIs are generally well tolerated. The most commonly occurring adverse effects are headache, diarrhea, constipation, abdominal pain, nausea and vomiting, and rash. The incidence of these effects is generally similar to that of placebo, occurring in fewer than 5% of patients. PPIs have also proved safe after long-term use; to date, none of the agents has been associated with an increased risk of gastric cancer or other clinically significant adverse sequelae.

**DRUG INTERACTIONS**

PPIs may interact with other drugs via two basic mechanisms: (1) by raising the pH of the stomach contents (which influences the absorption of concomitantly administered drugs) and (2) by altering the hepatic metabolism of other drugs.

All PPIs raise the gastric pH. Accordingly, each of these agents may inhibit the absorption of medications that require an acid environment for optimal absorption. These include ampicillin, griseofulvin, ketoconazole, itraconazole, iron, vitamin B$_{12}$, and enoxacin. In addition, all PPIs are metabolized to varying degrees by the hepatic cytochrome P-450 enzymatic system. They may thus alter the metabolism of other
medications by inducing or inhibiting cytochrome P-450 (Table 4). Despite this potential, however, few clinically significant drug interactions of this type have been reported.4

PHARMACOECONOMICS

The marked efficacy and safety of PPIs have led to widespread prescribing of these agents. In 2003, an estimated 95.2 million prescriptions for PPIs were filled in the U.S.60 Accordingly, PPIs have come to represent a significant cost item in the prescription budgets of managed health care systems and, as such, are objects of cost-containment efforts.

Just as in other disease states, however, the acquisition cost of medications used to treat acid-peptic disorders is only one component of the total cost of care. For example, although the acquisition cost of PPIs is greater than that of H₂RAs, major overall cost savings are associated with the use of PPIs as a result of their superior efficacy. Specific cost savings include reductions in expensive diagnostic tests, such as endoscopy, and reductions in patients’ utilization of providers. PPIs also reduce the occurrence of complications (such as strictures in GERD patients or hemorrhages in NSAID users) and, consequently, reduce hospital admissions and decrease the need for surgery, transfusion, intensive care, and the use of other expensive medications. They also shorten the duration of hospital stays and lower mortality rates.

There is debate as to the benefit of step-down or step-up approaches in the treatment of acid-peptic disorders.61 Step-down therapy employs a brief course of treatment with a PPI, followed by a re-evaluation of the patient. If the patient has improved, therapy may continue with a lower-dose PPI, an H₂RA, or simple lifestyle modifications. In the step-up approach, an H₂RA is tried before PPIs are considered.

Pharmacoeconomic Models

The extent to which real-world conclusions can be drawn from pharmacoeconomic models is inconclusive. Fairman et al. replicated two models of H. pylori eradication and then validated those models by replacing their assumptions with empirical data from a multi-payer claims database.62 The data represented claims from 435 commercially insured patients in the U.S. who had been treated with one of three regimens: bismuth plus metronidazole plus tetracycline (BMT), PPI plus clarithromycin, or PPI plus amoxicillin. Outcome measures included the cost per effectively treated (not re-treated) patient.

Without adjustment, the costs per effectively treated patient were $1,001, $980 and $1,730, respectively. When adjusted to reflect the authors’ empirically derived data, the estimates changed to $852, $1,118 and $1,131, respectively. Managed care organizations (MCOs) should thus first identify the source of the cost-effectiveness analysis (potential bias) and then carefully examine the key assumptions of the models before accepting them at face value, especially the issues of contract pricing, and whether benefit is being examined from the perspective of the patient or the provider.

Judgments relating to the utility of a given model must be based on its relevance to the individual institution’s costs of acquisition,
patient mix, practice patterns and guidelines, standard of care, and level of control over physicians and patients.

**Influencing Physician Prescribing**

In making decisions about prescribing, physicians are under conflicting pressures: optimally, they must meet the clinical needs of their patients, and they must contain escalating health care costs. A survey of primary care physicians found that many believe cost-containment measures, such as imposed prescribing thresholds for PPIs, clash with their commitment to provide the highest level of care.

However, implementing restrictive formularies does change prescribing patterns—both within and outside an MCO. As reported by Wang et al., within three months after the state of Maine selected pantoprazole as the only preferred PPI on its Medicaid formulary, its market share rose 79% among Medicaid prescriptions, 10% among cash prescriptions, and 7% among non-Medicaid, third-party prescriptions.

An alternative to prescribing restrictions is the implementation of incentive-based formularies such as those with tiered co-payments. Here, the intent is to preserve choice for patients and physicians by providing some level of coverage for most drugs while using the size of the co-payment to encourage selection of those drugs that are more cost-effective for the plan. Instituting such a program results in a significant shift from nonpreferred to preferred brands in classes of medications such as PPIs.

Still another option is to allow patients to regulate their own treatment. In research conducted in the United Kingdom, Pollock et al. conducted interviews with 82 patients who used prescription PPIs. Nearly half of those who had had their brand of PPI switched or their dosage reduced as a cost-containment measure ultimately reverted to their former regimens. However, more than one third of the subjects had taken the initiative to titrate their own dosage down to the lowest level that would control their symptoms.

**FORMULARY ISSUES**

At their recommended dosages, all PPIs are effective for the treatment of acid-peptic disorders, and all are tolerable and safe for short-term or long-term use. Although minor pharmacodynamic and pharmacokinetic differences exist among them, none has been shown in controlled clinical trials to possess meaningfully better efficacy or safety than another. Accordingly, acquisition cost becomes an obvious factor in determining which PPI a health system selects for preferred status. Other important considerations include approved indications (see Table 1), available formulations (see Table 2), and the drug-interaction profile (see Table 4).

Health systems also consider factors that are specific to their own sites; the nature of these varies with the setting. In MCOs, for example, such considerations might include their total disease-management costs with respect to acid-peptic disorders, the role and frequency of endoscopy in the network, the mix of patients receiving short-term and long-term therapy, and issues relating to patient compliance.

**CONCLUSION**

Acid-peptic disorders are highly prevalent in the U.S. and are an important cause of morbidity and mortality, of decrements in quality of life for patients, and of health care expenditures. PPIs are the most effective therapies available for the treatment of these disorders. They have proved to be safe and well tolerated, to present few clinically significant drug interactions, and to improve patient outcomes.

Numerous studies have repeatedly supported the superiority of PPIs over H$_2$RAs; thus, PPIs should be seriously considered for inclusion in most hospital and managed care formularies. Because agents in the class of PPIs may be considered to be therapeutically equivalent, with only minor differences in efficacy and pharmacokinetics among them, selecting an agent for inclusion on a formulary is often determined by financial considerations.

Each institution should determine which PPI is most cost-effective in relationship to its disease-state management, usage and dosage patterns, indications, acquisition costs, and administration costs. The acquisition cost at local pharmacies may be a factor for ambulatory and managed care patients.

The results of these individual institutional evaluations will be varied; thus, different decisions will be made as to the most appropriate PPI to be added to the formulary.

**REFERENCES**

PPIs and Acid-Peptic Disorders


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ADDITIONAL READINGS