ABSTRACT

The choice of a medical therapy to treat gastroesophageal reflux disease (GERD) centers around several factors, including the efficacy and safety of the agent and the severity of the patient's symptoms and complications. Although the efficacy of antacids and algic acid has not been proven definitively in clinical trials, these agents are effective against mild GERD symptoms in clinical practice. Along with sucralfate, these agents are also useful in special populations, such as pregnant women, for whom acid-suppressive therapy may not be the best option. The withdrawal of cisapride from the US market has lessened the role of promotility agents for treating GERD, as their efficacy must be weighed against their side effects. Acid-suppressive agents have become the drugs of choice for GERD. Both proton pump inhibitors (PPIs) and histamine H2-receptor antagonists effectively and safely treat GERD. However, PPIs have been shown to provide the highest levels of GERD symptom relief and esophageal healing to the most patients, in the shortest time, and with the fewest side effects.

Pharmacotherapy is considered first-line treatment for patients with gastroesophageal reflux disease (GERD). Although some guidelines recommend instituting lifestyle changes at the same time as an initial trial of empiric medical therapy, others note that these diet and lifestyle changes have little therapeutic benefit, and recommend medical therapy as initial treatment. The following medical therapies are available for the treatment of GERD:

- **Prokinetic agents**, which target the underlying motility dysfunction that causes GERD
- **Mucosal-protective agents**—ie, sucralfate, which binds with damaged mucosa to form a barrier against harmful acid reflux, and algic acid, which forms a foamy barrier on top of the refluxate to protect the esophagus
- **Acid neutralizers** (**antacids**), which work locally to raise the pH of the refluxate
- **Acid-suppressive agents**—ie, histamine H2-receptor antagonists (H2RAs) and proton pump inhibitors (PPIs), which inhibit acid production in the parietal cell.

Guidelines also differ on which medical therapy should be used as initial GERD treatment. Therapy for any disease must be effective and safe, and fit the needs of the patient. Other issues, such as concomitant conditions, recurrence of symptoms, and cost to treat, should also be considered when deciding on a course of therapy.

This article examines the safety and efficacy of the available medical therapies for GERD. End points for the efficacy of these agents include:

- **Symptom relief**, which is a measure of the reduction in symptoms (usually heartburn and regurgitation, but some studies assess noncardiac chest pain and other atypical or extraesophageal symptoms)
- **Symptom resolution**, which indicates the absence of symptoms
- **Erosive esophagitis healing rates**.

Maintenance studies have examined maintenance of erosive esophagitis healing and symptom recurrence. Safety considerations include adverse events and the effects of long-term treatment.

This article also presents data from placebo-controlled and comparative trials of the available H2RAs and the available PPIs, as well as trials comparing efficacy between H2RAs and PPIs. Much of the literature on GERD pharmacotherapy focuses on the safety and comparative efficacy of these acid-sup-
pressive agents. PPIs have been recognized as the most effective medical therapy for GERD symptom relief, for healing all grades of erosive esophagitis, and for maintenance of healing. Although some patients experience symptom relief and healing of erosive esophagitis with H2RAs, PPIs produce more frequent and rapid symptom relief and esophageal healing for a greater percentage of patients.1

Prokinetic agents that treat GERD increase lower esophageal sphincter pressure (LESP), accelerate gastric clearance, stimulate esophageal peristalsis, increase the amplitude of esophageal contractions, or perform a combination of two of these actions. All prokinetic agents (bethanechol, metoclopramide, domperidone, and cisapride) are effective, to varying degrees, in improving GERD symptoms and healing esophagitis. However, efficacy data for these agents come from small, sometimes poorly designed studies, often without a placebo control. Also, the adverse-event profile of these agents must be weighed against any clinical benefit of GERD treatment. Although domperidone (available in Canada but not in the United States) is well tolerated, metoclopramide and bethanechol have been associated with significant adverse events (Table 1).3 Cisapride, in particular, although the most effective of the prokinetic agents for treating GERD, was removed from the US market because of deaths associated with cardiac arrhythmia.

Bethanechol
Bethanechol is a direct-acting muscarinic receptor agent that acts by stimulating the parasympathetic nervous system to release acetylcholine. It has been shown to increase LESP and improve esophageal peristaltic clearing.

Clinical efficacy. Some small, double-blind, placebo-controlled studies have investigated the efficacy of bethanechol in GERD treatment, with mixed results. One placebo-controlled study conducted in 20 patients found that a 2-month course of bethanechol 25 mg four times daily reduced heartburn and reduced antacid use.1 However, in another study of 44 patients by Thanik and colleagues,4 the improvement of GERD symptoms in patients receiving bethanechol plus antacids was not statistically significantly different from that in patients receiving antacids plus placebo.

Results also differ among studies examining the efficacy of bethanechol in healing erosive esophagitis. In a comparative trial of bethanechol and cimetidine, the two agents had fairly similar healing rates (52% of patients receiving bethanechol and 68% of those receiving cimetidine experienced complete healing). Both agents were administered with high doses of antacids, which may have helped produce these high healing rates.1 Interestingly, although Thanik and colleagues4 found bethanechol to be no more effective than placebo in improving GERD symptoms, 45.5% of patients receiving bethanechol 25 mg four times daily experienced complete healing of erosive esophagitis, compared with 13.6% of patients receiving placebo plus antacids (P < 0.015).

Safety. Unfortunately, at the dosage level necessary to treat GERD (25 mg four times daily), bethanechol can cause significant side effects, such as abdominal cramping, blurred vision, fatigue, and increased urinary frequency. Side effects occur in about 10% to 15% of patients, and are more common in the elderly. Bethanechol is also associated with a long list of contraindications (Table 1) that compromise its use as an anti-GERD agent.1

Metoclopramide
Metoclopramide is a dopamine antagonist. Although its precise mechanism of action is unclear, it seems to sensitize tissues to the action of acetylcholine. It has been shown to increase the amplitude of gastric and esophageal contractions, increase LESP, and increase the speed of gastric emptying and intestinal transit.

Clinical efficacy. In two small, placebo-controlled studies in which 31 and 15 patients with GERD received metoclopramide 10 mg three times daily, symptom improvement did not differ significantly between the treatment and control groups. However, in studies conducted in 30 and 31 patients with GERD, a higher dosage of the agent, 10 mg four times daily, either alone or in combination with an antacid, was more effective than placebo at improving symptoms.5,6 Comparative studies have found that metoclopramide is as effective as H2RAs (cimetidine and ranitidine) in relieving heartburn and other GERD symptoms.7,8 All of these comparative trials were conducted in small patient populations,3 and all but one were conducted without a placebo control.8 The largest one, conducted in 73 patients, found no difference in symptom relief between patients given cimetidine 400 mg four times daily alone and those...
given a combination of cimetidine with metoclopramide 10 mg three times daily.9

Although symptom improvement has been demonstrated with metoclopramide, this agent does not seem to be significantly more effective than placebo at promoting healing of erosive esophagitis.3 In the one placebo-controlled study comparing it with cimetidine, metoclopramide improved the appearance of esophageal erosions in 82% of patients, but this was not significantly different from rate with either cimetidine or placebo (78% for each).8 In another comparative study, both metoclopramide and ranitidine produced significant healing, but metoclopramide was effective in fewer patients (52% healing rate, vs 81% with ranitidine).10 The recommended dosage of metoclopramide is 10 mg four times daily, whereas the recommended dosage of ranitidine is 75 mg twice daily.

Safety. To an even greater extent than with bethanechol, side effects are a significant drawback to GERD therapy with metoclopramide. Because it is a centrally acting dopamine antagonist that crosses the blood-brain barrier, antidopaminergic side effects are common, occurring in 20% to 30% of patients. Drowsiness and lassitude are most common, and anxiety, agitation, confusion, hallucinations, and motor restlessness have also been reported.3,11 The most serious effects are depression and tardive dyskinesia, which may be irreversible. Adverse events are most common at higher doses and in children, young adults, and the elderly. Other less common adverse events are listed in Table 1.

Domperidone
Domperidone is another dopamine antagonist, although it is not available in the United States. It stimulates esophageal peristalsis, increases LESP, and accelerates gastric emptying.

Clinical efficacy. As with bethanechol and metoclopramide, data on the efficacy of domperidone in GERD treatment come from small studies. The largest one, conducted in 45 patients, compared domperidone and ranitidine without a placebo control.

The efficacy of domperidone in GERD treatment has not been persuasively proven in well-controlled double-blind studies, and results with domperidone at dosages of 20 mg three or four times daily are inconsistent.3 In one study, domperidone was no more effective than placebo in reducing the number of reflux episodes or improving GERD symptoms, although antacids were used less frequently at the

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<td>Bethanechol</td>
<td>• Intravenous or intramuscular use may cause severe cholinergic reaction</td>
<td>• Abdominal cramping, blurred vision, fatigue, and increased urinary frequency in 10% to 15% of patients</td>
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<td>• Antidopaminergic side effects in up to 30% of patients, including drowsiness, lassitude, anxiety, agitation, and motor restlessness</td>
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<td>Domperidone</td>
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<td>• Dystonic reactions in 1% of patients</td>
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<tr>
<td></td>
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<td>• Parkinson symptoms (tremor, rigidity, akinesia, tardive dyskinesia) rare except with high doses (30–80 mg)</td>
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<td>• Gynecomastia, galactorrhea, and menstrual disorders</td>
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<td>• Otherwise well tolerated</td>
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TABLE 1
Contraindications and adverse events associated with prokinetic agents3

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end of the trial compared with baseline in the dom-
peridone group.12 Other studies have shown dom-
peridone to be effective in relieving symptoms but
not in healing esophagitis.3 In two non–placebo-
controlled comparative trials of domperidone and
H2RAs (ranitidine or famotidine), the two agents
proved to be similarly effective in symptom relief
and in promotion of esophageal healing. However,
the combination of domperidone with an H2RA
was not significantly better than each agent given
alone.13,14

Safety. Although domperidone is a dopamine
antagonist, it does not cross the blood-brain barrier
(unlike metoclopramide) and was developed to act
as a specific antagonist to the inhibitory effects of
dopamine on the gastrointestinal tract. It is well tol-
erated, with few significant side effects. The adverse
events that do occur are related to the stimulation
of prolactin release (Table 1) and are seen in
approximately 10% to 15% of patients. These
events can be seen with metoclopramide use but are
more common with domperidone because it is
administered in higher doses. Domperidone rarely
causes extrapyramidal side effects.3

Cisapride
Any discussion of cisapride must be prefaced with a
note on its profile and current market availability.
High blood concentrations of cisapride can cause
QT prolongation and cardiac arrhythmia, including
ventricular arrhythmia, such as torsades de pointes.
Coadministration of a number of drugs can reduce
hepatic metabolism of cisapride and increase the
likelihood of toxic concentrations.

Cisapride was removed from the US market in
July 2000 after 341 cases of arrhythmia and 80
deaths were spontaneously reported to the FDA
from July 1993 to May 1998. The agent is now
available only on a restricted basis through a limited-
access program for patients who have failed to
respond to or cannot receive alternate therapies.15

Cisapride acts locally on the gastrointestinal
tract and seems to facilitate release of acetylcholine
from postganglionic neurons in the myenteric
plexus. There is also evidence that it influences the
activity of other chemical mediators of mucosal and
muscular function in the gut, interacting with the
serotonin 5-HT4 receptor in the myenteric plexus.
Cisapride increases smooth muscle contractility,
increases LESP, and enhances esophageal peristaltic
function.

Clinical efficacy. Before its removal from the US
market, cisapride was indicated for supplemental
treatment of nocturnal heartburn symptoms. It was
the most effective promotility agent available for
the treatment of GERD, in terms of both higher
efficacy and fewer reported side effects. In clinical
trials, cisapride was consistently better than placebo
at improving the symptoms of GERD and promot-
ing healing of erosive esophagitis. Optimal efficacy
for relieving symptoms was achieved at a dosage of
10 mg three times daily, whereas 10 mg four times
daily showed efficacy in healing esophagitis. One
study found that 10 mg of cisapride given four times
daily was as effective as 20 mg given four times daily
in healing esophagitis.16

Comparative trials of cisapride and H2RAs yield-
ed similar efficacy rates in healing esophagitis.17 Gal-
miche and colleagues17 found that cimetidine 400
mg and cisapride 10 mg, each given four times daily,
produced endoscopic healing rates of 57% and 56%,
respectively, in patients with erosive esophagitis
grades I to III (ie, mild to moderate esophagitis).
(Here and except where noted otherwise, references
to erosive esophagitis grades in this article are to the
Savary-Miller classification system.)

MUCOSAL-PROTECTIVE AGENTS

Sucralfate
Sucralfate is a mucosal-protective agent that binds to
inflamed tissue, creating a protective barrier. It blocks
diffusion of gastric acid and pepsin across the barrier
and inhibits the erosive action of pepsin and bile.18

Sucralfate is available in the United States in

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**TABLE 2**

Results of comparative trials of sucralfate in the healing of erosive esophagitis

<table>
<thead>
<tr>
<th>Investigators</th>
<th>N</th>
<th>Weeks</th>
<th>Sucralfate</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon et al20</td>
<td>41</td>
<td>8</td>
<td>64%</td>
<td>68% (ranitidine)</td>
</tr>
<tr>
<td>Hameeteman et al21</td>
<td>42</td>
<td>8</td>
<td>31%</td>
<td>14% (cimetidine)</td>
</tr>
<tr>
<td>Laitinen et al22</td>
<td>68</td>
<td>6</td>
<td>53%</td>
<td>34% (alginate + antacid)</td>
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tablets and in suspension form. As suspension, sucralfate is administered in 1-g doses four times daily. Physicians rarely prescribe this agent to treat GERD, but it can be useful as an anti-GERD therapy in special populations, such as in women who are pregnant. Although sucralfate contains aluminum, which can be harmful to a fetus, little systemic absorption of the agent occurs. As a result, sucralfate is considered safe enough for the treatment of heartburn in pregnant women.

Clinical efficacy. The findings of three comparative, non–placebo-controlled studies examining the effects of sucralfate in patients with all grades of erosive esophagitis are summarized in Table 2. The trials compared sucralfate with H2RAs or with alginic acid plus antacids. Patients in all three studies had endoscopically confirmed reflux esophagitis, and the results of therapy were endoscopically confirmed as well. The degree of healing with sucralfate correlated with the degree of injury, with higher grades of erosive esophagitis responding less favorably to treatment. In all three trials, symptom improvement was rated as equally good for patients in all groups. Esophagitis healing rates among the sucralfate and H2RA recipients were not statistically significantly different in one trial but did differ in another study, with more patients showing healed or improved esophagitis in the sucralfate group. In the remaining study, sucralfate generated complete healing more often than did alginic acid/antacid. However, these studies are significantly limited by their relatively small size (40 to 70 patients) and lack of a placebo control.

Other studies have been conducted in more specific patient populations and have included a placebo arm as a comparison. Chiba and colleagues pooled data from several studies of the erosive esophagitis healing rates achieved with various agents, including sucralfate, in patients with grades II through IV esophagitis (Figure 1). Healing occurred in an average of 39% of patients who received sucralfate, but this healing rate was accompanied by a very large 95% confidence interval (3.6% to 74.8%), indicating that it was not statistically significantly different from the rate with placebo.

Sucralfate has also been studied in patients with GERD without erosive esophagitis. Simon and colleagues tested the effects of sucralfate gel and placebo in 141 patients with moderate to severe GERD but with no esophageal erosions or ulcers. The overall response rate after 6 weeks of treatment was 71% with sucralfate, compared with 29% with placebo (P < 0.0001). Improvement in the maximum severity of daytime and nighttime heartburn occurred in 77% and 67%, respectively, of patients given sucralfate, compared with 48% and 51%, respectively, of patients given placebo.

Alginic acid
Alginic acid is often given in combination with an antacid. The first component provides a floating barrier on the gastric pool to minimize contact between gastric contents and esophageal mucosa, while the antacid temporarily neutralizes stomach acid. Tytgat and Nio noted that improvement in GERD symptoms occurred in three of four studies that compared alginate/antacid combination therapy with placebo. However, when compared with antacids alone, the alginate combination therapy was superior in only one of four studies. Convincing proof of esophageal healing has never been obtained in any study, and alginic acid therapy is probably no better than antacid therapy in treating moderate to severe GERD.
practice, antacids help to control mild to moderate reflux symptoms in a large proportion of patients. 

Because they act locally, antacids are considered first-line therapy for pregnant women who experience heartburn. However, magnesium-containing agents should be avoided in the latter part of pregnancy.

Clinical efficacy. Despite widespread use of antacids, definitive evidence of their therapeutic benefit in the treatment of GERD is limited by the paucity of well-designed, large, placebo-controlled trials. For the placebo-controlled studies that are available, results are conflicting.

One placebo-controlled study comparing a high-dose antacid (10 mL seven times daily) with an H2RA in 37 patients with GERD found that symptom improvement was better in the antacid group than in the placebo group, but healing of erosive esophagitis was not. However, another study in 32 patients found that placebo actually performed slightly better than the high-dose antacid (15 mL seven times daily) in relieving GERD symptoms and in healing esophagitis.

Many studies of the efficacy of antacids in combination with algic acid have produced favorable results in terms of GERD symptom relief. However, data from these studies, including a non-placebo-controlled comparative trial in children, two open studies without placebo groups, a nonblinded study, and several comparative trials, are of limited use because of the lack of true placebo controls.

Most studies testing the efficacy of antacids have found that, even at high doses, their effect on healing erosive esophagitis is no better than that of placebo. For example, in a 4-week, randomized, double-blind, placebo-controlled trial, Furman and colleagues compared a high-dose liquid antacid (7 oz/day) given 15 minutes and 1 hour after meals with cimetidine 300 mg four times daily. Patients underwent endoscopy, biopsy, and acid perfusion testing at baseline and at the end of the study. They also were asked to complete symptom diary cards during the study. Only patients given cimetidine had a significant reduction in the frequency and severity of heartburn (P < 0.05). The liquid antacid was similar to placebo in its reduction of heartburn severity. No treatment improved regurgitation. Furthermore, neither cimetidine nor the liquid antacid improved any objective measure of GERD severity (endoscopy, acid perfusion test results).

Often in clinical trials, a reduction in the use of antacids is a hallmark of efficacy for other agents (ie, H2RAs or PPIs).

Histamine H2-Receptor Antagonists

Histamine H2-receptor antagonists are acid-suppressive agents that treat GERD by decreasing acid secretion and thus decreasing the causticity of the refluxate. The H2RAs approved for use in the United States are cimetidine, ranitidine, famotidine, and nizatidine. All are available by prescription and in over-the-counter formulations that are usually one half the standard prescription dose.

Pharmacokinetic/pharmacodynamic overview

Oral absorption of H2RAs is fairly rapid, with peak plasma concentrations attained within 1 to 3 hours after administration. A second peak after oral administration has been observed with all H2RAs except nizatidine. Mean oral bioavailability differs somewhat among the agents, ranging from a low of 40% with famotidine to a high of 80% with cimetidine.
Plasma concentrations of H$_2$RAs and inhibition of gastric acid secretion are directly related, implying a rapid equilibration between drug concentration in plasma and at the site of action.

In general, the acid-suppressive abilities of H$_2$RAs are more effective on nocturnal acid secretion. Duration of acid inhibition is longer when the drug is taken in the evening or before bedtime. Equipotent doses of H$_2$RAs equally inhibit acid secretion.

**Efficacy: symptom improvement**

Overall, H$_2$RAs relieve symptoms in 60% of patients with GERD, whereas placebo relieves symptoms in 27% (Figure 2). H$_2$RAs are effective in the control of nocturnal acid reflux episodes as well. In patients with no erosive esophagitis and with mild or intermittent GERD symptoms, symptomatic treatment response rates are 70% or higher. Patients with esophagitis experience lower rates of symptom relief and are more likely to have symptom relapse once therapy is stopped.

**Relapse.** Hallerback and colleagues examined symptom relapse in patients after a 4-week course of either ranitidine or placebo. The study included 423 patients with GERD symptoms, most of whom had mild reflux disease; 67.4% had either a normal-appearing esophagus or erythema only. Another 28.1% had grade I esophagitis, which consists of small, isolated lesions. Only 4.5% of this study population had esophagitis grades II through IV. Patients with more extensive injury were excluded.

Initially, patients were randomized to receive either ranitidine 150 mg twice daily or placebo for 2 weeks. After the initial trial, those who were satisfied with their treatment (ie, responded to therapy with either improved or complete relief) continued with that therapy. Patients who were not satisfied with their treatment were then re-randomized to receive ranitidine 150 mg two or four times daily for another 2 weeks. Patients whose symptoms did not respond after 4 weeks of therapy were removed from follow-up. After 4 weeks of therapy, all responders were taken off therapy and followed for an additional 24 weeks.

Figure 3 shows the symptomatic relapse rates in the total population and in patients with and without erosive esophagitis. At 24 weeks of follow-up, symptom relapse had occurred in 52% of patients with GERD who did not have erosive esophagitis compared with 67% of those who did have erosive esophagitis ($P = 0.013$).

**Dosage level.** In the Hallerback study, the percentage of patients who experienced symptom improvement or complete relief at week 4 was similar in all groups that received ranitidine, regardless of dosage level. This finding was confirmed in a similarly designed study of longer duration. In this study, Kahrilas and colleagues compared high-dose and standard-dose ranitidine therapy in patients who remained unresponsive after 6 weeks of ranitidine 150 mg twice daily. Of the 481 patients with GERD symptoms who initially received a 6-week course of 150 mg twice daily, 285 (59%) remained symptomatic. Of this group, 270 were re-randomized to receive either 150 mg or 300 mg of ranitidine twice daily. After an additional 8 weeks of therapy, only 44.8% of patients receiving the higher dose of ranitidine and 45.4% of those receiving the lower
dose achieved treatment response (mild or no heartburn) (Figure 4).

Efficacy: healing of erosive esophagitis
In general, the results of treatment with H2RAs are not as good in patients with severe erosive esophagitis. However, healing of erosions occurs in 50% of patients with erosive esophagitis who are treated with H2RAs.26,28

Placebo-controlled studies demonstrate that H2RAs provide better symptomatic relief of GERD and mucosal healing of erosive esophagitis than does placebo. Although many trials do not contain a placebo arm, Tougas and Armstrong26 cited a placebo healing rate of 16.5% at 12 weeks for patients with grade II to grade IV esophagitis in a review of the efficacy of H2RAs for treatment of GERD. That compared with a mucosal healing rate of 39.7% (P < 0.0005) for H2RAs in the same review. Placebo was associated with a 13% rate of overall symptom relief, compared with a 44% rate of overall relief with H2RAs (P < 0.001). All four H2RAs, when used at the usual recommended dose, were equally safe and effective, although their efficacy was limited in more severe forms of GERD, such as erosive esophagitis (endoscopic healing rates of 40% to 50%, symptom improvement rates of 40% to 60%).28

Some non–placebo-controlled comparative studies involving H2RAs have produced 12-week healing rates as high as 70%.25 For example, a comparative study of ranitidine (150 mg two or four times daily) and cimetidine (800 mg twice daily) for the healing of erosive esophagitis demonstrated 12-week healing rates ranging from 68% to 77% (Figure 5).32

Another study of esophagitis healing found that the 6-week healing rate with ranitidine was 78% for isolated erosions but dropped to 38% for confluent erosions and to only 23% for circumferential erosions (Figure 6).33

Tolerance
The suppression of intragastric acidity diminishes with repeated administration of H2RAs.34 A single dose of an H2RA (Table 3)35 inhibits acid secretion for approximately 4 to 8 hours and decreases stimulated acid secretion by approximately 70% in patients with esophagitis. However, H2RA treatment has several disadvantages, including a relatively short duration of action (compared with PPIs), incomplete inhibition of acid secretion in response to a meal, and the development of tolerance. It is therefore not easy for H2RAs to effectively heal the more severe forms of erosive esophagitis, even when very high doses are used. When severe erosive esophagitis is not present, relief of reflux symptoms has been obtained after 4 weeks using a twice-daily regimen. In grades I or II

### Table 3

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<thead>
<tr>
<th>H2RAs</th>
<th>Dosage (over-the-counter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nizatidine</td>
<td>75 mg twice daily, as needed</td>
</tr>
<tr>
<td>Famotidine</td>
<td>10 mg twice daily, as needed</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>200 mg twice daily, as needed</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>75 mg twice daily, as needed</td>
</tr>
</tbody>
</table>

![Figure 5](image5.png)  
**FIGURE 5.** Comparison of erosive esophagitis healing rates with ranitidine 150 mg two or four times daily and cimetidine 800 mg twice daily.32

![Figure 6](image6.png)  
**FIGURE 6.** Healing of erosive esophagitis with ranitidine 150 mg or 300 mg twice daily, by severity of disease.33
esophagitis, healing can be achieved with any of the H₂RAs in 40% to 60% of cases in 8 weeks. This success rate can be increased to 50% to 70% by a substantial increase in dose, but this entails cost and compliance considerations.

It is possible that tolerance may develop as a result of the down-regulation of H₂-receptors. Another possibility is that there are adaptive changes in acid secretion that are stimulated by acetylcholine, gastrin, or both.

A number of clinical studies have shown that tolerance to standard H₂RAs probably develops within the first 2 weeks of therapy. More recently, however, tolerance has been shown to develop within 72 hours when intravenous administration of ranitidine is used to control bleeding in the upper gastrointestinal tract. To avoid such tolerance, more frequent dosing of ranitidine, more careful monitoring of intragastric pH, and repeated dose adjustments would be needed.

**PROTON PUMP INHIBITORS**

Proton pump inhibitors are the most effective medical treatment for GERD. They profoundly suppress acid secretion through inhibition of H⁺,K⁺ adenosine triphosphatase (ATPase), the proton pump of the parietal cell responsible for acid production. Unlike H₂RAs, they block acid production regardless of the method of stimulation, providing a greater degree of acid suppression for a longer duration of time. All PPIs are prodrugs, so-called substituted benzimidazoles, which must be activated by acid to inhibit the proton pump. This translates into higher efficacy rates in terms of GERD symptom relief and healing of erosive esophagitis. A once-daily, morning dose of a PPI will relieve symptoms in 83% of patients with GERD and heal erosive esophagitis in 78%. Furthermore, these rates are achieved after only 4 to 8 weeks of therapy. As with H₂RAs, healing of esophagitis with PPIs correlates with the severity of esophagitis.

Excellent healing rates have been reported in even the most severe grades of esophagitis after PPI therapy. There is a wealth of study data on the safety and efficacy of omeprazole, the first PPI approved for treatment of GERD. Other available PPIs include lansoprazole, rabeprazole, and pantoprazole. Clinical efficacy in GERD and the safety profiles among this first generation of PPIs are very similar. The newest PPI, esomeprazole, the S-isomer of omeprazole, has demonstrated more complete symptom relief in patients with GERD and esophageal healing for a greater proportion of patients and in a shorter time period compared with omeprazole.

**Pharmacokinetics and pharmacodynamics**

All PPIs are metabolized in the liver via the cytochrome P450 system, specifically by the CYP2C19 and CYP3A4 enzymes. There are subtle differences, however, in how each PPI is metabolized within this system. An agent’s preference for one enzyme over another influences the metabolic pathway and leads to differences among the PPIs in interactions with other drugs (Table 4).

Because PPIs reduce gastric acidity, they may alter the absorption of other orally administered drugs. Elevated gastric pH has the potential to affect the stability of agents that are acid-labile or alkaline-labile, as well as the absorption of agents that have pH-dependent formulations. Whether these interactions are clinically significant is more difficult to determine. However, PPIs reduce the area

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**TABLE 4** Possible drug interactions with PPIs resulting from metabolism via the cytochrome P450 system

<table>
<thead>
<tr>
<th>PPI</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>• Inhibits metabolism of phenytoin, diazepam, antipyrine, aminopyrine, and the s-isomer of warfarin</td>
</tr>
<tr>
<td></td>
<td>• Does not inhibit metabolism of propranolol, theophylline, or the s-isomer of warfarin</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>• No clinically significant interactions with most drugs metabolized through the cytochrome P450 system</td>
</tr>
<tr>
<td></td>
<td>• Increases metabolism rate of theophylline by 10%</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>• No clinically significant interactions with drugs metabolized through the cytochrome P450 system</td>
</tr>
<tr>
<td></td>
<td>• No interactions with oral contraceptives</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>• No clinically significant interactions with drugs metabolized through the cytochrome P450 system</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>• No clinically significant interactions with drugs metabolized through the cytochrome P450 system</td>
</tr>
</tbody>
</table>
under the curve (AUC) and the peak plasma levels of ketoconazole to such an extent that patients starting therapy with ketoconazole may need to discontinue PPI therapy.40

Individual PPIs differ in clinical pharmacology. The following sections identify selected features of the clinical pharmacology of the five available PPIs.

Omeprazole is inactivated when it is exposed to gastric acid, so it has been formulated in granules that release the drug only when the pH is greater than 6.0, resulting in a bioavailability of approximately 50%. Peak plasma concentrations occur 2 to 4 hours after oral administration and increase during the first days of therapy. The plasma half-life of omeprazole is approximately 1 hour. Food intake has no effect on the drug’s pharmacokinetics.40

Omeprazole differs from other PPIs in that its bioavailability increases with repeat dosing. A single dose of omeprazole has a bioavailability of approximately 35%, which increases with repeat dosing to around 60%. Mean AUC and peak plasma concentrations also increase disproportionately between days 1 and 5 of treatment.40

One 20-mg dose of omeprazole inhibits acid secretion by 65% after 4 to 6 hours, dropping to 25% after 24 hours. Inhibition increases after subsequent doses and plateaus after four to six doses. Steady-state inhibition varies widely among patients, ranging from 35% to 65% based on acid secretion measurements taken 24 hours after drug inhibition, and from 30% to 100% based on measurements of 24-hour gastric acidity based on intragastric pH.41 In one study, 20-mg and 40-mg doses resulted in a mean intragastric pH greater than 4.0 for approximately 42% and 62%, respectively, of a 24-hour period after 5 days of administration.42

In general, when larger doses of omeprazole are given, variation of acid inhibition in patients is reduced, and acid inhibition is increased.41

Lansoprazole. Like other PPIs, lansoprazole is acid-labile. The drug is rapidly absorbed, with peak plasma concentration reached only 1.7 hours after administration. Food intake with lansoprazole delays the drug’s absorption.60 Multiple dosing does not alter its pharmacokinetics. Lansoprazole’s bioavailability is approximately 80%, and its elimination half-life is less than 2 hours.43

Some, but not all, studies have shown that lansoprazole’s ability to suppress acid secretion is dose-dependent and increases with repeated administration. In clinical trials, a 30-mg dose resulted in an intragastric pH greater than 4.0 for 41% of a 24-hour period on the first day of administration, rising to 66% on the fifth day. A 15-mg dose yielded an intragastric pH greater than 4.0 for 22% of a 24-hour period on the first day of administration and for 49% of a 24-hour period by the fifth day. The onset of antisecretory activity also differs between doses, with the 30-mg dose causing an increase in intragastric pH in 1 to 2 hours after administration and the 15-mg dose causing an increase in 2 to 3 hours. This time decreased with repeated dosing for both dosage strengths.43

Pantoprazole. All PPIs are rapidly degraded by acidic conditions, but pantoprazole is slightly more stable than omeprazole and lansoprazole under neutral conditions or conditions that are mildly acidic (pH ≈ 3.5 to pH ≈ 7.4). Pantoprazole is therefore easier to produce in intravenous form.42 A 40-mg dose of pantoprazole reaches peak plasma concentrations 2 to 4 hours after administration. The estimated bioavailability of 77% reflects a slow first-pass hepatic extraction. Food intake delays absorption of pantoprazole. The drug’s mean plasma terminal elimination half-life is 0.9 to 1.9 hours. Repeated dosing does not alter the pharmacokinetics of pantoprazole.42 In this way, pantoprazole is similar to lansoprazole but unlike omeprazole.

Steady-state acid inhibition by a repeated once-daily dose of pantoprazole is dose-related over the range of 20 mg to 60 mg. However, minimal additional inhibition occurs with higher doses. After 5 days of oral administration of 40 mg or 60 mg, significant reductions in basal, nocturnal, and 24-hour intragastric pH occurred. The 40-mg dose achieved an intragastric pH greater than 4.0 for approximately 41% of a 24-hour cycle after 5 days of administration.42

Rabeprazole is degraded by acid in a manner similar to lansoprazole and omeprazole and is less stable at a neutral pH than other PPIs. Maximum plasma concentrations occur 3 to 4 hours after a single dose, regardless of the dosage strength. The bioavailability of rabeprazole following a 20-mg single dose is approximately 52%. Peak plasma concentrations and the AUC increase with rising dosages, but the pharmacokinetics are not altered by multiple doses. Rabeprazole’s plasma half-life is similar to that of omeprazole at approximately 1 hour. The time to achieve maximum plasma concentration is significantly prolonged by food intake. This is of no clinical significance, however, as the AUC is not altered
to a significant extent. It has been suggested that the effect of food on the time to maximum plasma concentration is secondary to the effect of food in prolonging the gastric emptying time of the enteric-coated tablets.40

The acid-suppressive effects of rabeprazole do not increase to a significant extent with increasing doses. For instance, patients with GERD achieved an intragastric pH of 4.0 or greater for approximately 16 hours after 5 days of administration of 20 mg of rabeprazole, compared with approximately 18 hours after 5 days of administration of 40 mg.44

Esomeprazole. Discussion of esomeprazole requires brief mention of stereoisomers, which are molecules with one or more “chiral” centers that allow the possibility of forms with the same chemical formula but differing spatial arrangements. These differences can translate into clinical differences in terms of a compound’s efficacy and toxicity.

Esomeprazole is the S-enantiomer of racemic S,R-omeprazole. It has been shown to be stable, with more than 40% of each dose showing conversion to the R-isomer.45

Esomeprazole reaches maximum plasma concentration approximately 2 hours after administration of a single dose. As with omeprazole, the bioavailability of esomeprazole is altered by repeat dosing. In clinical studies, a 20-mg dose of esomeprazole was 50% bioavailable on day 1 of administration, increasing to 68% on day 5. The total AUC increased by 90% over 5 days. With a 40-mg dose of esomeprazole, bioavailability increased from 64% on day 1 to 89% on day 5, with an AUC increase of 159%.46 The plasma clearance rate of esomeprazole decreases from 22 L/hour to 16 L/hour over a 5-day period, and its plasma elimination half-life increases from 0.8 hours to 1.2 hours with repeat dosing.

The pharmacokinetic and pharmacodynamic profile of esomeprazole differs from that of omeprazole. Esomeprazole given daily for 5 days had a 70% higher AUC than the same dosage of omeprazole given over the same period.47 Furthermore, although there is variability in omeprazole’s acid inhibition among individual patients, this effect is substantially reduced with esomeprazole.

Efficacy: symptom improvement

Symptom relief is the primary goal of medical therapy for GERD and is highly predictive of endoscopic healing if esophagitis is present.48 Interestingly, the severity of a patient’s heartburn is not necessarily predictive of the severity of erosive esophagitis that he or she experiences. This was clearly shown in a clinical trial by Venables and colleagues,49 who found that chronic GERD symptoms were unreliable in predicting the presence of underlying esophagitis in patients at trial entry. Although patients with severe heartburn may have normal endoscopy findings, many will have undetected erosive esophagitis. This study compared the efficacy of omeprazole 10 mg or 20 mg daily with that of ranitidine 150 mg twice daily for relief of heartburn. The 20-mg omeprazole dose was the most effective initial therapy for relief of GERD symptoms.49

Many studies have compared the effects of H2RAs and PPIs on symptom improvement. In general, PPIs are more effective than H2RAs and work at a faster rate. Additionally, omeprazole has been compared with other PPIs for symptom improvement in several trials. Overall, there is not a significant difference in efficacy among the PPIs; however, there is some variability in different clinical trials.

In their meta-analysis of the efficacy of GERD therapies for treating grades II through IV erosive esophagitis, Chiba and colleagues23 showed that PPIs provide complete heartburn relief in a higher percentage of patients and at a faster rate compared with H2RAs. They found that more patients became heartburn-free by the second week of treatment with PPIs (58.0% ± 16.9%) than by 8 weeks of therapy with H2RAs (48.8% ± 16.2%). The speed of heartburn relief was faster with PPIs than with H2RAs: at week 2, patients treated with PPIs became heartburn-free at a rate of 31.8% (±7.9%) per week, compared with a rate of 17.9% (±5.8%) per week for patients treated with H2RAs (Figure 7).

In the same analysis, PPIs also provided the greatest overall symptom relief, as 77.4% (±10.4%) of PPI-treated patients became heartburn-free, compared with 47.6% (±15.5%) of patients treated with H2RAs.23

In a pair of randomized, double-blind, multicenter trials, Richter and colleagues50 compared lansoprazole with ranitidine in 901 patients with symptomatic reflux disease confirmed by endoscopy to be nonerosive GERD. The frequency of antacid use served as an end point for evaluating these agents’ efficacy in relieving heartburn symptoms. Compared with patients who received either of two dosages of lansoprazole, patients treated with ranitidine reported ingesting antacids on a significantly higher per-
percentage of days (Figure 8) and ingesting a significantly higher number of antacid tablets per day. Across all treatment groups, the frequency of antacid use was associated with the frequency of days or nights with heartburn.

Variations among PPIs. Although all PPIs provide a comparably high level of symptom improvement, there are some variations in PPI performance in comparative clinical trials. Castell and colleagues evaluated two doses of lansoprazole (15 mg and 30 mg once daily) in comparison with omeprazole (20 mg once daily) and placebo in 1,284 patients with endoscopically confirmed erosive esophagitis.

All PPI-treated groups experienced relief of daytime and nighttime heartburn, regurgitation, and belching to a significantly greater degree than did the placebo group, as judged by investigators and patients. Omeprazole and the 30-mg dose of lansoprazole were more effective than placebo in relieving investigator-assessed painful swallowing, whereas the 15-mg lansoprazole dose was not significantly more effective than placebo. There were no differences between the omeprazole and lansoprazole 30-mg treatment groups in investigator-assessed symptom relief, but there were differences in patient-assessed relief. After 8 weeks of therapy, patients who received omeprazole reported experiencing heartburn on 11.8% of days and 8.9% of nights during the trial, whereas those receiving 30 mg of lansoprazole reported experiencing heartburn on 8.6% of days and 6.5% of nights ($P < 0.05$ vs omeprazole). Patients receiving placebo reported experiencing heartburn on 60% of days and 45% of nights.

Mössner and colleagues investigated symptom relief in 286 patients with grades II or III erosive esophagitis randomized to receive 40 mg of pantoprazole or 20 mg of omeprazole daily for 8 weeks. Investigator-assessed symptom relief was recorded after 2 weeks and 4 weeks of therapy. Differences between the treatment groups in relieving heartburn, regurgitation, and painful swallowing were not statistically significant at 2 weeks or 4 weeks. At 2 weeks, 59% of patients receiving pantoprazole and 69% of those receiving omeprazole were symptom-free; at 4 weeks, these percentages rose to 83% and 86%, respectively (not statistically significant).

Dekkers and colleagues compared the efficacy of

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**FIGURE 8.** Four-week and 8-week comparisons of the median percentage of days antacids were used by patients with nonerosive GERD while receiving either ranitidine or one of two dosages of lansoprazole for relief of heartburn symptoms.50

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Days of Antacid Use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine (150 mg bid)</td>
<td>32.1</td>
</tr>
<tr>
<td>Lansoprazole (15 mg qd)</td>
<td>28.5</td>
</tr>
<tr>
<td>Lansoprazole (30 mg qd)</td>
<td>16.7*</td>
</tr>
</tbody>
</table>

* = $P < 0.001$ vs ranitidine. † = $P = 0.01$ vs ranitidine.
omeprazole 20 mg daily and rabeprazole 20 mg daily in an 8-week trial in 202 patients with erosive or ulcerative reflux disease. Similar improvements in heartburn frequency rates and in daytime and nighttime heartburn severity were seen in the two treatment arms. At 8 weeks, 73% of patients receiving rabeprazole and 76% of those receiving omeprazole reported a lessening of heartburn frequency. In terms of heartburn severity, 68% of patients receiving rabeprazole reported resolution of daytime heartburn and 64% reported resolution of nighttime heartburn, which were comparable to the rates in the omeprazole group (66% and 67%, respectively).

Kahrilas and colleagues compared symptom relief with omeprazole 20 mg daily and esomeprazole 20 mg or 40 mg daily in 1,960 patients with erosive esophagitis. After 4 weeks of therapy, esomeprazole 40 mg daily provided more effective relief of symptoms: patients who received this regimen reported experiencing no heartburn on 72.7% of days and 84.7% of nights during the trial, whereas those receiving omeprazole reported experiencing no heartburn on 67.1% of days and 80.1% of nights ($P < 0.05$). Onset of symptom relief was also faster with esomeprazole 40 mg daily, as 46.6% of patients receiving this regimen reported no heartburn on the first day of treatment, compared with 37.0% of patients receiving omeprazole.

Finally, a study by Richter and colleagues of 2,425 patients with GERD demonstrated better resolution of investigator-assessed heartburn and regurgitation after 4 weeks of treatment with esomeprazole 40 mg daily than with omeprazole 20 mg daily (Figure 9).

**Symptom relief in nonerosive GERD.** PPIs have also been tested in patients who have GERD symptoms but do not have erosive esophagitis. Lind and colleagues compared omeprazole 10 mg or 20 mg daily with placebo in 509 patients with GERD but without erosive esophagitis. After 4 weeks of therapy, 46% of patients receiving omeprazole 20 mg reported complete absence of heartburn, compared with 31% of patients receiving omeprazole 10 mg and 13% of placebo recipients (Figure 10). A study by Bate and colleagues of 209 patients with GERD symptoms but no esophagitis yielded similar results. This study tested only the 20-mg dose of omeprazole against placebo. After 4 weeks of therapy, 57% of patients in the omeprazole group were free of heartburn (vs 19% in the placebo group [Figure 10]), 75% experienced no regurgitation (vs 47% with placebo), and 43% were completely asymptomatic (vs 14% with placebo).

While PPIs are significantly more effective than placebo in relieving heartburn in patients with erosive esophagitis, they are not as effective in patients with nonerosive reflux disease. Carlsson and colleagues conducted a 4-week comparison of two dosages of omeprazole in 277 patients with erosive esophagitis and 261 patients with GERD symptoms without erosive esophagitis. Omeprazole 10 mg daily achieved complete symptom relief in 37% of patients with erosive esophagitis, compared with 31% of patients without erosive esophagitis. Similarly, omeprazole 20 mg daily achieved complete symptom relief in 48% of patients with erosive esophagitis vs 29% of those without erosive esophagitis.

**Dosage level.** Dosage is an important consideration in PPI therapy. In the absence of esophagitis, when symptoms are mild or intermittent, a standard-dose PPI has been found to be effective. If symptoms are particularly troublesome or there is moder-
ate or severe erosive esophagitis, a twice-daily dosage may be necessary for a period of time. (However, no prospective data exist to support this recommendation.) Following this, dose reduction should be attempted and a plan formulated for long-term therapy. Dosage level is significant to controlling symptoms and maximizing the success of PPI therapy.

Nocturnal acid breakthrough. Several studies have assessed various therapeutic regimens for controlling the persistent problem of nocturnal acid breakthrough, including double-dose PPI therapy and single- or double-dose PPI therapy combined with an H2RA. Khoury and colleagues found that combination therapy with 20 mg of omeprazole in the morning and 150 mg of ranitidine at night is not as effective in controlling intragastric pH as omeprazole 20 mg twice daily (one dose in the morning and one at night). In 20 healthy volunteers, the median percentage of time that intragastric pH was less than 4 when participants were upright was 29.7% in the ranitidine group and 18.9% in the double-dose omeprazole group (P = 0.003). The median percentages of time that intragastric pH was less than 4 when participants were recumbent were 44.75% and 23.45%, respectively (P = 0.02). In this study, ranitidine administered at bedtime did not eliminate the need for a second dose of omeprazole.

Peghini and colleagues compared three different regimens for controlling nocturnal acid breakthrough in 12 healthy volunteers. All participants received omeprazole 20 mg twice daily. They also received either an additional dose of omeprazole, 150 or 300 mg of ranitidine, or placebo at bedtime. Participants who received placebo at bedtime experienced an intragastric pH of less than 4 for 48% of the night. A third dose of omeprazole reduced this percentage to 31% (P < 0.005), but ranitidine was the most effective therapy: participants who received 150 or 300 mg of ranitidine at bedtime experienced an intragastric pH of less than 4 for only 5% and 6% of the night, respectively (P < 0.01 vs omeprazole 20 mg three times daily). These data suggest that double-dose PPI therapy daily plus an H2RA at bedtime may be an effective regimen for control of nocturnal acid breakthrough.

Efficacy: healing of erosive esophagitis
In their above-mentioned meta-analysis (Figure 1), Chiba and colleagues noted that PPIs were more effective than H2RAs in treating patients with grades II through IV erosive esophagitis. PPIs provided more complete relief of symptoms and faster healing of esophagitis (Figure 7). At week 2, the healing rate per week was 31.7% (± 3.3%) for PPIs, compared with 15.0% for H2RAs. The healing rate per week slowed for both agents at each subsequent 2-week interval. However, PPIs maintained a therapeutic advantage because more patients were healed earlier in the course of PPI therapy, leaving fewer patients who were available to heal in later weeks.

Overall, PPIs produced healing at a rate of 11.7% (± 0.5%) per week, which was twice as fast as the healing rate per week with H2RAs (5.9% ± 0.2%) and four times as fast as that with placebo (2.9% ± 0.2%). A mean of 83.6% (± 11.4%) of patients with erosive esophagitis were healed with PPI therapy, compared with 51.9% (± 17.1%) with H2RA therapy. These numbers compare with a healing rate of 28.2% (± 15.6%) with placebo.

A meta-analysis by Caro and colleagues also found that PPIs were significantly more effective than H2RAs. The investigators analyzed 53 randomized controlled trials, 38 of which involved acute therapy, although 12 of these were subsequently excluded and 15 involved maintenance treatment. Of the 26 acute therapy trials, 18 compared a PPI with an H2RA. Of the 15 maintenance therapy trials, 5 compared a PPI with an H2RA. No study of pantoprazole met the inclusion criteria for maintenance therapy. Combined efficacy rates from both acute and maintenance studies yielded a risk ratio that was highly favorable to PPIs.

Variations among PPIs. In the same analysis, Caro and colleagues compared the efficacy of lansoprazole, pantoprazole, and rabeprazole with that of omeprazole and found no differences in those head-to-head comparisons. Similar results were obtained by other investigators, including teams led by Castell, Mössner, and Dekkers.

Although the study by Castell and colleagues found differences in patient-assessed symptom relief between groups receiving omeprazole 20 mg daily or lansoprazole 30 mg daily, esophageal healing rates were not statistically different between the groups. Eight-week courses of each regimen healed erosive esophagitis in approximately 91% of patients. In the study by Mössner and colleagues, patients with esophagitis received an 8-week course of either pantoprazole 40 mg daily or omeprazole 20 mg daily. The healing rate with pantoprazole (94%) was not statistically different from that with omeprazole (90%). Finally, Dekkers and colleagues found that an 8-week course...
of rabeprazole 20 mg daily healed 92% of patients with erosive esophagitis, compared with 94% for an 8-week course of omeprazole 20 mg daily.

In the Castell study,\textsuperscript{51} lansoprazole 15 mg daily healed 79% of patients, a significantly lower percentage than those achieved with lansoprazole 30 mg daily and omeprazole 20 mg daily ($P < 0.05$). A similar dose-dependent pattern occurred in a study by Lundell and colleagues\textsuperscript{64} between 10-mg and 20-mg doses of omeprazole. These researchers analyzed the efficacy of omeprazole in the healing of Los Angeles (LA) classification grades A through C erosive esophagitis by grade (mild through moderate-to-severe injury). With omeprazole 10 mg daily, healing efficacy was directly correlated to the grade of esophagitis: 77% of patients with grade A were healed, 50% of patients with grade B, and 20% of patients with grade C. However, this gradation in healing did not occur with omeprazole 20 mg daily, which healed roughly the same percentage (approximately 80%) of patients with grades A and B esophagitis. The 20-mg dose of omeprazole healed fewer patients with grade C esophagitis (approximately 40%) than with other grades, although it also healed more patients with this severity grade than did the 10-mg dose. A dose-related increase in healing efficacy with omeprazole was not observed, however, above the 20-mg dose.

Sontag and colleagues\textsuperscript{65} compared 20-mg and 40-mg daily doses of omeprazole with placebo in 230 patients with GERD symptoms and erosive esophagitis. Whereas both doses of omeprazole were superior to placebo in all measures, symptom relief and esophagitis healing rates were similar in the two omeprazole groups. By the eighth week, 73.5% of patients receiving omeprazole 20 mg had complete esophageal healing, compared with 74.7% of patients receiving omeprazole 40 mg and 14.0% of placebo recipients. Omeprazole 20 mg achieved complete relief of daytime heartburn in 79.5% of patients and complete relief of nighttime heartburn in 79.5% of patients, compared with 81.6% and 85.1%, respectively, for omeprazole 40 mg, and 37.2% and 34.9%, respectively, for placebo. Although the higher dose of omeprazole resulted in faster relief of symptoms, differences between the treatment arms were not statistically significant.

A recent meta-analysis by Edwards and colleagues\textsuperscript{66} found that esomeprazole 40 mg daily produced higher healing rates than omeprazole 20 mg daily at 4 and 8 weeks after treatment (Figure 11).

In their analysis of 12 randomized controlled trials, these investigators found no significant differences among omeprazole and lansoprazole, pantoprazole, or rabeprazole at 4 and 8 weeks. They postulated that the superiority of esomeprazole to omeprazole may be related to its more effective suppression of intragastric acid. Recent acid-suppression studies\textsuperscript{67} show that esomeprazole maintains intragastric pH above 4 significantly longer than lansoprazole, pantoprazole, or rabeprazole do, which may account for the differences in healing among the agents observed in this meta-analysis.

One of the studies included in the meta-analysis, conducted by Kahrilas and colleagues\textsuperscript{38} (described in “Efficacy: symptom improvement” above), compared healing rates among omeprazole 20 mg daily and esomeprazole 20 mg daily. After 8 weeks of therapy, esomeprazole 40 mg healed esophagitis in 94.1% of patients, whereas omeprazole did so in 86.9% of patients ($P < 0.05$).

The study by Richter and colleagues\textsuperscript{39} in 2,425 patients with erosive esophagitis confirmed these findings. After 8 weeks of therapy, erosive esophagitis was healed in 93.7% of patients receiving esomeprazole, compared with 84.2% of patients receiving omeprazole (by intention-to-treat analysis). Esomeprazole was more effective than omeprazole in healing.
all grades of esophagitis, as shown in Figure 12. Among patients with LA grades C and D esophagitis, esomeprazole healed 85.8% of patients after 8 weeks of therapy, whereas omeprazole healed 68.1%.

More recently, a study by Castell and colleagues68 showed that esomeprazole demonstrated a slightly but significantly higher healing rate (92.6%) than lansoprazole (88.8%) at week 8. The difference in healing rates between esomeprazole and lansoprazole increased as the baseline severity of erosive esophagitis increased.

Maintenance of healing. Lauristen and colleagues69 demonstrated that esomeprazole was more effective than lansoprazole in maintaining the healing of all grades of esophagitis (Figure 13). They compared esomeprazole 20 mg once daily with lansoprazole 15 mg once daily in the maintenance treatment of 1,231 patients with healed reflux esophagitis. Analysis of remission rates based on the LA classification system showed that esomeprazole maintained patients in remission more consistently across all grades of reflux esophagitis, whereas the efficacy of lansoprazole decreased to a greater extent with increasing severity of disease.

Other studies have demonstrated the low relapse rate with esomeprazole therapy over a 6-month period. In a study conducted by Johnson and colleagues50 of 318 patients with erosive esophagitis, 40-mg and 20-mg doses of esomeprazole once daily were highly effective at maintaining healing of erosive esophagitis over 6 months. Rates of erosive esophagitis recurrence were 6% and 7% with esomeprazole 40 mg and 20 mg, respectively, compared with 71% with placebo. Also, more than 70% of patients remained symptom-free at 6 months.

Table 5 presents the common dosing regimens and the efficacy rates of the available PPIs for the maintenance of erosive esophagitis healing.70–75

Intravenous PPI therapy

Intravenous pantoprazole is the only PPI currently indicated in the United States for short-term treatment (7 to 10 days) of GERD in patients with a history of erosive esophagitis who are unable to take the oral formulation. In a double-blind placebo-controlled study, IV and oral pantoprazole were shown to be similar in their ability to suppress maximum and basal acid output. The study involved 65 patients with erosive esophagitis who were given 20 mg or 40 mg of oral pantoprazole for 10 days and then randomized to receive either IV pantoprazole or placebo for 7 days. Acid output was determined 24 hours after the last day of oral medication and on the first and last days of IV administration. Among patients receiving IV pantoprazole, acid suppression was comparable to that seen with oral pantoprazole and was significantly better than that achieved by patients receiving IV placebo. The recommended adult dosage of IV pantoprazole is 40 mg daily for 7 to 10 days.76

Omeprazole has been used in injectable form in some studies around the world in an effort to prevent rebleeding following treatment for bleeding ulcers. A study in Hong Kong by Lau and colleagues37 demonstrated the efficacy of omeprazole (given as an 80-mg bolus injection followed by a
continuous infusion of 8 mg/hour for 72 hours) in preventing recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. This study showed that a high-dose infusion of omeprazole reduced the rate of recurrent bleeding, decreased the need for endoscopic treatment and blood transfusions, and shortened the length of hospitalization.

Failure of therapy
Treatment of GERD with PPIs provides fast and complete relief to a larger percentage of patients than any other medical therapy. As well as PPIs work, however, they do not cure GERD and may not relieve symptoms or heal esophagitis in all patients.

Treatment with a PPI may fail in some patients because their symptoms are not caused by GERD. PPI therapy may also fail in a patient who does have GERD if the PPI dosage or the duration of therapy is insufficient to control symptoms or heal esophagitis. Therapy may also be unsuccessful if the PPI fails to control gastric acidity, although such cases are rare. Several reasons have been postulated for why a PPI may fail to control gastric acidity. These include oral bioavailability differences, meal timing that influences ATPase activation, increased metabolism of the PPI by the cytochrome P450 system, and hypersecretion of acid (including Zollinger-Ellison syndrome).

Patients with higher grades of esophagitis and more severe disease are less likely to experience complete healing with PPIs. A study conducted by Holloway and colleagues in 61 patients with grades III or IV erosive esophagitis found that 30% of patients were not healed after 8 weeks of therapy with omeprazole 20 mg daily. These patients had greater total 24-hour esophageal acid exposure before treatment than those whose esophagitis was healed. Of those patients in whom the original course of therapy failed, 47% did not heal after 8 more weeks of therapy with a 40-mg daily dose of omeprazole. This final group of patients in whom both courses of therapy failed had levels of acid exposure before treatment that were similar to those of patients who were healed, but they had greater acid exposure during therapy, particularly at night while sleeping.

Several studies have been conducted with omeprazole to investigate the incidence of failure of PPI therapy. Leite and colleagues studied 88 patients with refractory GERD symptoms who received 20 mg of omeprazole twice daily—twice the usual dose. Twenty-four-hour pH monitoring was used to assess results. Of the 88 patients, 17 had an intragastric pH less than 4 for more than 50% of a 24-hour period (considered failure of therapy). These 17 were then compared with 19 of the original 88 patients with GERD and with 19 healthy volunteers who received either omeprazole 20 mg twice daily or placebo. The mean intragastric pH was found to be similar between the patients with persistent symptoms who were receiving omeprazole 20 mg twice daily and the healthy subjects receiving placebo. Gastric pH monitoring in 7 patients given 80 mg of omeprazole daily, however, demonstrated a significant reduction in the mean percentage of time that the pH was less than 4, indicating that response is often a dose-dependent phenomenon.

Up to 70% of healthy subjects given twice-daily PPI therapy experience an intragastric pH less than 4 for more than 1 hour overnight (between 10:00 PM and 6:00 AM). Katz and colleagues noted that nocturnal acid breakthrough in patients who take omeprazole 20 mg twice daily is often accompanied by esophageal reflux and, therefore, esophageal acid exposure. Of 61 patients with GERD, 70% experienced nocturnal acid breakthrough and 33% experienced nighttime esophageal acid exposure. Of 15 patients with Barrett’s esophagus, 80% experienced nocturnal acid breakthrough and 50% experienced esophageal acid exposure. In the control group (patients without GERD), these percentages were 67% (not significantly different) and 8% (P < 0.03), respectively. Nocturnal acid breakthrough accom-

### Table 5

<table>
<thead>
<tr>
<th>PPI</th>
<th>FDA approval date</th>
<th>Prescribed dose (mg/d)</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>1989</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>77</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>1995</td>
<td>15</td>
<td>67–79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>55–90</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>1999</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>2000</td>
<td>20</td>
<td>70–72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>83–86</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>2001</td>
<td>20</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>94</td>
</tr>
</tbody>
</table>

* In controlled clinical trials for maintenance of healing.
panied by esophageal reflux in patients on twice-
daily PPI therapy has important implications for
medical therapy in patients with severe GERD or
Barrett’s esophagus.

As previously discussed, Peghini and colleagues62
found that the combination of an H2 RA and a PPI
may be effective in managing nocturnal acid break-
through. A recent study by Fackler and colleagues82
yielded differing results. The Fackler study showed
that, because tolerance developed to 300 mg of ran-
itidine in patients with nocturnal acid break-
through, there was no difference in acid suppression
between omeprazole 20 mg twice daily and omepra-
zole 20 mg twice daily plus ranitidine 1 week after a
combination therapy.

Safety
In general, PPIs are a remarkably safe and well-tol-
erated class of drugs. Headache and diarrhea are the
most frequently reported side effects, and they
develop at rates that do not differ significantly from
those in placebo-treated patients.83 Serious side
effects resulting from PPI treatment are rare.

The long-term safety of PPIs has been a topic of
some debate because most randomized controlled
trials of their effects have not extended beyond 1
year. Thjodleifsson and colleagues84 addressed this
concern in a 5-year controlled trial comparing efficacy
and safety between rabeprazole and omepra-
zole. They concluded from their results that both
PPIs were safe and well tolerated during the 5-year
study period, contributing to a growing body of evi-
dence confirming the long-term safety of PPIs in
acid suppression.

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