

SECTION

V

# Gastrointestinal Disorders



# Heartburn and Dyspepsia

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Heartburn and dyspepsia are common symptoms that originate in the upper gastrointestinal (GI) tract and are frequently treated with nonprescription medications. Heartburn (pyrosis) is a burning sensation that usually arises from the substernal area (lower chest) and moves up toward the neck or throat.<sup>1</sup> Postprandial heartburn usually occurs within 2 hours after eating or when bending over or lying down. Nocturnal heartburn occurs during sleep and often awakens the individual. Most patients experience “simple” heartburn, which is typically mild, infrequent, episodic, and often associated with diet or lifestyle.<sup>1</sup> Others have more frequent heartburn that occurs 2 or more days a week. Heartburn that is frequent and persistent (3 or more months) is the most common symptom of gastroesophageal reflux disease (GERD). GERD is defined as symptoms, esophageal damage, or both resulting from the abnormal reflux of gastric contents into the esophagus.<sup>2</sup> About one half of all GERD cases are associated with endoscopic esophagitis.<sup>3</sup> However, patients with GERD may suffer heartburn even when esophageal injury is not present (nonerosive gastroesophageal reflux disease, NERD). Although it is not life-threatening, patients with frequent heartburn limit their food choices and often suffer from disruptions in sleep and work.<sup>4,5</sup> In 2000, the treatment of GERD ranked the highest in total direct and indirect costs (9.8 billion) among 17 selected GI diseases, with drug costs responsible for 63% of the direct costs.<sup>6</sup>

Dyspepsia (bad digestion) is a consistent or recurrent discomfort located primarily in the upper abdomen (epigastrium).<sup>7</sup> The discomfort is a subjective feeling that does not reach the level of pain and is usually characterized by bloating, belching, postprandial fullness, nausea, and early satiety, but is not necessarily restricted to meal-related symptoms. Patients with GERD, peptic ulcer disease (PUD), gastritis, delayed gastric emptying (e.g., gastroparesis), and irritable bowel syndrome often complain of dyspeptic symptoms.<sup>7</sup> The Rome II consensus definition and regulatory agencies in the United States have adopted definitions of dyspepsia for research purposes that exclude heartburn, while other definitions consider heartburn an accompanying symptom of dyspepsia.<sup>8</sup> Dyspepsia may be associated with an underlying cause such PUD and GERD or may not have any known cause.<sup>7,9</sup> Dyspeptic patients may have uninvestigated (no endoscopy has been performed) or investigated (endoscopy has been performed)

dyspepsia. Nonulcer dyspepsia is a diagnosis that is made after endoscopy indicating that “ulcerlike” dyspeptic symptoms were not related to a peptic ulcer.<sup>7</sup> It is estimated that about 18 million adults in the United States take nonprescription medications for “indigestion.”<sup>2</sup> The most widely used nonprescription medications include antacids, histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RA), and proton pump inhibitors (PPI).

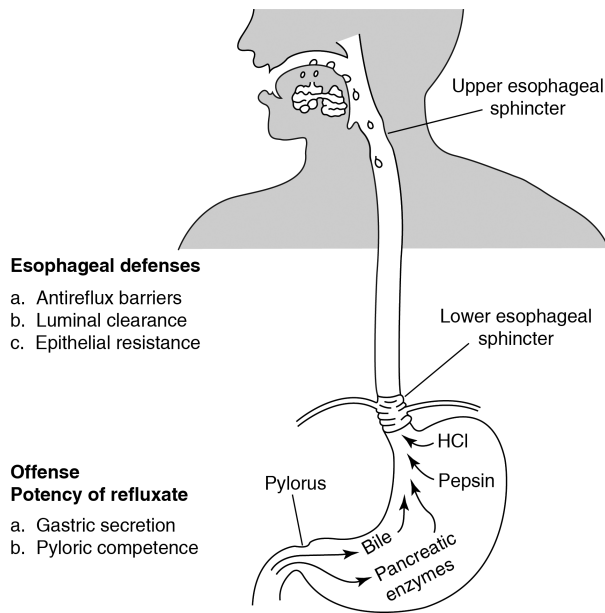
In clinical practice, it is not always possible to predict the cause of heartburn or dyspepsia on the basis of symptom assessment alone, as individuals may not describe adequately what they actually feel, and there is considerable overlap of symptoms. In addition, heartburn and dyspepsia may occur in association with other acid-related disorders, such as GERD and PUD. However, empirical treatment with nonprescription medications is appropriate and reasonable for most patients who have symptoms suggestive of heartburn and dyspepsia. Thus, assessment of the patient is most important in determining if the condition is self-treatable or if the individual should be referred for further evaluation. Medical referral is indicated if the patient is unresponsive to nonprescription medications, symptoms are severe, alarm symptoms are present, or symptoms suggest complicated disease.

This chapter focuses on the self-treatment and prevention of heartburn and dyspepsia. Emphasis is placed on distinguishing individuals who are appropriate candidates for self-treatment from those who require further medical evaluation. Specific recommendations for self-treatment, including dietary and lifestyle modifications and nonprescription medications, are provided.

## Epidemiology of Heartburn and Dyspepsia

The overall prevalence of heartburn in the United States is approximately 45% (about 110 million people) with an equal distribution between men and women of all age groups.<sup>1</sup> Among individuals who experience heartburn, 45% report heartburn 2 or more days a week, while 7% to 10% report heartburn daily.<sup>10</sup> Sixty-five percent of adults who experience heartburn at least once a week indicate that they have both daytime and nighttime heartburn.<sup>4</sup> Most women who are pregnant experience heartburn during the course of their pregnancy.<sup>1</sup> Approximately 25% of adults in the United States report having dyspeptic symptoms, with equal prevalence between men and women.<sup>7</sup> About 40% have dyspepsia associated with either PUD or GERD.<sup>7</sup> Gastric and esophageal cancer are less common causes, but may also be associated with dyspeptic symptoms.

**Editor’s Note:** This chapter is based, in part, on the 14th edition chapter with the same title, which was written by Robert P. Henderson and Valerie T. Prince.



**FIGURE 14-1** Esophageal defense mechanisms and offensive factors associated with heartburn. (Reprinted with permission from Yamada T, Alpers DH, Laire L, et al., eds. *Textbook of Gastroenterology*. 3rd ed. Philadelphia: JB Lippincott; 1999:1236.)

Dyspepsia accounts for 20% to 70% of the GI complaints seen by general practitioners, and about 30% of these require referral to a gastroenterologist.<sup>7</sup>

## Anatomy and Physiology of the Esophagus and Stomach

### Esophagus

The esophagus is a tube that serves as a conduit between the pharynx and the stomach. The openings at both ends are guarded by specialized smooth muscle located where the pharynx meets the esophagus (upper esophageal sphincter) and at the lower end where the esophagus meets the stomach (lower esophageal sphincter; LES) (Figure 14-1). When the LES is functioning normally, it permits the passage of food into the stomach and serves as the primary antireflux barrier by preventing backflow of stomach contents upward into the esophagus. Although the LES is contracted at rest, healthy individuals experience relaxations of the LES throughout the day, often in association with swallowing.<sup>1</sup> When reflux occurs, the refluxate is cleared from the esophagus by peristaltic contractions brought on by swallowing, the neutralization of the refluxate by bicarbonate in the swallowed saliva and, when in the upright position, gravity. Esophageal mucosal resistance minimizes epithelial damage from noxious stomach contents. Thus, transient episodes of gastroesophageal reflux in healthy persons usually go unnoticed and do not damage the esophagus.

### Stomach

The stomach contains parietal cells that secrete hydrochloric acid and intrinsic factor (necessary for vitamin B<sub>12</sub> absorption), G cells that secrete gastrin, mucus-secreting cells, and chief cells that secrete pepsinogen.<sup>11,12</sup> Pepsinogen,

an inactive precursor of pepsin, is converted to the proteolytic enzyme pepsin at an intragastric pH of 1.8 to 3.5, but is inactivated when the pH exceeds 5.<sup>11</sup> The parietal cells have receptors for histamine, acetylcholine, and gastrin, all of which stimulate hydrochloric acid secretion. When any of these substances comes into contact with its receptors on the parietal cell, intracellular calcium and cyclic adenosine monophosphate (cAMP) concentrations increase.<sup>11</sup> The increased levels of calcium and cAMP activate a unique proton pump, adenosine triphosphatase (H<sup>+</sup>/K<sup>+</sup>/ATPase), found only on the membranes of parietal cells. When stimulated, the proton pump secretes hydrogen ions in the stomach lumen in exchange for potassium. Thus, the proton pump is the final common pathway for gastric acid secretion.

The gastric mucosa withstands the acidic environment of the stomach through a combination of defense and repair mechanisms collectively called the gastric mucosal barrier.<sup>11</sup> Mucosal defense mechanisms include mucous and bicarbonate secretion, intrinsic epithelial cell defense, and mucosal blood flow.<sup>11,12</sup> The near neutral pH of the mucous-bicarbonate barrier protects the stomach from its acidic contents. Maintenance of mucosal integrity and repair is mediated by the production of endogenous prostaglandins.

## Etiology of Heartburn and Dyspepsia

Risk factors that may contribute to heartburn include diet, lifestyle, medications, and certain diseases (Table 14-1).<sup>1,13-15</sup> However, evidence to support each of the proposed risk factors is limited. Foods and beverages including coffee, tea, chocolate, and citrus, the regular use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), life stress, and tobacco smoking are widely recognized as precipitators of individual heartburn episodes.<sup>11</sup> Heartburn may also occur during certain types of exercise (e.g., weight lifting, cycling, or sit-ups). Obesity and pregnancy contribute to reflux by a direct physical effect (e.g., disrupting the intraabdominal pressure). Genetic factors may predispose to neurologic dysfunction of the LES.<sup>14,15</sup> Diseases such as gastroparesis and scleroderma increase intraabdominal pressure and lower LES pressure, respectively.

NSAIDs, including aspirin and cyclooxygenase-2 inhibitors, represent the most important cause of drug-induced dyspepsia.<sup>7</sup> Bisphosphonates, potassium or iron supplements, digoxin, theophylline, and certain antibiotics (e.g., erythromycin, ampicillin) are often associated with dyspeptic symptoms. Alcohol ingestion, tobacco, caffeine, and stress may contribute to dyspepsia.

## Pathophysiology of Heartburn and Dyspepsia

Heartburn arises from the sensory nerve endings in the esophageal epithelium and is most likely stimulated by spicy foods or by the reflux of acidic gastric contents into the esophagus.<sup>1</sup> The noxious quality of the refluxate (acid, pepsin) is central to the development of symptoms, esophageal damage, and complications (Figure 14-1). Individuals with an incompetent pylorus may reflux duodenal contents (bile, pancreatic enzymes) into the stomach, which

**TABLE 14-1** Risk Factors That May Contribute to Heartburn<sup>1,13-15</sup>

<b>Dietary</b>	<b>Medications</b>
Fatty foods	Bisphosphonates
Spicy foods	Aspirin/NSAIDs
Chocolate	Iron
Table salt	Potassium
Garlic or onions	Quinidine
Mint (e.g., spearmint, peppermint)	Tetracycline
Alcohol (ethanol)	Zidovudine
Caffeinated beverages	Anticholinergic agents
Carbonated beverages	$\alpha$ -Adrenergic antagonists
Citrus fruit or juices	Barbiturates
Tomatoes/juice	$\beta_2$ -Adrenergic agonists
	Calcium channel blockers
<b>Lifestyle</b>	Benzodiazepines
Exercise	Dopamine
Smoking (tobacco)	Estrogen
Obesity	Narcotic analgesics
Stress	Nitrates
Supine body position	Progesterone
Tight-fitting clothing	Prostaglandins
Pregnancy	Theophylline
	TCA's
<b>Diseases</b>	Chemotherapy
Motility disorders (e.g., gastroparesis)	<b>Other</b>
Scleroderma	Genetics
PUD	
Zollinger-Ellison syndrome	

Key: NSAID, nonsteroidal anti-inflammatory drug; PUD, peptic ulcer disease; TCA, tricyclic antidepressant.

increases the noxious quality of the gastric refluxate. Most patients with heartburn secrete normal amounts of gastric acid.<sup>1</sup> Esophageal tissue damage is caused primarily by gastric acid, pepsin, and bile salts. The esophageal epithelium is not as tolerant as that of the stomach to repetitive exposure of gastric acid.<sup>1</sup> What usually distinguishes individuals with heartburn from those with normal physiologic reflux is the increased frequency and duration of reflux episodes, which may result in esophageal tissue damage ranging from inflammation (esophagitis) to erosions and ulcers. However, there is no direct correlation between heartburn severity and underlying esophageal injury. The refluxed acidic contents also may damage the oropharynx, larynx, and respiratory system.<sup>1</sup>

Many patients with heartburn have transient LES relaxations.<sup>1</sup> In these patients, the higher pressure in the stomach creates enough force to overcome the LES pressure, allowing reflux of gastric contents into the lower esophagus (Figure 14-1). Hiatal hernia (a weakening in the diaphragmatic muscles resulting in the protrusion of the upper portion of the stomach into the thoracic cavity) may also contribute to heartburn by disrupting the gastroesophageal junction and lowering the LES pressure.<sup>1</sup> Delayed gastric emptying increases the volume of the noxious refluxate and increases intra-abdominal pressure. A sudden increase in intra-abdominal pressure such as when a person strains, coughs, or bends over, may also be associated

with reflux. Impaired esophageal acid clearing mechanisms (peristalsis, saliva, gravity) prolong the duration of contact between the refluxate and the esophageal epithelium and are less operative during sleep or when the patient is lying down. Age-related decreases in saliva production or pH and esophageal motility may contribute to esophageal damage in older individuals.<sup>16</sup> Although controversial, *Helicobacter pylori* (*H. pylori*) infection does not appear to play a pathogenic role, but potentially may be protective.<sup>1,17</sup>

The pathophysiology of dyspepsia remains unclear. Dyspeptic symptoms may be associated with PUD, GERD, gastric cancer, *H. pylori*, or GI dysmotility, or may lack any identifiable cause.<sup>7</sup>

### Association of Heartburn With Other Acid-related Disorders

Heartburn may occur alone or be associated with acid-related disorders such as dyspepsia, GERD, and PUD (Table 14-2). Heartburn is highly specific for GERD and may suggest esophageal complications.<sup>1</sup> However, the frequency and severity of the heartburn do not predict esophageal injury, as patients with frequent and severe heartburn may not have esophageal damage (NERD). Upper endoscopy is the standard for determining the type and extent of esophageal mucosal damage. Patients with esophageal injury may have varying grades of severity as well as strictures (a narrowing of the esophageal lumen).<sup>1</sup> Symptomatic GERD is the strongest risk factor for the development of esophageal adenocarcinoma.<sup>18</sup> Barrett's esophagus, a precancerous condition, develops in the lower esophagus and is related to longstanding (greater than 5 years) moderate to severe erosive/ulcerative esophagitis.<sup>1,19</sup> This condition is more prevalent in men and increases with age. Barrett's esophagus is associated with an increased risk of esophageal adenocarcinoma with an annual incidence of less than 1%.<sup>1,18,19</sup>

Alarm symptoms result from complications associated with GERD (Table 14-2). Dysphagia (difficulty in swallowing) occurs initially with the ingestion of solid foods such as toast or crackers. It is evident in about 30% of patients with chronic GERD and may indicate severe erosive esophagitis, stricture, or cancer.<sup>1</sup> Odynophagia (painful swallowing) is less common, but may be reported with severe ulcerative esophagitis or esophageal cancer. However, its presence should raise questions about other causes of esophagitis including pill-induced (e.g., tetracycline, potassium chloride, quinine, vitamin C, aspirin, NSAIDs, bisphosphonates) and infections (e.g., herpes, fungal candidiasis).<sup>1</sup> Upper GI bleeding (e.g., hematemesis, melena, occult bleeding, anemia), may also result from esophageal complications.

Abnormal gastric reflux of stomach contents may also cause atypical (extraesophageal) manifestations of GERD (Table 14-2).<sup>1</sup> The atypical symptoms may or may not be accompanied by heartburn, making recognition of GERD difficult. GERD-related chest pain is usually substernal, but may mimic ischemic cardiac pain, radiating to the back, neck, jaw, or arms. It often worsens after meals, during periods of emotional stress, and may awaken the patient from sleep. Severe, crushing chest pain—especially if

**TABLE 14-2** Differentiation of Simple Heartburn from Other Acid-related Disorders

	Simple Heartburn	GERD	Dyspepsia	PUD
Etiology	See Table 14-1	See Table 14-1	Food, alcohol caffeine, stress, and medications contribute to dyspepsia; chronic dyspepsia associated with PUD, GERD, gastric cancer; or may lack an identifiable cause.	Gastric or duodenal ulcer caused most commonly by <i>H. pylori</i> infection and/or NSAIDs
Typical symptoms	Burning sensation behind the breastbone, which may move upward toward the neck or throat	Heartburn, acid regurgitation (acid taste in the mouth), hypersalivation	Primary: epigastric discomfort Other: belching or burping, bloating, nausea, early satiety; may be accompanied by heartburn and acid regurgitation	Gnawing or burning epigastric pain, occurring during day and frequently at night; may be accompanied by heartburn and dyspepsia
Complications		Erosive esophagitis, strictures, bleeding, Barrett's esophagus, esophageal cancer		Perforation, obstruction, penetration, bleeding
Alarm symptoms		Dysphagia; odynophagia; chest pain; upper GI bleeding; unexplained weight loss; continuous nausea, vomiting, and diarrhea		Upper GI bleeding; unexplained weight loss; continuous nausea, vomiting, and diarrhea
Atypical symptoms		Asthma, chronic laryngitis, hoarseness, cough, globus sensation (sensation of a lump in the throat), noncardiac chest pain, dental erosions		

Key: GERD, gastroesophageal reflux disease; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PUD, peptic ulcer disease.

accompanied by nausea, vomiting, and sweating—suggests ischemic pain and possibly myocardial infarction. Other atypical symptoms result from the aspiration of refluxate into the upper airways and lungs.

## Treatment of Heartburn and Dyspepsia

### Treatment Goals

The goals of self-treatment of heartburn are to render the patient symptom-free, prevent meal- or exercise-related symptoms, improve quality of life, and prevent complications by using the most cost-effective therapy. The primary goal of self-treatment of dyspepsia is aimed at relieving abdominal discomfort.

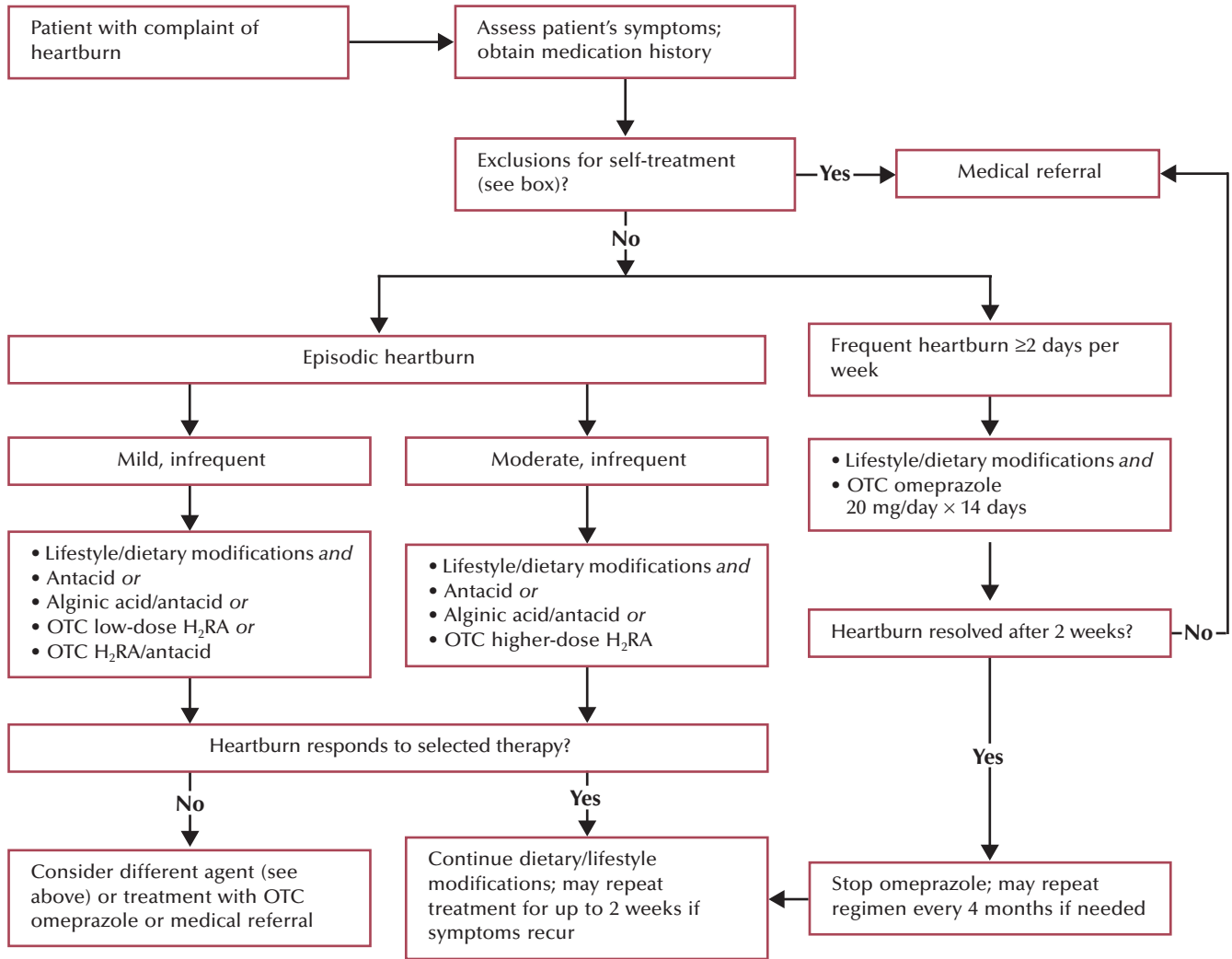
### General Treatment Approach

The approach to self-treatment of heartburn and dyspepsia requires an initial assessment to determine whether the patient is a candidate for self-treatment (Figure 14-2). Individuals with exclusions to self-treatment should be referred for further medical evaluation. If the individual is a candidate for self-treatment (see box Patient Education for

Heartburn and Dyspepsia), nondrug measures should be recommended and continued throughout treatment. If appropriate, a recommendation should also be made for a nonprescription medication. Antacids and nonprescription H<sub>2</sub>RAs should be recommended for individuals with mild, infrequent heartburn and dyspepsia. Antacids are advantageous because they provide rapid relief of symptoms (Table 14-3). The use of antacids, however, is limited by their short duration when taken on an empty stomach. The duration of relief may be prolonged for several hours by taking the antacid after a meal. When used in recommended dosages, the antacids are interchangeable despite differences in antacid salts and potency. Products that contain antacids plus alginic acid are also effective in relieving heartburn, and may be superior to antacids alone.<sup>2</sup> Antacid/alginic acid products are usually more expensive than antacids and therefore are considered second-line agents for treating mild, occasional heartburn.

A nonprescription H<sub>2</sub>RA is preferred to an antacid when individuals with mild to moderate, episodic heartburn require more prolonged relief of symptoms. Though H<sub>2</sub>RAs do not relieve heartburn or dyspepsia as rapidly as an antacid (Table 14-3), this may not be a major factor for some individuals.<sup>2</sup> The H<sub>2</sub>RAs may also be used to prevent

Exclusions for Self-Treatment	
<ul style="list-style-type: none"> <li>■ Frequent heartburn for more than 3 months</li> <li>■ Heartburn while taking recommended dosages of nonprescription H<sub>2</sub>RA or PPI</li> <li>■ Heartburn that continues after 2 weeks of treatment with a nonprescription H<sub>2</sub>RA or PPI</li> <li>■ Heartburn and dyspepsia that occur when taking a prescription H<sub>2</sub>RA or PPI</li> <li>■ Severe heartburn and dyspepsia</li> <li>■ Nocturnal heartburn</li> <li>■ Difficulty or pain on swallowing solid foods</li> </ul>	<ul style="list-style-type: none"> <li>■ Vomiting up blood or black material or black tarry stools</li> <li>■ Chronic hoarseness, wheezing, coughing, or choking</li> <li>■ Unexplained weight loss</li> <li>■ Continuous nausea, vomiting, or diarrhea</li> <li>■ Chest pain accompanied by sweating, pain radiating to shoulder, arm, neck, or jaw, and shortness of breath</li> <li>■ Pregnancy</li> <li>■ Nursing mothers</li> <li>■ Children younger than 12 years (for antacids, H<sub>2</sub>RAs) or younger than 18 years (for omeprazole)</li> </ul>



**FIGURE 14-2** Self-treatment of heartburn. Key: H<sub>2</sub>RA, histamine<sub>2</sub>-receptor antagonist; OTC, over-the-counter; PPI, proton pump inhibitor.

heartburn and acid indigestion when given 1 hour prior to a heavy or spicy meal and exercise. A combination product containing an H<sub>2</sub>RA plus an antacid may be recommended when rapid relief and longer duration are desirable (Table 14-3). Nonprescription H<sub>2</sub>RA products containing the lower doses (e.g., famotidine 10 mg twice daily) should be recommended for patients with mild, infrequent heartburn, while higher nonprescription dosages (e.g., famotidine 20 mg twice daily) should be

reserved for moderate symptoms. When used in recommended and comparative dosages, the H<sub>2</sub>RAs are interchangeable despite minor differences in potency, onset, and duration of action. Patients taking continuous daily doses of a nonprescription H<sub>2</sub>RA should not exceed 14 days of self-treatment without consulting their primary care provider.

Nonprescription PPIs are the drugs of choice for treating individuals with frequent heartburn occurring 2 or

**TABLE 14-3** Effectiveness of Nonprescription Medications in Relieving Heartburn

Medication	Onset of Relief	Duration of Relief	Symptomatic Relief
Antacids	<5 minutes	20-30 minutes*	Excellent
H <sub>2</sub> RAs	30-45 minutes	4-10 hours	Excellent
H <sub>2</sub> RA + antacid	<5 minutes	8-10 hours	Excellent
PPIs	2-3 hours	12-24 hours	Superior

Key: H<sub>2</sub>RAs, histamine<sub>2</sub>-receptor antagonist; PPI, proton pump inhibitor.

\* Food prolongs duration of relief.

more days a week and for those who do not respond to nonprescription H<sub>2</sub>RAs. The onset of symptom relief following an oral dose of omeprazole is slower than that of an H<sub>2</sub>RA (Table 14-3), and complete relief of symptoms may take 1 to 4 days after initiating treatment. However, PPIs provide superior symptom relief and a prolonged duration of action, compared with the nonprescription H<sub>2</sub>RAs. Optimal relief of symptoms is obtained when the PPI is taken 30 minutes before a meal (preferably breakfast). Patients should be advised not to take the nonprescription PPI for more than 14 days and not to re-treat more often than every 4 months unless under the supervision of a primary care provider.

The selection of a nonprescription medication for the self-treatment of heartburn and dyspepsia should be based on the frequency, duration, and severity of symptoms, the cost of the medication, potential drug interactions, and the patient's preference. Antacids, nonprescription H<sub>2</sub>RAs, and PPIs should not be used beyond 2 weeks unless the individual is under the care of a primary care provider. Individuals with severe, recurrent, or persistent symptoms should be referred for medical evaluation.

### Nonpharmacologic Therapy

Dietary and lifestyle modifications should be recommended for all patients with heartburn and dyspepsia despite the fact that evidence supporting their effectiveness is either lacking or equivocal.<sup>2,14,15,20,21</sup> These maneuvers may benefit many individuals, but changes alone are unlikely to completely relieve symptoms in the majority of patients.<sup>2</sup> Nonpharmacologic approaches to reducing the frequency and severity of heartburn include actions to increase the LES pressure, decrease the intragastric pressure, assist in the movement of gastric contents, and minimize exposure to triggering factors. A complete and accurate history will assist in identifying contributing factors. Recommendations should be tailored to the individual on the basis of specific dietary and lifestyle patterns.

Individuals should be asked to keep a diary to track dietary, lifestyle, and medication “triggers” (Table 14-1). Weight loss should be encouraged, although there is some controversy as to whether this will significantly decrease symptoms.<sup>15,20-22</sup> For nocturnal symptoms, some relief may be attained from elevating the head of the bed by placing 6-inch blocks underneath the legs of the head of the bed, or placing a foam wedge (e.g., GERD pillow) beneath the

patient's upper torso and head.<sup>22-24</sup> Use of traditional pillows may worsen symptoms, as it requires bending at the waist, which contributes to an increase in intragastric pressure.

Individuals should be educated about factors that contribute to heartburn and how to manage them (see box Patient Education for Heartburn and Dyspepsia). Most importantly, heartburn sufferers should be counseled to eat smaller meals, to reduce intake of dietary fat, and to not eat at least 3 hours before going to bed or lying down. Prescription and nonprescription medications should be evaluated for potential effects on heartburn and dyspepsia. When possible, individuals should be advised to switch to less troublesome nonprescription medications or consult their prescriber about prescription drugs that may be exacerbating their symptoms. Use of tobacco products should be discouraged. If alcohol or caffeine consumption is a contributing factor, individuals should be advised to limit or discontinue use.

### Pharmacologic Therapy

#### Antacids

Antacids relieve heartburn and dyspepsia by neutralizing gastric acid. Nonprescription antacid products contain at least one of the following salts: magnesium salts (hydroxide, carbonate, trisilicate), aluminum salts (hydroxide, phosphate), calcium carbonate, and sodium bicarbonate (Table 14-4). Over the last few years, many of the pharmaceutical manufacturers have reformulated antacid products with longstanding trade names (e.g., Mylanta) and introduced new products (e.g., Mylanta Supreme) and dosage forms (e.g., Mylanta Gelcaps, Mylanta Ultra) with similar trade names. Many of these modifications have led to the addition of calcium to the formulation or replacement of another antacid salt with calcium (e.g., Maalox Total Stomach Relief Maximum Strength). Most antacids are relatively inexpensive, making them desirable products for the temporary relief of mild and infrequent heartburn and dyspepsia.

**Mechanism of Action/Pharmacokinetics** Antacids act as buffering agents in the lower esophagus, gastric lumen, and duodenal bulb. The cations react with chloride, whereas the anionic portion of the molecule reacts with hydrogen ions to form water and other compounds. As a result, a small, but noticeable increase in intragastric pH

**TABLE 14-4** Selected Antacid and Bismuth Products and Dosage Regimens

Trade Name	Primary Ingredients	Adult Dosage (Maximum Daily Dosage)
Alka-Mints Chewable Antacid	Calcium carbonate 850 mg	Chew 1 or 2 tablets q2h as needed (8 tablets)
Alka Seltzer Heartburn Relief	Sodium bicarbonate 1940 mg; citric acid 1000 mg	Dissolve 2 tablets in 4 oz of water every hour as needed (8 tablets)
Alka Seltzer Original	Sodium bicarbonate 1916 mg; citric acid 1000 mg; aspirin 325 mg	Dissolve 2 tablets in 4 oz of water every hour as needed (8 tablets)
Alternagel Liquid	Each 5 mL contains aluminum hydroxide 600 mg	1-2 tsp between meals and at bedtime (18 tsp)
Gaviscon Extra Strength Liquid	Each 5 mL contains* aluminum hydroxide 254 mg; magnesium carbonate 237 mg	2-4 tsp 4 times a day, after meals and at bedtime (16 tsp)
Gelusil Tablets	Aluminum hydroxide 200 mg; magnesium hydroxide 200 mg; simethicone 25 mg	Chew 2 to 4 tablets; repeat hourly if symptoms return (12 tablets)
Maalox Liquid Regular Strength Antacid/Antigas	Each 5 mL contains aluminum hydroxide 200 mg; magnesium hydroxide 200 mg; simethicone 20 mg	2-4 tsp 4 times a day (16 tsp)
Maalox Quick Dissolve Regular Strength Chewable Antacid Tablets	Calcium carbonate 600 mg	Chew 1-2 tablets as symptoms occur (12 tablets)
Maalox Total Stomach Relief Maximum Strength	Each 15 mL contains bismuth subsalicylate 500 mg	2 tbsp q1/2-1h as required (up to 4 doses or 8 tbsp)
Mylanta Gelcaps	Calcium carbonate 550 mg; magnesium hydroxide 125 mg	Swallow 2-4 gelcaps as needed (12 gelcaps)
Mylanta Maximum Strength Liquid	Each 5 mL contains aluminum hydroxide 400 mg; magnesium hydroxide 400 mg; simethicone 40 mg	2-4 tsp between meals and at bedtime (12 tsp)
Mylanta Regular Strength Liquid	Each 5 mL contains aluminum hydroxide 200 mg; magnesium hydroxide 200 mg; simethicone 20 mg	2-4 tsp between meals and at bedtime (24 tsp)
Mylanta Supreme Liquid	Each 5 mL contains calcium carbonate 400 mg; magnesium hydroxide 135 mg	2-4 tsp between meals and at bedtime (18 tsp)
Mylanta Ultra Chewable Tabs	Calcium carbonate 700 mg; magnesium hydroxide 300 mg	Chew 2-4 tablets between meals and at bedtime (10 tablets)
Pepto Bismol Maximum Strength Liquid	Each 15 mL contains bismuth subsalicylate 500 mg	2 tbsp q1/2-1h as required (4 doses or 8 tbsp)
Pepto Bismol Original Liquid	Each 15 mL contains bismuth subsalicylate 262 mg	2 tbsp q1/2-1h as required (8 doses or 16 tbsp)
Phillips Milk of Magnesia Original	Each 5 mL contains magnesium hydroxide 400 mg	1-3 tsp q4h (4 times/day or 12 tbsp)
Roloids Antacid Tablets	Calcium carbonate 550 mg; magnesium hydroxide 110 mg	Chew 2-4 tablets hourly as needed (12 tablets)
Tums E-X Extra Strength Tablets	Calcium carbonate 750 mg	Chew 2-4 tablets as needed symptoms (10 tablets)
Tums Regular Strength Tablets	Calcium carbonate 500 mg	Chew 2-4 tablets as needed symptoms (15 tablets)

\* Sodium alginate (alginic acid) is listed as an inactive ingredient.

occurs.<sup>25</sup> Increasing the intragastric pH above 5 blocks the conversion of pepsin to pepsinogen.<sup>25</sup> Antacids may also increase LES pressure.<sup>1</sup>

Sodium bicarbonate rapidly reacts with gastric acid to form sodium chloride, carbon dioxide, and water. Its duration of action is shortened by its quick elimination from the stomach.<sup>25</sup> Of the magnesium salts, magnesium

hydroxide is used most often. Magnesium hydroxide rapidly reacts with gastric acid to form magnesium chloride and water. Its duration of action is shorter than that of calcium carbonate and aluminum hydroxide. Calcium carbonate is a potent antacid that dissolves slowly in gastric acid to form calcium chloride, carbon dioxide, and water. Its onset of action is slower, but its duration of effect is

longer than magnesium hydroxide or sodium bicarbonate. Aluminum hydroxide reacts with hydrochloric acid to form aluminum chloride and water. It has a slower onset, but a longer duration than magnesium hydroxide.

Liquid antacids usually have a faster onset than tablets, because they are already dissolved or suspended and provide a maximal surface area for action. Of the tablet dosage forms, the quick-dissolve antacid tablets may provide the most rapid relief of symptoms. The duration of action for all antacids is transient, lasting only as long as the antacid remains in the stomach. The presence of food affects the duration of action of antacids. When administered within 1 hour after a meal, antacids may remain in the stomach for up to 3 hours.<sup>25</sup>

Differences in antacids are determined primarily on the cation, specific salt, and potency. Antacid potency is based on the number of milliequivalents of acid neutralizing capacity (ANC), which is defined as the amount of acid buffered per dose over a specified period of time. Factors that contribute to the ANC include product formulation, ingredients, and concentration.<sup>25</sup> As a result, ANC is product specific, which means equal volumes of liquid antacids or the same number of tablets are not necessarily equal in potency.

Most antacids are minimally absorbed into the systemic circulation. About 90% of calcium is converted to insoluble calcium salts, and the remaining 10% is absorbed systemically.<sup>25</sup> Approximately 15% to 30% of magnesium and 17% to 30% of aluminum may be absorbed and then excreted renally; therefore, accumulation may occur in patients with renal insufficiency.<sup>25</sup> In contrast, sodium bicarbonate is readily absorbed and eliminated.

**Indications** Antacids are indicated for the treatment of mild, infrequent heartburn, sour stomach, and acid indigestion. Combination products containing aspirin or acetaminophen are indicated for overindulgence in food and drink, and hangover. Individuals with mild dyspepsia may experience some relief with an antacid, but no studies demonstrate their effectiveness.<sup>9,25</sup>

**Dosage and Administration Guidelines** Antacids are administered orally. The effective dose of an antacid varies depending on product ingredients, milliequivalents of acid neutralizing capacity, formulation, and the frequency and severity of symptoms. Individuals should be instructed to take product-specific recommended dosages at the onset of symptoms. Dosing may be repeated in 1 to 2 hours, if needed, but should not exceed the maximum daily dosage for a particular product (Table 14-4). Individuals should be reevaluated if antacids are used more than twice a week or regularly for over 2 weeks. Frequent antacid users may need to be switched to a longer-acting product such as an H<sub>2</sub>RA, an H<sub>2</sub>RA plus an antacid, or a PPI.

**Safety Considerations** Antacids are usually well tolerated. Side effects are generally associated with the cation. The most common side effect associated with magnesium-containing antacids is a dose-related diarrhea. Diarrhea may be reduced by combining magnesium-containing antacids

with aluminum hydroxide. However, when higher dosages are used, the predominating effect is diarrhea. Magnesium excretion is impaired in patients with renal disease and may result in systemic accumulation of magnesium. Magnesium-containing antacids should not be used in patients with a creatinine clearance of less than 30 mL/minute.<sup>25</sup>

Aluminum-containing antacids are associated with dose-related constipation. Aluminum hydroxide binds dietary phosphate in the GI tract, increasing phosphate excretion in the feces. Frequent and prolonged use of aluminum hydroxide may lead to hypophosphatemia.<sup>25</sup> Chronic use of aluminum-containing antacids in renal failure may lead to aluminum toxicity and should be avoided.

Calcium carbonate may cause belching and flatulence as a result of carbon dioxide production. Patients may complain of constipation when taking calcium antacids, but there is little evidence to support this side effect.<sup>25</sup> Acid rebound with calcium-containing antacids has been reported. Although calcium stimulates gastric acid secretion, the clinical importance of this finding remains uncertain.<sup>1,26</sup> If renal elimination is impaired, hypercalcemia may occur and accumulation of calcium may result in the formation of renal calculi. Because many antacids have been reformulated to contain calcium, the risk of hypercalcemia exists when high and frequent dosages of calcium-containing antacids are taken with other calcium-containing medications such as prenatal vitamins or foods such as milk or orange juice with added calcium. Up to 2500 mg/day of elemental calcium can be ingested safely in individuals with normal renal function.<sup>27</sup>

Sodium bicarbonate frequently causes belching and flatulence resulting from the production of carbon dioxide.<sup>25</sup> The high sodium content (274 mg sodium/gram sodium bicarbonate) may cause fluid overload in patients with congestive heart failure, renal failure, cirrhosis, pregnancy, and those on sodium-restricted diets. In individuals with normal renal function, additional bicarbonate is excreted, whereas in patients with impaired renal function, retained bicarbonate may cause systemic alkalosis. A high intake of calcium along with an alkalinizing agent (such as sodium bicarbonate or calcium carbonate) may produce a condition referred to as milk-alkali syndrome. Signs and symptoms include hypercalcemia, alkalosis, irritability, headache, nausea, vomiting, weakness, and malaise.<sup>25,26</sup> Individuals who take additional calcium, such as pregnant and postmenopausal women should avoid using sodium bicarbonate as an antacid.

All antacids may potentially increase or decrease the absorption of other oral medications when given concomitantly, by adsorbing or chelating the other drug or increasing intragastric pH.<sup>25,28</sup> Medications such as tetracyclines, azithromycin, and fluoroquinolones bind to divalent and trivalent cations, potentially decreasing antibiotic absorption.<sup>25,28</sup> The absorption of medications such as itraconazole, ketoconazole, and iron, that depend on a low intragastric pH for disintegration, dissolution, or ionization, may also be decreased.<sup>25,28</sup> Specific antacids, such as aluminum hydroxide, may decrease the absorption of isoniazid. The absorption of enteric-coated products may be increased with concurrent administration of antacids.<sup>28</sup> The intraluminal interactions of antacids with other oral medications can

**TABLE 14-5** Nonprescription H<sub>2</sub>RA and PPI Products and Dosage Regimens

Trade Name	Primary Ingredients	Adult Dosage (Maximum Daily Dosage)
Tagamet HB	Cimetidine 200 mg	1 tablet with a glass of water (2 tablets)
Axid AR	Nizatidine 75 mg	1 tablet with a glass of water (2 tablets)
Pepcid AC	Famotidine 10 mg	1 tablet with a glass of water (2 tablets)
Pepcid AC Maximum Strength	Famotidine 20 mg	1 tablet with a glass of water (2 tablets)
Zantac 75	Ranitidine 75 mg	1 tablet with a glass of water (2 tablets)
Zantac 150	Ranitidine 150 mg	1 tablet with a glass of water (2 tablets)
Pepcid Complete	Famotidine 10 mg; calcium carbonate 800 mg; magnesium hydroxide 165 mg	Chew and swallow 1 tablet (2 tablets)
Prilosec OTC	Omeprazole 20 mg	1 tablet with a glass of water 30 minutes before morning meal; take daily for 14 days (1 tablet)

usually be avoided when potentially interacting drugs are separated by at least 2 hours. Antacid-induced alkalization of the urine may increase urinary excretion of salicylates and decrease blood concentrations.<sup>28</sup> In contrast, an increase in urine pH may decrease urinary excretion and increase blood concentrations of amphetamines and quinidine.<sup>25</sup>

**Additional Ingredients** Alginic acid reacts with sodium bicarbonate in saliva to form a viscous layer of sodium alginate that floats on the surface of gastric contents, theoretically forming a protective barrier against esophageal irritation.<sup>1</sup> Alginic acid by itself does not neutralize acid. Because there is insufficient evidence supporting its efficacy as a single agent, the Food and Drug Administration (FDA) has not granted alginic acid category I status. However, alginic acid may be found as an inactive ingredient in several antacid products (Table 14-4). Combination products of alginic acid and an antacid may be superior to an antacid alone.<sup>2</sup> Several antacid products contain simethicone to decrease discomfort related to intestinal gas. See Chapter 15 (Intestinal Gas), for a more detailed description of simethicone.

### Histamine<sub>2</sub>-Receptor Antagonists

The H<sub>2</sub>RAs relieve heartburn and dyspepsia by decreasing gastric acid secretion. The four H<sub>2</sub>RAs available for nonprescription use are cimetidine, ranitidine, famotidine, and nizatidine (Table 14-5). Initially, these medications were only available for nonprescription use at one half of the prescription dose. Today, nonprescription H<sub>2</sub>RAs also are available in the higher prescription dosages. For the most part, the four H<sub>2</sub>RAs are considered interchangeable, despite differences in onset and duration of symptom relief, side effects, and the potential for drug interactions. However, cimetidine does have the greatest potential for serious hepatic CYP 450 drug interactions and is associated with impotence in males.

**Mechanism of Action/Pharmacokinetics** H<sub>2</sub>RAs decrease gastric acid secretion by inhibiting the effect of histamine on the histamine<sub>2</sub> receptor of the parietal cell. In addition,

H<sub>2</sub>RAs decrease the volume of secreted acid. Acid secretion is decreased regardless of the presence of food, which make these agents effective for fasting and nocturnal symptoms.<sup>23</sup> Their bioavailability is not affected by food, but may be reduced modestly by antacids. All of the H<sub>2</sub>RAs are eliminated by a combination of renal and hepatic metabolism, with renal elimination being the most important. Onset of symptom relief is not as quick as that of antacids, but their duration of effect is longer lasting (Table 14-3).<sup>1,29</sup> Cimetidine is the shortest-acting H<sub>2</sub>RA, with a duration of action of 4 to 8 hours, while ranitidine, famotidine, and nizatidine have a somewhat longer duration. Tolerance to the gastric antisecretory effect may occur when H<sub>2</sub>RAs are taken daily (versus as needed) and may be responsible for diminished efficacy.<sup>1</sup>

**Indications** Nonprescription H<sub>2</sub>RAs are indicated for the treatment of mild to moderate infrequent, episodic heartburn and for the prevention of heartburn associated with acid indigestion and sour stomach. H<sub>2</sub>RAs have been shown to be more effective than placebo for relief of mild to moderate heartburn<sup>2,4</sup> and provide moderate improvement in patients with mild dyspeptic symptoms.<sup>9,30</sup> The combined antacid (magnesium hydroxide and calcium carbonate) and H<sub>2</sub>RA (famotidine) product is indicated for individuals with postprandial heartburn who have not premedicated with an H<sub>2</sub>RA.

**Dosage and Administration Guidelines** H<sub>2</sub>RAs may be used at the onset of symptoms or 30 minutes to 1 hour prior to an event (meal or exercise) in which heartburn is anticipated. Self-treatment dosing should be limited to no more than two times a day. If the H<sub>2</sub>RA is used more than twice a week, or for more than 2 weeks, follow-up with a primary care provider is recommended. The combined antacid and H<sub>2</sub>RA product both provides immediate relief and prevents symptoms. Because tolerance to the antisecretory effect may develop, it is best to take an H<sub>2</sub>RA on an as-needed basis rather than by continuous daily dosing.<sup>1</sup> All four H<sub>2</sub>RAs require a dosage reduction in patients with reduced renal function.<sup>12</sup> Patients of advanced age, in particular, are at greatest risk for side effects when the H<sub>2</sub>RA daily dose is not reduced appropriately.<sup>31</sup>

**Safety Considerations** The four H<sub>2</sub>RAs are well tolerated and have a low incidence of side effects.<sup>11</sup> The most common side effects occur with all four agents and include headache, diarrhea, constipation, dizziness, and drowsiness.<sup>11,12</sup> Cimetidine is associated with a weak antiandrogenic effect that may result in decreased libido, impotence, or gynecomastia in men.<sup>12</sup> Cimetidine binds to hepatic cytochrome P450 (3A4, 2D6, 1A2, and 2C9), inhibiting the metabolism of numerous drugs including phenytoin, warfarin, theophylline, tricyclic antidepressants, and amiodarone.<sup>28,32</sup> Ranitidine also binds to the cytochrome P450 system, but to a lesser extent, so interactions are uncommon at nonprescription doses. Famotidine and nizatidine do not interact with the cytochrome P450 system. Medications such as ketoconazole, itraconazole, and iron salts are dependent on an acidic environment for absorption.<sup>11,28</sup> When administered with an acid-reducing product, their absorption may be reduced. Cimetidine may inhibit the renal tubular secretion of drugs such as procainamide.<sup>28</sup>

### Proton Pump Inhibitors

PPIs are potent antisecretory drugs that relieve heartburn and dyspepsia by decreasing gastric acid secretion. Omeprazole was the first PPI to become available for nonprescription use in the United States at an oral dosage of 20 mg, which is identical to the prescription dosage.

**Mechanism of Action/Pharmacokinetics** The PPIs inhibit hydrogen potassium ATPase (the proton pump), irreversibly blocking the final step in gastric acid secretion.<sup>33,34</sup> PPIs have a more potent and prolonged antisecretory effect than do the H<sub>2</sub>RAs (Table 14-3).<sup>34</sup> The relative bioavailability of the prescription dosage form (enteric-coated granules contained in a capsule) increases from 35% to 65% with continued daily dosing.<sup>33</sup> The nonprescription dosage form, available as a magnesium salt, is formulated as a tablet containing multiple enteric-coated pellets<sup>36</sup> and has a similar oral bioavailability.<sup>10</sup> Omeprazole is almost completely absorbed after oral administration, regardless of the presence of food.

The onset of symptom relief following an oral dose occurs in 2 to 3 hours, but complete relief may take 1 to 4 days.<sup>33,35</sup> However, the results of a recent study indicate that on day 1, the percentage of time the intragastric pH was greater than 4 with Prilosec OTC taken once daily was higher than with Pepcid AC taken twice a day and comparable to famotidine 20 mg twice daily.<sup>36</sup> In addition, the intragastric pH with Prilosec OTC was consistently higher than with both famotidine regimens on subsequent treatment days. Because the PPIs inhibit only those proton pumps that are actively secreting acid, they are most effective when taken 30 minutes before meals.<sup>37</sup>

**Indications** Nonprescription omeprazole is indicated for the treatment of frequent heartburn in patients who have symptoms 2 or more days a week. It is not intended for immediate relief of occasional or acute episodes of heartburn or for dyspepsia.

**Dosage and Administration Guidelines** Omeprazole should be taken 30 minutes before eating every morning for 14 days. Treatment of heartburn may be repeated after 4 months if symptoms recur.<sup>35</sup> If heartburn continues while taking omeprazole, persists for more than 2 weeks, or recurs within 4 months, follow-up with a primary care provider is recommended. The tablets should not be chewed or crushed, as this may decrease the effectiveness of the drug.

**Safety Considerations** The most common side effects of the PPIs are similar to those reported for the H<sub>2</sub>RAs (e.g., diarrhea, constipation, and headache).<sup>33</sup> A recent retrospective review reported a higher incidence of community-acquired pneumonia in patients taking antisecretory drugs than in those who were not taking them.<sup>38</sup> The PPIs had a 1.89 and the H<sub>2</sub>RAs had a 1.63 adjusted relative risk of pneumonia, compared with those who stopped PPIs and H<sub>2</sub>RAs. The findings for PPIs were dose related. Possible increased risk of pneumonia may result from a decrease in the antibacterial action of gastric juice, which when aspirated may lead to an overgrowth of pathogens. Risk factors include asthma, chronic obstructive pulmonary disease, young or old age (e.g., children and elderly), and immunocompromised state. The clinical importance of these findings for ambulatory patients requiring PPI therapy is questionable.

Omeprazole may interact with other medications that depend on the hepatic CYP 2C19 for metabolism.<sup>33,34</sup> Although evidence for clinically important drug interactions is minimal given the widespread use of the omeprazole over the last decade, patients taking medications such as diazepam, phenytoin, and warfarin should be warned about the potential for a drug interaction.<sup>35</sup> Similar to antacids and H<sub>2</sub>RAs, PPIs increase intragastric pH and may decrease the absorption of pH-dependent drugs<sup>33</sup> (see drug interaction section of antacids and H<sub>2</sub>RAs). PPIs may increase the bioavailability of digoxin, but the clinical importance of this effect is unknown.

### Bismuth Subsalicylate

Bismuth subsalicylate (BSS) is indicated for heartburn, upset stomach, indigestion, nausea, and diarrhea. It is likely that BSS may eventually be approved by FDA for the relief of upset stomach associated with belching and gas resulting from overindulgence in food and drink. It is uncertain how BSS relieves heartburn, but for upset stomach, it is believed to act by a topical effect on the stomach mucosa. When used to treat acid-related symptoms, the adult dose of BSS is 262 to 500 mg every 1/2 to 1 hour as needed (Table 14-4). Recently, numerous nonprescription products have been reformulated to contain BSS. In the past, common trade name products, such as Maalox, contained only antacids. Today, product line extensions, such as Maalox Total Stomach Relief contain BSS and no antacid (Table 14-4). Thus, patients and health care providers are often confused and may not know what they are recommending or purchasing. Individuals taking these products need to know that bismuth salts may cause the stool and tongue to turn black. Dark-colored stools may be interpreted

as an upper GI bleed, prompting a needless colonoscopy. For a complete discussion of BSS, see Chapter 17.

### Product Selection Guidelines

**Special Populations** Careful consideration should be given to the elderly before recommending self-treatment for new onset of heartburn or dyspepsia. Older patients are more likely to take medications that can contribute to heartburn and dyspepsia. In addition, they are at higher risk for developing complications and may have a more severe underlying disorder.<sup>1,16</sup> If self-treatment is appropriate, an assessment should be made to determine if the individual has renal impairment and to identify potentially interacting medications. Patients with decreased renal function should be cautioned about using aluminum- and magnesium-containing antacids. The daily H<sub>2</sub>RA dose should also be reduced, especially in those taking the higher nonprescription dosages. Omeprazole may be used in patients with renal impairment. Sodium bicarbonate should be avoided in patients taking cardiovascular medications.

Antacid selection for eligible patients should be based, in part, on potential side effects. For example, if a patient has a tendency toward constipation, a less constipating antacid, such as magnesium hydroxide, may be more appropriate, while constipating antacids, such as aluminum hydroxide, should be avoided.

Children under 12 years of age with heartburn or dyspepsia should be referred to their primary care provider for further evaluation.<sup>39</sup> Nonprescription antacids, such as calcium carbonate and magnesium hydroxide are labeled for children 12 years and older. If antacids are recommended, an assessment of the child's average daily intake of calcium may help guide the recommendation. The recommended daily intake of calcium for children 9 to 18 years old is 1300 mg.<sup>27</sup> Nonprescription H<sub>2</sub>RAs are labeled for patients age 12 or older, and nonprescription omeprazole is indicated for patients age 18 years and older.

Infrequent and mild heartburn in pregnant women should be treated initially with dietary and lifestyle modifications.<sup>24</sup> Calcium- and magnesium-containing antacids are pregnancy category B agents, and may be used safely if the recommended daily dosages are not exceeded.<sup>40</sup> Special attention should be given to the recommended intake of calcium during pregnancy (1300 mg/day), as with pediatric patients.<sup>27</sup> If a woman is meeting the recommendations, the addition of a calcium-containing antacid may cause her to exceed the upper limit of 2500 mg of calcium per day. Pregnant women with more frequent and severe heartburn should be referred to a primary care provider. Although cimetidine, famotidine, ranitidine, and nizatidine are listed as pregnancy category B and have been used during pregnancy, women should seek advice from their primary care provider prior to self-treating with an H<sub>2</sub>RA. Omeprazole is a pregnancy category C drug and should not be used by pregnant women without the advice of their primary care provider.

Magnesium hydroxide and aluminum hydroxide are not secreted into breast milk in substantial amounts.<sup>24</sup> Therefore, these antacids may be safely recommended for self-treatment of heartburn in nursing mothers. The

American Academy of Pediatrics considers cimetidine to be compatible with breast-feeding.<sup>41</sup> However, ranitidine and famotidine are less concentrated in the breast milk, and may be preferable. There is insufficient information regarding the use of omeprazole in women who are breast-feeding, so it cannot be recommended for nursing mothers at this time.<sup>42</sup>

**Patient Preferences** Antacids and antisecretory drugs are available in a wide range of prices, flavors, and dosage forms. Once the most appropriate nonprescription medication is determined, the individual should be involved in selecting a product that is affordable, palatable, and practical to administer. Other nonactive ingredients such as dyes, sodium, and sugar should be considered for individuals with allergies, sensitivities, or dietary restrictions.

### Complementary Therapies

A small number of herbal remedies have been used traditionally to treat heartburn and dyspepsia, but few have been well studied (Table 14-6; see also Chapter 53).<sup>43-51</sup> There is no evidence that herbal products increase intragastric pH and relieve heartburn. A few studies have shown an improvement in dyspeptic symptoms with combination herbal therapies. A product marketed as STW 5 contains iberis, peppermint, and chamomile and has been shown to be more effective than placebo, with no serious adverse effects.<sup>46</sup> Another product marketed as STW 5-II contains extracts of bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root, and lemon balm. In patients with nonulcer dyspepsia, the combination relieved symptoms better than placebo.<sup>47</sup> A combination of peppermint oil and caraway oil was shown to be effective for dyspepsia.<sup>51</sup>

### Assessment of Heartburn and Dyspepsia: A Case-based Approach

Cases 14-1 and 14-2 illustrate the assessment of patients with heartburn and dyspepsia.

### Patient Counseling for Heartburn and Dyspepsia

Many cases of uncomplicated heartburn and dyspepsia are self-treatable. For optimal outcomes, individuals need to understand how to treat symptoms appropriately and when to seek additional care. This information is provided in the box Patient Education for Heartburn and Dyspepsia.

### Evaluation of Patient Outcomes for Heartburn and Dyspepsia

Individuals taking antacids or an H<sub>2</sub>RA for infrequent heartburn and dyspepsia should obtain symptom relief within 30 minutes to 1 hour. Patients taking omeprazole may require up to 4 days for complete relief of symptoms, but most individuals are asymptomatic within 1 or 2 days. Self-treating individuals should be encouraged to contact their health care provider to report on the effectiveness of therapy and problems, such as side effects, that may arise during treatment. In some cases, the clinician may

**TABLE 14-6** Botanical Medicines Used to Treat Heartburn and Dyspepsia<sup>43-51</sup>

Botanical Medicine (Scientific Name)	Risks	Effectiveness
Artichoke leaf ( <i>Cynara scolymus</i> )	Likely safe in amounts found in foods; possible allergic reaction; artichoke extract: possible increased flatulence in some patients	Improvement in dyspepsia symptoms shown in small studies
Caraway oil ( <i>Carum carvi</i> )	Likely safe in amounts found in foods; some reports of substernal burning, belching, and nausea when used with peppermint oil.	Possibly effective in when used combination with peppermint oil
Carrageenan ( <i>Chondrus crispus</i> )	Likely safe in amounts found in foods; associated with intestinal ulcerations and neoplasms in animals	Insufficient evidence
Chamomile ( <i>Matricaria recutita</i> )	Rare allergic reactions	Possibly effective when used in combination with iberis and peppermint oil
Coriander seed ( <i>Coriandrum sativum</i> )	Likely safe in amounts found in foods; possible laxative effect	Insufficient evidence
Ginger ( <i>Zingiber officinale</i> )	Likely safe in amounts found in foods; possible prolonged bleeding times in patients on oral anticoagulants	Insufficient evidence
Licorice ( <i>Glycyrrhiza glabra</i> ) and deglycyrrhizinated licorice	Possible pseudoaldosteronism with large doses (>50 g/day), resulting in hypokalemia, water retention, and hypertension; contraindicated in pregnancy, cholestatic liver, cirrhosis, hypokalemia, renal impairment	Insufficient evidence
Peppermint ( <i>Mentha piperita</i> )	Likely safe in amounts found in foods; may decrease LES pressure	Possibly effective when used in combination with caraway oil
Sage ( <i>Salvia officinalis</i> )	Likely safe in amounts found in foods; possibly unsafe in greater amounts; sage oil: possible CNS toxicity in higher doses	Insufficient evidence
Turmeric ( <i>Curcuma longa</i> )	Likely safe in amounts found in foods; possible GI disturbances with overuse; contraindicated in patients with bile duct obstruction, gallstones, gastric ulcers, or hyperacidity disorders	Insufficient evidence

Key: CNS, central nervous system; GI, gastrointestinal; LES, lower esophageal sphincter.

### CASE 14-1

#### Relevant Evaluation Criteria

#### Scenario/Model Outcome

#### Information Gathering

1. Gather essential information about the patient's symptoms, including:

- |   |  |
|---|--|
| a. description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)                 | Patient experiences heartburn 3-4 times/week during the day and sometimes in the evening, occurring off and on for the past month. He rates discomfort as 3-5 on a scale of 1-10 (1 = no pain; 10 = worst pain imaginable), describes it as burning, accompanied by belching, and denies other symptoms. |
| b. description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s) | More noticeable when he eats larger meals later in the evening; lying down after eating makes it worse   |
| c. description of the patient's efforts to relieve the symptoms   | Has taken Tums in the past with temporary relief and tried Pepcid AC, but is looking for something less chalky tasting, more effective, and longer lasting   |

## CASE 14-1 (continued)

Relevant Evaluation Criteria	Scenario/Model Outcome
2. Gather essential patient history information:	
a. patient's identity	Greg Samuels
b. age, sex, height, and weight	38 yo M, 5'10", 195 lb
c. patient's occupation	Exterminator
d. patient's dietary habits	Primarily meat and potatoes-based meals; drinks one cup of coffee in the morning
e. patient's sleep habits	Stays up late when he experiences heartburn because it is uncomfortable to lie down; his sleep is not disrupted; rises for work at 6 AM
f. concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Tylenol 1000 mg 1-3 times a month for tension-type headaches; lovastatin 40 mg once daily for hyperlipidemia
g. allergies	Penicillin
h. history of other adverse reactions to medications	None
i. other (describe)_____	Denies alcohol and tobacco use
<b>Assessment and Triage</b>	
3. Differentiate the patient's signs/symptoms and correctly identify the patient's primary problem(s) (see Table 14-2).	Postprandial heartburn associated with large meals and recumbence. Evaluate specific dietary triggers associated with daytime symptoms.
4. Identify exclusions for self-treatment (see Figure 14-2).	None. Alarm symptoms (see Table 14-2) and contraindications to self-treatment are absent.
5. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine if triage to a medical practitioner is required, and share this information with the patient.	Options include: (1) Recommend self-care with an appropriate nonprescription product and advise on nondrug measures. (2) Recommend self-care with an appropriate nonprescription product and advise on nondrug measures until Greg can contact his PCP. (3) Refer Greg to his PCP for medical evaluation of his symptoms. (4) Take no action.
<b>Plan</b>	
6. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	The patient meets the criteria for self-treatment with OTC omeprazole combined with nondrug measures. A swallowed tablet will avoid the "chalky taste" he dislikes. The PPI should be more effective in managing frequent symptoms.
7. Describe the recommended therapeutic approach to the patient.	Take Prilosec OTC 20 mg once daily, 30 minutes before breakfast for 14 days. Avoid risk factors that may contribute to heartburn (see Table 14-1).
8. Explain to the patient the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	Seeing a PCP, that is, primary care provider, may not be necessary if adequate relief is obtained from appropriate use of omeprazole and if symptoms do not recur within 4 months.
<b>Patient Education</b>	
9. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient, including:	
a. appropriate dose and frequency of administration	Take one tablet every morning. See the box Patient Education for Heartburn and Dyspepsia.

## CASE 14-1 (continued)

Relevant Evaluation Criteria	Scenario/Model Outcome
b. maximum number of days the therapy should be employed	14 days; may repeat every 4 months if symptoms return
c. product administration procedures	Take with a glass of water 30 minutes before breakfast.
d. expected time to onset of relief	2 to 3 hours; complete relief within 1 to 4 days
e. degree of relief that can be reasonably expected	Complete relief of symptoms
f. most common side effects	Headache, diarrhea, constipation
g. side effects that warrant medical intervention should they occur	Severe headache, diarrhea, constipation; allergic reaction to medication, e.g., rash, fever
h. patient options in the event that condition worsens or persists	A PCP should be consulted if the symptoms persist, worsen, or recur within 4 months, or if alarm symptoms develop.
i. product storage requirements	Store at 68°-77°F (20°-25°C); protect from heat and humidity.
j. specific nondrug measures	Eat dinner at least 3 hours prior to bedtime. Eat smaller meals. Consider starting a weight loss program. Elevate the head of the bed or use a foam wedge.
10. Solicit patient's follow-up questions.	Could I take an antacid for immediate relief before omeprazole starts to work?
11. Answer patient's questions.	Yes. It is safe to take Tums or another antacid initially until your symptoms are relieved. If a supplemental antacid continues to be necessary, contact your PCP.

Key: OTC, over-the-counter; PCP, primary care provider; PPI, proton pump inhibitor.

## CASE 14-2

Relevant Evaluation Criteria	Scenario/Model Outcome
<b>Information Gathering</b>	
1. Gather essential information about the patient's symptoms, including:	
a. description of symptom(s) (i.e., nature, onset, duration, severity, associated symptoms)	Patient describes daily heartburn, bloating, and epigastric pain that occur during the day, often between meals, and sometimes awakens her at night. She rates discomfort as a 5-7 on a scale of 1-10 (1 = no pain; 10 = worst pain imaginable). Pain is diffuse and accompanied by nausea and sometimes vomiting. Pain started 3 months ago, and is increasing in frequency and severity.
b. description of any factors that seem to precipitate, exacerbate, and/or relieve the patient's symptom(s)	Food seems to diminish symptoms temporarily.
c. description of the patient's efforts to relieve the symptoms	She has taken Milk of Magnesia and Pepto Bismol in attempts to self-treat. They seemed to help early on, but she is not getting adequate relief with increasing doses.
2. Gather essential patient history information:	
a. patient's identity	Ursula Alvarez
b. age, sex, height, and weight	58 y/o F, 5'6"145 lb
c. patient's occupation	Homemaker
d. patient's dietary habits	Balanced diet; used to drink coffee in the mornings but quit when symptoms began
e. patient's sleep habits	Averages 7-8 hours per night
f. concurrent medical conditions, prescription and nonprescription medications, and dietary supplements	Diclofenac 75 mg 2 times/day for back pain for 5 years; Motrin Cold and Sinus 1 tablet 3 times/day for the last few weeks as she has been fighting a cold

## CASE 14-2 (continued)

Relevant Evaluation Criteria	Scenario/Model Outcome
g. allergies	NKA
h. history of other adverse reactions to medications	None
i. other (describe)_____	Smokes half-pack of cigarettes/day for the past 30 years; quit drinking alcohol 4 years ago
<b>Assessment and Triage</b>	
3. Differentiate the patient's signs/symptoms and correctly identify the patient's primary problem(s) (see Table 14-2).	Unable to identify primary problem without further medical evaluation. Symptoms are not consistent with self-treatable heartburn or dyspepsia. Relief of symptoms with food is not consistent with self-treatable heartburn. Alarm symptoms indicate referral. Use of multiple NSAIDs increases the risk of PUD.
4. Identify exclusions for self-treatment (see Figure 14-2).	Symptoms increasing in frequency and severity for 3 months; nocturnal symptoms. Inadequate relief with self-treatment.
5. Formulate a comprehensive list of therapeutic alternatives for the primary problem to determine if triage to a medical practitioner is required, and share this information with the patient.	Options include: (1) Recommend self-care with an appropriate nonprescription product and advise on nondrug measures. (2) Recommend self-care with an appropriate nonprescription product and advise on nondrug measures until Ursula can contact her PCP. (3) Refer Ursula to her PCP for medical evaluation of her symptoms. (4) Take no action.
<b>Plan</b>	
6. Select an optimal therapeutic alternative to address the patient's problem, taking into account patient preferences.	Refer Ursula to her PCP for further medical evaluation. Recommend that she discontinue the Motrin Cold and Sinus, which contains ibuprofen 200 mg and pseudoephedrine 30 mg, since she is taking diclofenac. If needed, suggest taking only the pseudoephedrine for her cold. If unable to see PCP within the next few days, recommend that Ursula take either Pepcid AC Max or Prilosec OTC. Instruct Ursula to tell her PCP what OTC medication she is taking until her appointment. Emphasize importance of seeing PCP as soon as possible.
7. Describe the recommended therapeutic approach to the patient.	You should see your PCP, that is, primary care provider, for evaluation of your symptoms.
8. Explain to the patient the rationale for selecting the recommended therapeutic approach from the considered therapeutic alternatives.	Seeing a PCP is necessary because your symptoms are not consistent with self-treatable conditions. Pepcid-AC Max or Prilosec OTC may provide temporary relief until you can see your PCP.
<b>Patient Education</b>	
9. When recommending self-care with nonprescription medications and/or nondrug therapy, convey accurate information to the patient, including:	Pepcid AC Max 20 mg; take 1 tablet twice daily for 14 days. Onset of symptom relief should occur within 30 to 45 minutes. See Case 14-1 for Prilosec OTC instructions.
10. Solicit follow-up questions from patient.	What natural products are effective for these symptoms?
11. Answer patient's questions.	There is insufficient information and evidence to support the use of natural products for your symptoms.
Key: NKA, no known allergies; NSAID, nonsteroidal anti-inflammatory drug; OTC, over-the-counter; PCP, primary care provider; PUD, peptic ulcer disease.	

## PATIENT EDUCATION FOR HEARTBURN AND DYSPESIA



Heartburn and dyspepsia (indigestion) are often self-treatable conditions. Heartburn is characterized by a burning sensation in the chest, usually occurring after meals. Dyspepsia is characterized by discomfort in the upper abdomen. The objectives of self-treatment are to (1) provide complete relief of symptoms, (2) reduce frequency of intermittent episodes, (3) manage factors that contribute to the development of symptoms, (4) prevent and manage side effects of selected treatment, and (5) improve quality of life.

### Nondrug Measures

- Avoid food, beverages, and activities associated with an increased frequency and severity of symptoms.
- If possible, avoid the use of medications that may aggravate heartburn or dyspeptic symptoms.
- Avoid eating large meals.
- Stop or reduce smoking.
- Lose weight if overweight and not pregnant.
- Wear loose-fitting clothing.
- If nocturnal symptoms are present:
  - Avoid lying down within 3 hours of a meal.
  - Elevate the head of the bed using 6-inch blocks, or use a foam pillow wedge.

### Nonprescription Medications

- Store all medications at 68°F to 77°F (20°C to 25°C), and protect them from heat, humidity, and moisture. Discard after expiration date.

### Antacids

- Antacids (sodium bicarbonate, calcium carbonate, magnesium hydroxide, aluminum hydroxide) are available alone and in combination with each other and other ingredients.
- Antacids work by neutralizing acid in the stomach.
- Antacids may be used for relief of mild, infrequent heartburn or dyspepsia (indigestion).
- Antacids are usually taken at the onset of symptoms. Onset of symptom relief usually occurs within 5 minutes.
- Because antacids come in a variety of strengths and concentrations, it is essential to consult the label of an individual product for correct dosing quantities and frequencies. Usually antacids should not be used more than four times a day, or regularly for more than 2 weeks.
- If symptoms are not relieved with recommended dosages, consult with a health care provider.
- Diarrhea may occur with magnesium- or magnesium/aluminum-containing antacids; constipation may occur with aluminum- or calcium-containing antacids. Consult with a health care provider if these effects are severe or do not resolve in a few days.
- Patients with renal impairment should consult with their primary care provider prior to self-treatment with antacids.
- Patients taking tetracyclines, fluoroquinolones, azithromycin, digoxin, ketoconazole, itraconazole, and iron supplements should not take antacids within 2 hours of taking any of these medications.

### Histamine<sub>2</sub>-Receptor Antagonists

- H<sub>2</sub>RAs (cimetidine, famotidine, nizatidine, ranitidine) work by decreasing acid production in the stomach.

- H<sub>2</sub>RAs should be used for relief of mild to moderate, infrequent, and episodic heartburn and indigestion when a longer effect is needed; use the lower dosages for mild, infrequent heartburn; use the higher dosages for moderate infrequent symptoms.
- H<sub>2</sub>RAs may be used to prevent heartburn and indigestion associated with meals.
- H<sub>2</sub>RAs are usually taken at the onset of symptoms or 1 hour before symptoms are expected. Onset of symptom relief can be expected within 30 to 45 minutes. The combination product that contains both an antacid and an H<sub>2</sub>RA provides more rapid symptom relief.
- H<sub>2</sub>RAs generally provide symptom relief for 4 to 10 hours. H<sub>2</sub>RAs can be taken when needed up to twice daily for 2 weeks.
- If symptoms are not relieved with recommended doses, or persist after 2 weeks of treatment, consult with a primary care provider.
- Side effects are uncommon. Consult with a health care provider if side effects are severe or do not resolve with a few days.
- Cimetidine may interact with certain prescription medications. Consult your health care provider if you are taking a blood thinner such as warfarin, an antifungal such as ketoconazole, antidepressants, anticonvulsants, theophylline, or amiodarone.

### Proton Pump Inhibitors

- Proton pump inhibitors (omeprazole) work by decreasing acid production in the stomach.
- Omeprazole is indicated for mild to moderate frequent heartburn that occurs 2 or more days a week. It is not intended for the relief of mild, occasional heartburn.
- Omeprazole should be taken with a glass of water every morning 30 minutes before breakfast for 14 days. Make sure that you take the full 14-day course of treatment.
- Do not take more than 1 tablet a day.
- Complete resolution of symptoms should be noted within 4 days of initiating treatment.
- If symptoms persist, or are not adequately relieved after 2 weeks of treatment, or if symptoms recur before 4 months, consult your primary care provider.
- Do not crush or chew tablet, or crush tablet in food or beverage as this may decrease omeprazole's effectiveness.
- Side effects are uncommon. Consult with a health care provider if side effects are severe or do not resolve with a few days.
- Ask a health care provider if you are also taking blood thinners such as warfarin, antifungals such as ketoconazole, or anti-anxiety medications such as diazepam, or digoxin.

⚠ You should consult your primary care provider if any of the following symptoms occur:

- Heartburn or dyspepsia for over 3 months
- Heartburn or dyspepsia while taking recommended dosages of nonprescription medications
- Heartburn or dyspepsia after 2 weeks of continuous treatment with a nonprescription medication
- Heartburn that awakens you during the night
- Difficulty or pain on swallowing foods
- Lightheadedness, sweating, dizziness accompanied by vomiting blood or black material or black tarry bowel movements
- Chest pain or shoulder, arm, neck pain, with shortness of breath
- Chronic hoarseness, cough, choking, or wheezing
- Unexplained weight loss
- Continuous nausea, vomiting, or diarrhea
- Severe stomach pain

provide a follow-up phone call to assess therapeutic outcomes. Patients should be asked to describe the change in frequency and severity of symptoms since they initiated therapy. They should be questioned regarding side effects, and any new symptoms that may have developed. If an inadequate response is noted, the individual should be reevaluated to determine if a different product is suitable, or if referral to a primary care provider is necessary. Side effects may be managed by adjusting dosage or switching to another product. Development of atypical or alarm symptoms (Table 14-2) should be referred to a primary care provider.

### Key Points for Heartburn and Dyspepsia

- Limit the self-treatment of heartburn and dyspepsia to mild or moderate symptoms including postprandial burning in the upper abdomen or centralized abdominal discomfort.
- Refer patients with atypical or alarm symptoms (Table 14-2) for further evaluation.
- Refer children younger than 12 years with heartburn or dyspepsia to their primary care provider.
- Counsel patients with heartburn on nondrug measures such as dietary and lifestyle modifications (see box Patient Education for Heartburn and Dyspepsia).
- Advise self-treating individuals of the advantages and disadvantages of various antacids and acid-reducing products so they can select a product that is best suited for them.
- Antacids provide temporary relief for mild and infrequent heartburn and dyspepsia. Dosages are product specific because of variability in antacid ingredients and concentrations.
- H<sub>2</sub>RAs are indicated for mild, infrequent heartburn or dyspepsia. They may be taken at the onset of symptoms or 1 hour prior to an event (meal or exercise) that causes symptoms.
- Combining an antacid with an H<sub>2</sub>RA provides immediate relief of heartburn and is also effective in preventing further symptoms.
- The nonprescription PPI omeprazole is indicated for the treatment of frequent heartburn (heartburn that occurs 2 or more days a week) and is not intended for immediate relief of infrequent symptoms.
- Advise individuals with self-treatable symptoms that if symptoms worsen or do not improve after 14 days of effective self-treatment, they should contact their primary care provider.

### References

1. Richter JE. Gastroesophageal reflux disease. In: Yamada T, Alpers DH, Kaplowitz N, et al., eds. *Textbook of Gastroenterology*. 4th ed. Philadelphia: Lippincott Williams & Williams; 2003:1196-224.
2. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol*. 2005;100:190-200.
3. Sonnenberg A, El-Serag HHP. Clinical epidemiology and natural history of gastroesophageal reflux disease. *Yale J Biol Med*. 1999; 72:81-92.
4. Peterson WL, Berardi RR, El-Serag H, et al. American Gastroenterological Association Consensus Development Panel. In: *Improving the Management of GERD: Evidence-based Therapeutic Strategies*. Bethesda, Md: AGA Press; 2002:1-21.
5. Rivicki DA., Wood M, Maton PN, et al. The impact of gastroesophageal reflux disease on health-related quality of life. *Am J Med*. 1998;104:252-8.
6. Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. *Gastroenterology*. 2002;122:1500-11.
7. Talley NJ, Holtmann G. Approach to the patient with dyspepsia and related functional gastrointestinal complaints. In Yamada T, Alpers DH, Kaplowitz N, et al, eds. *Textbook of Gastroenterology*. 4th ed. Philadelphia: Lippincott Williams & Williams; 2003:655-77.
8. Vakil N. Dyspepsia and GERD: breaking the rules. *Am J Gastroenterol*. 2005;100:1489-90.
9. Erstad BL. Dyspepsia: initial evaluation and treatment. *J Am Pharm Assoc*. 2002;42:460-8.
10. Procter & Gamble. Data on file. Cincinnati, Ohio; 2002.
11. Del Valle J, Chey WD, Scheiman JM. Acid-peptic disorders. In: Yamada T, Alpers DH, Kaplowitz N, et al., eds. *Textbook of Gastroenterology*. 4th ed. Philadelphia: Lippincott Williams & Williams; 2003:1321-76.
12. Berardi RR, Welage LS. Peptic ulcer disease. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. McGraw-Hill, Inc; 2005:629-48.
13. Oliveria SA, Christos PJ, Talley NJ, et al. Heartburn risk factors, knowledge, and prevention strategies: a population-based survey of individuals with heartburn. *Arch Intern Med*. 1999;159:1592-8.
14. Nilsson M, Johnsen R, Ye W, et al. Lifestyle related risk factors in the aetiology of gastroesophageal reflux. *Gut*. 2004;53:1730-5.
15. Nandurkar S, Locke III GR, Fett S, et al. Relationship between body mass index, diet, exercise and gastro-oesophageal reflux symptoms in a community. *Aliment Pharmacol Ther*. 2004;20:497-505.
16. Ferrioli E, Oliveira RB, Matsuda NM, et al. Aging, esophageal motility, and gastroesophageal reflux. *J Am Geriatr Soc*. 1998;46: 1534-7.
17. McColl KEL. Review article: Helicobacter pylori and gastro-oesophageal reflux disease—the European perspective. *Aliment Pharmacol Ther*. 2004;20(suppl 8):36-9.
18. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med*. 1999;11:825-31.
19. Spechler SJ. Barrett's esophagus. *N Engl J Med*. 2002;346:836-42.
20. Dent J, Brun J, Fendrick AM, et al. An evidence-based appraisal of reflux disease management—the Genval Workshop Report. *Gut*. 1999;44:S1-16.
21. Dent J. Management of reflux disease. *Gut*. 2002;50: 67-71.
22. Howden CW, Chey WD. Gastroesophageal reflux disease. *J Family Practice*. 2003;52:240-7.
23. Scott M, Gelhot AR. Gastroesophageal reflux disease: diagnosis and management. *Am Family Physician*. 1999; 59:1161-9.
24. Broussard CN, Richter JE. Treating gastro-esophageal reflux disease during pregnancy and lactation: what are the safest therapy options? *Drug Safety*. 1998;19:325-37.
25. Maton PN, Burton ME. Antacids revisited: a review of their clinical pharmacology and recommended therapeutic use. *Drugs*. 1999;57:855-70.
26. Hade JE, Spiro HM. Calcium and acid rebound: a reappraisal. *J Clin Gastroenterol*. 1992;15:37-44.

27. Food and Nutrition Information Center Dietary Reference Intakes (DRI) and Recommended Dietary Allowances (RDA) National Agricultural; Library, United States Department of Agriculture. Available at: <http://www.nal.usda.gov/fnic/etext/000105.html>. Accessed July 15, 2005.
28. Welage LS, Berardi RR. Drug interactions with antiulcer agents: considerations in the treatment of acid-peptic disease. *J Pharm Pract.* 1994;7:177-95.
29. Marsh TD. Nonprescription H<sub>2</sub>-receptor antagonists. *J Am Pharm Assoc.* 1997;37:552-6.
30. Bytzer P. H<sub>2</sub> receptor antagonists and prokinetics in dyspepsia: a critical review. *Gut.* 2002;50(suppl IV):iv58-62.
31. Rodgers PT, Brengel GR. Famotidine-associated mental status changes. *Pharmacotherapy.* 1998;18:404-7.
32. Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy.* 1998;18:84-112.
33. Berardi RR. Proton pump inhibitors: an effective, safe approach to GERD management. *Postgrad Med Special Report.* 2001;25-35.
34. Welage LS, Berardi RR. Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases. *J Am Pharm Assoc.* 2000;40:52-62.
35. Proctor & Gamble. Prilosec OTC package insert. Cincinnati, Ohio; September 2003.
36. Miner PP, Graves MR, Grender JM, et al. Comparison of gastric acid pH with omeprazole magnesium 20.6 mg (Prilosec OTC) qd, famotidine 10 mg bid (Pepcid AC) and famotidine 20 mg bid over 14-days of treatment. *Am J Gastroenterol.* 2004;99(suppl): S8. abstract.
37. Hatlebakk JG, Katz PO, Camacho-Lobato L, et al. Proton pump inhibitors: better acid suppression when taken before a meal than without a meal. *Aliment Pharmacol Ther.* 2000;14:1267-72.
38. Laheij RJF, Sturkenboom MCJM, Hassing R, et al. Risk of community acquired pneumonia and use of gastric acid suppressive drugs. *JAMA.* 2004;292:1955-60.
39. Gremse DA. Gastroesophageal reflux disease in children: an overview of pathophysiology, diagnosis, and treatment. *J Ped Gastroenterol Nutr.* 2002;35:S297-9.
40. Baron TH, Ramirez B, Richter JE. Gastrointestinal motility disorders during pregnancy. *Ann Intern Med.* 1993;118:366-75.
41. American Academy of Pediatrics, Committee on Drugs. The transfer of drugs and other chemicals into human milk. *Pediatrics.* 2001;108:776-89.
42. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation.* 6th ed. Baltimore: Williams & Wilkins; 2002.
43. Indigestion—dyspepsia. In: Robbers JE, Tyler VE, eds. *Tyler's Herbs of Choice: The Therapeutic Use of Phytomedicinals.* New York: Haworth Press; 1999:65-88.
44. Murray WJ. Herbal medications for gastrointestinal problems. In: Miller LG, Murray WJ, eds. *Herbal Medicinals. A Clinician's Guide.* New York: Haworth Press; 1998:79-93.
45. Blumenthal M, Goldberg A, Brinkman J. *Herbal Medicine: Expanded Commission E Monographs.* Austin, Tex: American Botanical Council, 2000.
46. Thompson CJ, Ernst E. Systematic review: herbal medicinal products for non-ulcer dyspepsia. *Aliment Pharmacol Ther.* 2002;16: 1689-99.
47. Madisch A, Holtmann G, Mayr G, et al. Treatment of functional dyspepsia with a herbal preparation. A double-blind, randomized, placebo-controlled, multicenter trial. *Digestion.* 2004;69:45-52.
48. Melzer J, Rosch J, Reichling R, et al. Meta-analysis: phytotherapy of functional dyspepsia with the herbal drug preparation STW 5 (Iberogast). *Aliment Pharmacol Ther.* 2004;20:1279-87.
49. Bundy R, Walker AF, Middleton RW, et al. Artichoke leaf extract reduces symptoms of irritable bowel syndrome and improves quality of life in otherwise healthy volunteers suffering from concomitant dyspepsia: a subset analysis. *J Altern Complement Med.* 2004;10:667-9.
50. Holtmann G, Adams B, Haag S, et al. Efficacy of artichoke leaf extract in the treatment of patients with functional dyspepsia: a six-week placebo-controlled, double-blind, multicentre trial. *Aliment Pharmacol Ther.* 2003;18:1099-105.
51. May B, Kohler S, Schneider B. Efficacy and tolerability of a fixed combination of peppermint oil and caraway oil in patients suffering from functional dyspepsia. *Aliment Pharmacol Ther.* 2000; 14:1671-7.