



FREQUENT HEARTBURN:

An Evidence-Based Approach to Cost-Effective Management

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LEARNING OBJECTIVES FOR THIS CONTINUING EDUCATION ARTICLE*

Upon completion of this program, participants will be able to:

1. Differentiate symptoms of frequent heartburn (FHB) from episodic heartburn.
2. Counsel patients appropriately on lifestyle changes and determine pharmacotherapeutic interventions for FHB.
3. Evaluate the cost-effectiveness of intermittent therapy for FHB.
4. Identify patients who need further evaluation of heartburn symptoms.

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Heartburn is a sensation of burning discomfort that generally starts in the retrosternal area and moves upward toward the throat.¹ It may be accompanied by a sour taste in the mouth ("acid indigestion"), and is caused by reflux of gastric contents into the esophagus. Heartburn may be self-limited, or it may be a symptom of gastroesophageal reflux disease (GERD), a condition characterized by frequent gastroesophageal (GE) symptoms and/or mucosal damage of the upper gastrointestinal (GI) tract.² It may occur on an episodic basis (eg, after eating a hot spicy meal), an intermittent basis (once monthly to once weekly), or a frequent basis (≥ 2 times per week). This article focuses on the diagnosis and treatment of frequent heartburn (FHB), which may overlap with the approach to GERD.

Although many patients self-treat their heartburn symptoms with over-the-counter (OTC) medications, they should consult their healthcare professional for guidance in this regard. Primary care nurse practitioners (NPs) need to be able to distinguish between episodic and frequent heartburn—each has different treatments and health implications—and then guide patients in choosing the best agent for them, one that is not only effective but is also cost-effective in "extinguishing" the problem.

PREVALENCE AND DEMOGRAPHICS

Heartburn afflicts nearly two thirds of US adults at some point in their lives.³ According to a large survey conducted 16 years ago by the Gallup Organization, 44% of adults suffer from heartburn at least once a month, 20% experience it at least once a week, and 7% have it every day.⁴ In 1997, a population-based study of 2200 residents of Olmstead County, Minnesota, came up with the same findings in terms of the proportion of US adults who experience heartburn and/or acid regurgitation on at least a weekly basis: 19.8%.⁵ In 2004, a cross-sectional survey of 496 employees at a Veterans Administration medical center revealed that heartburn occurring at least weekly was reported by 27% of blacks, 23% of whites, and 24% of members of other racial groups; thus the rate of heartburn was similar across racial lines.⁶ Heartburn does show a “preference” for gender, though: Among persons with FHB—that is heartburn occurring at least twice a week, 58% are female and 42% are male.^{7,8} The average FHB sufferer is between the ages of 45 and 50.⁷

In 2000, the American Gastroenterological Association (AGA) commissioned the Gallup Organization to conduct a poll of individuals with heartburn occurring on at least a weekly basis to find out more about the pattern of their symptoms.⁹ Among 1000 respondents, 79% reported having nocturnal heartburn—with 60% experiencing symptoms that were severe enough to disturb their sleep and compromise their work and quality of life (QoL) the next day.

ADVERSE CONSEQUENCES OF UNTREATED HEARTBURN

At the very least, FHB can restrict normal activities and have an adverse impact on QoL:

- One study showed that patients who had a history of heartburn for at least 6 months, when compared with a random sample of healthy US adults, fared significantly worse on all eight scales of the Medical Outcomes Study short-form 36 Health Survey: physical function, bodily pain, physical role limitations, vitality, general health perceptions, social function,

emotional role limitations, and mental health.¹⁰

- This same group of patients had lower scores on a test of emotional well-being than did patients with diabetes or hypertension.¹⁰
- The 2000 Gallup survey showed that, among 1000 respondents with heartburn, the following proportions reported moderate to severe impairment in their:
 - ability to eat/drink what they want: 46%
 - ability to get a good night's sleep: 40%
 - ability to sleep when they want to: 36%
 - ability to eat/drink when they want: 36%
 - mood and general well-being: 35%
 - day-to-day functioning: 25%
 - social activities: 23%
 - functioning at work: 23%
 - spouse's sleep: 18%.⁹

If FHB is a manifestation of full-blown GERD, then patients are at risk for the sequelae of prolonged esophageal injury.¹¹

RISK FACTORS

The aforementioned study of people in Olmstead County, Minnesota, revealed that obesity and a positive family history were the main risk factors for frequent reflux symptoms.¹² Other risk factors cited in this study included a past history of smoking, consuming seven or more drinks per week, and a higher psychosomatic symptom checklist score. The following diet/lifestyle choices and behaviors are also associated with an increased risk of heartburn:

- exercising after eating;
- lying down shortly after meals;
- bending over or straining soon after meals;
- drinking several alcoholic, carbonated, and/or caffeinated beverages daily;
- eating fried, fatty, acidic, or spicy foods; and
- eating chocolate or spearmint/peppermint candy.

Genes may play a major role in determining heartburn risk. A study of more than 8000 twin pairs aged 55 years or older showed an increased concordance

for reflux in monozygotic pairs, as compared with dizygotic pairs, suggesting genetic, rather than environmental, effects.¹³ The investigators stated that heritability accounted for 31% (23%-39%) of the tendency to develop reflux disease in this population. Finally, estrogens may exacerbate the risk: A population-based, cross-sectional, case-control study revealed that the association between obesity and reflux symptoms was significantly stronger among premenopausal women than among postmenopausal women, and that the use of hormone replacement therapy (HRT) in the postmenopausal group significantly increased the strength of the association.¹⁴

PHYSIOLOGY AND PATHOPHYSIOLOGY

In normal, healthy individuals, billions of tiny pumps in the stomach manufacture hydrochloric acid, which breaks down food. The lower esophageal sphincter (LES) in these individuals keeps the acidic gastric contents from rising back into the esophagus. In some individuals, however, the LES temporarily relaxes, allowing reflux of the acidic gastric contents into the esophagus, which causes the sensation of heartburn.

Transient LES relaxation may be caused by eating certain foods or beverages or by pressure on the stomach. Increased abdominal pressure may be caused by frequent bending and lifting, vigorous exercise, or pregnancy.¹⁵⁻¹⁷ Conditions such as hiatal hernia, gastroparesis, defective esophageal acid clearance, impaired mucosal defense, and delayed gastric emptying can also predispose individuals to heartburn and GERD. In addition, certain medications, including calcium antagonists (eg, amlodipine [Norvasc®], diltiazem [Cardizem®], nifedipine [Adalat®, Procardia®], verapamil [Calan, Isoptin]), theophylline, HRT, and muscle relaxants, can reduce LES pressure.¹⁷

Not all reflux is pathologic: Normal persons may experience up to 50 episodes of reflux per day, with acid present in the esophagus for up to 4% of a given 24-hour period.¹⁸ In healthy persons, gravity and peristalsis clear the refluxed material, and bicarbonate ions in the saliva and secretions from submucosal glands in the esophagus neutralize the acid that remains

in the esophagus. Heartburn and, in many cases, GERD develop when these protective mechanisms and/or mucosal defenses are impaired. That is, peristalsis may be ineffective, or salivary or esophageal secretions may be reduced, leading to inadequate clearance or neutralization of refluxate.

It is important to note that not all patients with heartburn or even GERD have esophageal damage: 53% to 71% of heartburn sufferers have endoscopically normal esophageal mucosa.¹⁹ This condition is sometimes called nonerosive reflux disease, or NERD.²⁰ Some patients with NERD experience heartburn symptoms despite having normal levels of esophageal acid exposure as assessed by 24-hour pH study (see section on “Ambulatory Esophageal pH Monitoring”); these patients, may, in fact, have esophageal hypersensitivity to physiologic degrees of acid reflux. Other patients with NERD have abnormal acid exposure but have not developed overt mucosal injury.

DIAGNOSIS HISTORY

When patients present with typical symptoms of heartburn and no complications, the diagnosis is usually straightforward and can be made from the medical history.¹¹ Most patients with heartburn describe the following symptoms:

- a retrosternal burning sensation that radiates toward the throat;
- a sensation that food is “coming back up”;
- a sour or bitter taste in the throat and/or mouth; and/or
- pain that increases when bending over, lying down, exercising, or lifting heavy objects.²¹

Symptom Duration and Severity—

Symptoms may last a few minutes to a few hours. Their severity depends on the reason for LES relaxation, the amount of acid entering the esophagus, and the degree to which the patient's saliva is able to neutralize the acid.²¹ Of note, patients without macroscopic mucosal lesions do not necessarily have milder symptoms than those with more severe esophagitis.²²

Symptom Frequency: Episodic Versus Frequent Heartburn—

NPs will need

to distinguish between episodic or intermittent heartburn (1 episode/week) and FHB (≥ 2 episodes per week), because the treatment approaches differ. In the subset of patients with FHB, they may need to determine whether other pathophysiologic processes are going on, and whether damage to esophageal tissue has occurred.

Differential Diagnosis—In taking the history, NPs need to distinguish heartburn/GERD from entities such as gastritis, infectious esophagitis (typically caused by *Candida species*), peptic ulcer disease (typically caused by *Helicobacter pylori* infection), non-ulcer dyspepsia, biliary tract disease, coronary artery disease, and esophageal motor disorders.²³ Another common cause of heartburn-like pain is pill esophagitis, which occurs when a pill is swallowed into the esophagus but gets “stuck” on the esophagus wall and burns the lining of the esophagus, causing chest pain and esophageal ulcers. Medications associated with pill esophagitis include non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin[®]), naproxen sodium (Aleve[®]), aspirin, and celecoxib (Celebrex[®]), and bisphosphonates such as alendronate (Fosamax[®]) and risedronate (Actonel[®]). Pill esophagitis can be avoided if patients swallow pills according to the package directions.

DIAGNOSTIC TESTING

It is not necessary to perform a diagnostic evaluation in all patients who complain of heartburn, particularly in those with infrequent symptoms.²² Even with GERD, symptom analysis offers reasonable sensitivity and specificity, and most typical cases can be diagnosed on the basis of symptoms alone. Diagnostic testing is recommended in the following cases:

- the history is atypical and the diagnosis is unclear;
- symptoms are long-term, frequent, and/or refractory to treatment;
- continuous long-term therapy is likely needed;
- complications arise (eg, adenocarcinoma of the esophagus, Barrett's esophagus, esophageal bleeding and ulcers, esophagitis, strictures, ulcerations);^{11,23,24} and/or

- “alarm” symptoms (anemia, bleeding, chest pain, dysphagia [difficulty swallowing], hematemesis, involuntary weight loss, melena, odynophagia [severe pain on swallowing], persistent vomiting) are present.²⁵

Endoscopy—Routine endoscopy is not recommended for patients with heartburn and regurgitation only;²⁵ most patients who have heartburn more than twice per week have no endoscopic esophageal mucosal damage.²⁶ However, patients who have symptoms for 7 to 10 years should undergo screening endoscopy for Barrett's esophagus. Endoscopy is also recommended in patients who are experiencing alarm symptoms and/or extra-esophageal manifestations of GERD (eg, asthma; chronic bronchitis, cough, or sinusitis; noncardiac chest pain; excessive throat clearing; hoarseness; otalgia; pharyngitis; stridor).²⁷ This test is particularly useful for diagnosing GERD complications, although it is neither highly sensitive nor highly specific for GERD itself.^{11,23}

Ambulatory Esophageal pH Monitoring—

According to guidelines from the American College of Gastroenterology (ACG), ambulatory esophageal pH monitoring helps to confirm GE reflux in patients with persistent symptoms without evidence of mucosal damage.²⁴ A pH monitor is placed in the esophagus above the LES for 24 hours. While the monitor is in place, patients keep a diary of symptom occurrence. This test is highly sensitive and specific, but it is not widely available and it is invasive, time-consuming, and expensive. The AGA recommends pH recording for patients with equivocal or abnormal endoscopy results and persistent reflux symptoms that are refractory to proton pump inhibitor (PPI) therapy.²⁸ It is also beneficial in patients with atypical or extra-esophageal symptoms.

Barium X-rays—An upper GI series is taken after patients drink a barium solution. Only one third of patients with GERD, and an even smaller minority of patients with documented abnormal pH, have radiologic signs of esophagitis.¹¹ Therefore, this test is considered to be of little practical value in patients with FHB or GERD, although it may be helpful in the detection of esophageal strictures or hiatal hernias in patients

with dysphagia. It may also be helpful in identifying pathologies unrelated to GERD, including diverticula, swallowing dysfunction, and motility dysfunction.

MANAGEMENT

Goals of heartburn management are to reduce inappropriate LES relaxation, to reduce production of gastric acid, to neutralize gastric acid, and, in some cases, to promote gastric emptying. A broader goal is to prevent complications such as esophageal stricture and Barrett's esophagus. These goals may be accomplished to some extent by lifestyle modifications, although hard evidence is lacking that these interventions work.^{25,29} If patients have difficulty instituting these changes, then they may try one or more of three classes of OTC medications. The efficacy of these agents has been supported by scientific research. Of note, one of these classes has been shown to be particularly *cost effective* for patients with FHB. Patient education, counseling, and encouragement should be ongoing throughout the course of therapy. Patients whose symptoms or treatment refractoriness suggests that their condition is more serious than FHB may need to undergo a full round of diagnostic tests and be referred to a gastroenterologist or other specialist. Table 1 offers NPs practical tips for the general management of heartburn.

LIFESTYLE MODIFICATIONS

A variety of lifestyle alterations can, at least in theory, mitigate, alleviate, or even prevent heartburn (Table 2). Despite the lack of extensive evidence supporting the effectiveness of these changes as the sole approach, they will likely enhance the effectiveness of pharmacotherapy. In fact, the ACG recommends that lifestyle modification be initiated and continued throughout the course of therapy.²⁴ The college also asserts that, despite the lack of data, it is reasonable to educate patients about factors that may precipitate reflux. Because many patients will not be able to institute or maintain these lifestyle changes, periodic drug therapy for symptom relief is in order.

OTC MEDICATIONS

Patients with mild and/or intermittent heartburn typically seek relief on their

TABLE 1. MANAGING HEARTBURN IN "THE REAL WORLD": EASY-TO-DIGEST PRACTICE TIPS

- Encourage patients who present with episodic, intermittent, or frequent heartburn to institute lifestyle modifications to reduce or eliminate heartburn triggers.
- Recommend use of an antacid or OTC H2RA in patients whose episodic or intermittent heartburn persists despite lifestyle changes.
- Recommend a PPI (either OTC or prescription) in patients with FHB.
- Make sure that PPI users are using the product correctly.
- Counsel patients about the basic mechanics of reflux, the importance of lifestyle adjustments, the reason for taking the PPI, and the dosing recommendations for the PPI.
- Instruct patients with FHB who are using the OTC PPI to take omeprazole magnesium once daily, 30-60 minutes before the first meal of the day, for 14 days.
- Ask patients whose symptoms persist beyond 2 weeks to contact you for further instructions.

OTC = over-the-counter; H2RA = histamine H₂-receptor antagonist; PPI = proton pump inhibitor; FHB = frequent heartburn.

TABLE 2. LIFESTYLE MODIFICATIONS TO EASE HEARTBURN^{11,24,30}

Dietary Recommendations

Avoid or limit ingestion of caffeinated products, alcohol, carbonated soft drinks, chocolate, tomato-based products, spearmint, peppermint, spicy foods, fatty or greasy foods, onions, garlic, and citrus fruits and juices.

Avoid eating before bedtime or 3 to 4 hours before lying down.

Avoid eating large-volume meals.

Lose weight if necessary.

Physical Recommendations

Elevate the head of the bed by 4 to 8 inches (in patients with nocturnal symptoms).

Avoid wearing clothing that is tight around the waist.

Avoid excessive bending over (eg, gardening) or lifting, especially after meals.

Miscellaneous Recommendations

Review medications that may potentiate heartburn symptoms, including calcium antagonists, bisphosphonates, and theophylline.

Stop smoking.

Chew gum or suck on hard candy or lozenges to stimulate saliva production.

Eat several small meals instead of three large meals throughout the day.

own from one of the many medications available OTC (Table 3). According to one data set, more than 86% of FHB sufferers report using OTC medications.³³ Before the US Food and Drug Administration (FDA) approved an OTC PPI (Prilosec OTC™) specifically for the treatment of FHB symptoms,

- 80% of patients with FHB used antacids;
- 58% had spoken to their healthcare provider about heartburn;
- 55% took medications for heartburn prevention;

- 47% self-medicated for more than 2 days in a row;
- 34% had used a prescription medication to manage heartburn; and
- 4% used OTC histamine H₂-receptor antagonists (H2RAs).³⁴

Of interest, approximately 25% of patients with FHB use 70% of the OTC heartburn products.

OTC medications are divided into two main groups: antacids, which neutralize gastric acid,^{31,32} and acid suppressants, which reduce gastric acid secretion and include H2RAs and PPIs.

TABLE 3. OTC HEARTBURN MEDICATIONS: FHB INDICATION, DURATION AND MECHANISM OF ACTION, ADVERSE EFFECTS

Medication Class	Trade Name(s)	Indicated Specifically for FHB	Duration of Action (one dose)	Mechanism of Action	Potential Adverse Effects ¹¹
Antacids	Tums® Rolaids® Maalox® Mylanta® Gaviscon® and others	No	1-2 hours	Rapidly elevate esophageal pH and neutralize esophageal acid for up to 90 minutes after dosing ^{31,32}	<i>Aluminum salts:</i> constipation, accumulation in patients with renal failure, hypophosphatemia, osteomalacia (rare); <i>calcium salts:</i> constipation, milk-alkali syndrome with high doses, rebound hyperacidity (dose-dependent); <i>magnesium salts:</i> diarrhea, accumulation in patients with renal failure; sodium bicarbonate: milk-alkali syndrome with high doses (these agents should be avoided in sodium-restricted patients); <i>magnesium/aluminum combinations:</i> minor changes in bowel function
H2RAs	Tagamet HB 200® Zantac 75® Pepcid® AC Axid AR®	No	Up to 12 hours	Inhibit gastric acid secretion	Diarrhea, headache, constipation; gynecomastia and low sperm count (in male users of high-dose cimetidine)
PPI	Prilosec OTC™	Yes	Up to 24 hours*	Shuts down the active pumps that make gastric acid	Diarrhea, headache, nausea, abdominal pain

*As part of a 14-day course of therapy.

OTC = over-the-counter; FHB = frequent heartburn; H2RA = histamine H₂-receptor antagonist; PPI = proton pump inhibitor.

Antacids—Many patients with heartburn self-treat with OTC antacids such as Mylanta®, Maalox®, Rolaids®, Tums®, or Gaviscon®, the lattermost of which also contains alginic acid. Alginic acid reacts with saliva to produce a foam barrier on top of the stomach that buffers the refluxed material. Antacids are composed of different combinations of three salts (magnesium, calcium, and aluminum) with hydroxide or bicarbonate ions. They are effective for quick relief of *episodic* heartburn. For maximum relief, antacids should be used as needed, and should be taken immediately after meals if symptoms occur.¹³ Many clinical studies conducted in the 1970s, 1980s, and 1990s have shown that antacids are more effective than placebo in relieving heartburn. However, in addition to having side effects in some patients (eg, diarrhea, abdominal discomfort, constipation), antacids can interact adversely with a host of other drugs by preventing or limiting their absorption. For example, a combination OTC antacid containing aluminum hydroxide, magnesium hydroxide, calcium carbonate, and simethicone may interact adversely with the

following medications:³⁵

- allopurinol (Zyloprim)
- aspirin, salicylates
- benzodiazepines (Valium®, Xanax®)
- anticoagulants (Coumadin®)
- chloroquine (Aralen®)
- corticosteroids (prednisone, Deltasone®, Medrol)
- diabetes medicines (Diabinese®, Micronase®, Glucotrol®)
- digoxin (Lanoxin®)
- iron (Feosol®, ferrous sulfate, Nu-Iron®)
- isoniazid (INH)
- nitrofurantoin (Macrochantin®)
- penicillamine (Depen®, Cuprimine®)
- phenothiazines (Thorazine®, Stelazine®, Compazine®)
- phenytoin type drugs (Dilantin®, Mesantoin®, Peganone®, Cerebyx®)
- quinidine (Quinidex®, Quinaglute®)
- tetracycline
- thyroid hormone (Synthroid®, levothyroxine)
- ticlopidine (Ticlid®)
- ulcer medications (Tagamet®, Zantac®, Pepcid®, Axid®)

Antacids are less appropriate for patients with FHB: Their short duration of action means that FHB sufferers would need to take multiple doses per day, which would likely lead to side effects even if patients did adhere to the regimen.¹¹ Another drawback is their inadequacy as heartburn prophylaxis.

Histamine H₂-Receptor Antagonists—

Three types of receptors trigger production of hydrochloric acid in the stomach. H2RAs block *one* of these receptors—the histamine H₂ receptor—on the gastric parietal cell, thereby impeding the formation of hydrochloric acid. H2RAs that are available OTC include cimetidine (Tagamet HB 200®), ranitidine (Zantac 75®), famotidine (Pepcid® AC), and nizatidine (Axid AR®). Dosages of these OTC versions are one half of the standard lowest prescription dosage. (OTC famotidine was recently approved at the original prescription dosage.) Although these four agents differ somewhat in potency, they can be used interchangeably according to the ACG.²⁴ They are particularly useful in patients with episodic heartburn

who take the medication before an activity that is likely to produce reflux symptoms (eg, eating a heavy or spicy meal).

Comparisons between antacids and the H2RAs are limited, but it has been suggested that the former provide a more rapid response (onset of action, 30 minutes vs up to 90 minutes),³⁶ whereas the latter are generally more effective and have a much longer duration of action.^{24,36} Efficacy trials have shown that the H2RAs are superior to placebo for the relief of episodic heartburn.³⁷⁻⁴⁰ Placebo-controlled studies have also demonstrated the efficacy of these agents in preventing heartburn.^{41,42}

Side effects of H2RAs include diarrhea, headache, and constipation.¹¹ In males, high-dose cimetidine may cause gynecomastia and/or a decreased sperm count.⁴³ Drug interactions occur more frequently with cimetidine than with the other H2RAs because cimetidine impedes hepatic metabolism of these other drugs.¹¹ This list of drugs includes warfarin, theophylline, phenytoin, diazepam, propranolol, calcium channel blockers, metronidazole, lidocaine, certain tricyclic antidepressants (TCAs), and other drugs metabolized by the hepatic cytochrome P (CYP)-450 isoenzyme system.¹¹ In addition, any H2RA may decrease the bioavailability of drugs whose effects depend on an acidic gastric pH.⁴⁴

Proton Pump Inhibitor—Like H2RAs, PPIs suppress gastric acid production. However, they do so at the source, by blocking parietal cell hydrogen/potassium ion adenosine triphosphatase, known as the *proton pump*. This is the final common pathway in the process of gastric acid secretion. Only one PPI, omeprazole, is available over the counter: Prilosec OTC™. This medication contains the equivalent of prescription-strength omeprazole, although it is formulated as a magnesium salt tablet. Bioavailability of omeprazole is similar in both formulations.⁴⁵ Omeprazole magnesium is the only OTC medication specifically indicated for FHB. According to the package labeling, this medication is to be taken once daily for 14 days.

The efficacy of omeprazole 20 mg was demonstrated in a study comparing it with omeprazole 10 mg and placebo

in 355 patients with symptomatic GERD without esophagitis.⁴⁶ On days 7 and 27, respectively, daily proportions of patients who were heartburn-free were higher in the 20-mg omeprazole group (62% and 74%) than in the 10-mg omeprazole group (41% and 49%) or the placebo group (14% and 23%).

Clinical trials and post-marketing surveillance of the prescription formulation of omeprazole have demonstrated the excellent safety profile of this agent.⁴⁷ No new safety issues have emerged with the OTC formulation. PPI-related side effects include diarrhea, headache, nausea, and abdominal pain, and occur in fewer than 10% of users.⁴⁴ As an inhibitor of CYP-2C19, omeprazole may increase serum levels of other drugs metabolized by 2C19, including warfarin (Coumadin®), phenytoin (Dilantin®), and diazepam (Valium®), and it may alter absorption of medications such as itraconazole (Sporanox®) and digoxin (Lanoxin®). However, many patients can use PPIs safely with oral contraceptives and with medications for hypertension, arthritis, and angina.^{43,48,49}

PRESCRIPTION MEDICATIONS

Most patients with typical symptoms of GERD do not have esophagitis;²³ as mentioned earlier, many clinicians recognize this as a separate entity called nonerosive reflux disease or NERD. NPs must ascertain whether FHB is self-limited or a presenting symptom of GERD so that treatment can focus not only on relieving heartburn, but also on healing the mucosal damage to the esophagus and preventing further damage. Along with long-standing FHB, other signs and symptoms of GERD include regurgitation of sour-tasting material into the throat or mouth and frequent belching. Various prescription medications are FDA approved for GERD treatment.

H2RAs—When given in standard dosages used for peptic ulcer disease, H2RAs can alleviate mild to moderate symptoms of GERD.²⁴ In fact, before the introduction of PPIs, these agents were the treatment of choice for reflux and erosive esophagitis.²⁴ However, they are not as effective in either domain as the prescription-strength PPIs.^{24,50}

PPIs—In addition to omeprazole

(Prilosec®), this drug class includes lansoprazole (Prevacid®), pantoprazole (Protonix®), esomeprazole (Nexium®), and rabeprazole (Aciphex®). PPIs are highly effective in controlling symptoms and healing esophagitis, and are used as maintenance therapy to prevent GERD flare-ups.³⁰ In general, standard-dose PPIs will relieve symptoms and heal esophagitis in 85% to 90% of patients.⁵⁰ Patients with GERD are advised to take the PPI immediately before breakfast.⁵⁰

Prokinetic Agents—Instead of neutralizing stomach acid, prokinetic agents increase LES pressure, enhance gastric emptying, and improve peristalsis. Older prokinetics such as bethanechol (Urecholine®) and metoclopramide (Reglan®) are rarely used because of their side-effect profiles.²³ Although cisapride (Propulsid®) has been found to be equivalent to standard-dose H2RAs in relieving reflux symptoms and healing esophagitis, this medication has been associated with cardiac arrhythmias and is available on a limited basis. The manufacturer recommends that a baseline electrocardiogram be performed before cisapride therapy is started.⁵¹ Concurrent use of cisapride with agents that increase cisapride blood levels (eg, macrolides, nefazodone, antifungals, certain AIDS medications) or that predispose patients to fatal arrhythmias (eg, class IA or class III antiarrhythmics; certain TCAs, tetracyclic antidepressants, or antipsychotics) is contraindicated.⁵¹

Comparative Trials—Many studies and two meta-analyses involving prescription-strength medications have demonstrated that PPIs are more effective than other drug classes or placebo in relieving heartburn in patients with GERD or NERD.

■ A randomized, double-blind trial conducted on 310 patients who received omeprazole 20 mg daily or cimetidine 400 mg 4 times daily revealed that after 4 weeks of treatment, a significantly larger proportion of omeprazole recipients than cimetidine recipients were asymptomatic (46% vs 22%; $P < 0.001$).⁵² In addition, diary cards completed during the first 2 weeks showed that omeprazole users experienced fewer daytime and night-time symptoms.

- A meta-analysis of 43 studies that enrolled 7635 patients with GERD showed that PPIs, relative to H2RAs, provided faster and more complete relief of heartburn.⁵³ A much larger proportion of PPI recipients than H2RA recipients were rendered heartburn free during the treatment period (77.4% vs 47.6%).
- A randomized, double-blind, multicenter trial was conducted on 677 patients with GERD (heartburn and normal endoscopy findings or mild erosive changes) who received omeprazole 10 to 20 mg daily or ranitidine 150 mg twice daily for 2 weeks.⁵⁴ Participants were followed for 12 months, during which time they could reinstitute therapy for heartburn recurrences. Omeprazole 20 mg daily, as compared with the H2RA, provided faster relief of heartburn in patients with erosive or nonerosive disease. Intermittent treatment was effective in managing symptoms in half of the patients with uncomplicated GERD.
- The Dutch Reflux Study Group evaluated acute and long-term treatment of 446 patients with mild GERD with standard-dose omeprazole or high-dose ranitidine, and found that the proportions of patients who were asymptomatic after 4 and 8 weeks of treatment were 61% and 74% for omeprazole recipients, respectively, and 31% and 50% for ranitidine recipients, respectively.⁵⁵
- Another Dutch team performed a meta-analysis of 23 trials in which nearly 9000 patients underwent empiric treatment for heartburn associated with GERD or treatment for NERD (these patients had undergone endoscopy).⁵⁶ PPIs were superior to both H2RAs and prokinetic agents in achieving heartburn remission. H2RAs were also effective in promoting symptom remission, but the prokinetics were less helpful.

COST-EFFECTIVENESS DATA

Several studies have focused on the cost-effectiveness of various strategies for treating heartburn, which is usually in the setting of GERD:

- In 1996, when H2RAs and PPIs were available by prescription only, a review

of published economic studies of GERD treatments showed that PPIs were more cost-effective than H2RAs because of their fast healing of esophagitis, early relief of symptoms, and prevention of recurrent esophagitis and development of complications.⁵⁷

- In 2000, researchers at Stanford University sought to determine the cost-effectiveness of various first-line empiric therapies for patients with typical symptoms of GERD.⁵⁸ The six treatment arms included (1) lifestyle therapy, including antacids; (2) H2RA therapy, with endoscopy performed in nonresponders; (3) step-up therapy with H2RAs followed by PPIs in nonresponders; (4) step-down therapy with a PPI followed by an H2RA as needed; (5) PPI on-demand therapy (8 weeks of treatment for symptomatic recurrence, with no more than 3 treatments/year); and (6) PPI continuous therapy. Results showed that the PPI on-demand therapy was the most cost-effective approach.
- Another 2000 study entailed a cost-utility analysis of four alternatives to treat uncomplicated heartburn: empiric PPI with dose escalation for nonresponders, empiric H2RA with PPI for nonresponders, esophagogastroduodenoscopy (EGD) followed by treatment, and upper GI series followed by treatment.⁵⁹ Empiric treatment appeared to be the optimal initial management strategy for patients with heartburn, with a PPI projected to provide the greatest quality-adjusted survival and an H2RA projected to be less costly. In other words, the choice of a PPI versus an H2RA should depend on the impact of heartburn on a patient's QoL.
- In 2002, investigators at the Cedars-Sinai Health System in Los Angeles used decision analysis to assess the clinical and economic impact of two competing management strategies for GERD.⁶⁰ They studied the "traditional" strategy, which incorporates a step-up approach (sequential therapeutic trials with more intensive therapy), followed by sequential invasive diagnostic testing in nonresponders; and the "PPI test" strategy,

which entails a 7-day course of high-dose omeprazole followed by a step-down approach (sequential therapeutic trials with less intensive therapy), with sequential invasive diagnostic testing in nonresponders. Over 1 year, the PPI test strategy, as compared with the traditional strategy, resulted in greater symptom relief and improved QoL, as well as more appropriate utilization of invasive diagnostic testing.

- Because many patients with mild GERD and infrequent symptom relapses use a PPI only when symptoms demand, one researcher looked at the results of four randomized, controlled studies, and found that the use of on-demand or intermittent PPIs reduced symptoms, improved QoL, and was cost-effective.⁶¹
- A summary of findings to date states that, "in terms of economics, the management strategies that appear to result in the most cost-efficient gains in health appear to be PPI-based step-down or 'on-demand' strategies" [versus H2RAs and prokinetics].⁶²

Table 4 lists the cost of a 2-week course of various OTC H2RAs and the OTC PPI. These prices are approximations, and may not reflect the cost of each medication in every part of the country. The concept of cost-effectiveness represents not only the actual cost of the medication, but also the amount of time that patients are rendered symptom free after the course of therapy such that further medication is not needed, at least in the short run.

REFERRAL

NPs can diagnose and manage most cases of FHB, and even GERD, especially when no other symptoms are present and the problem can be controlled with medication. NPs should refer patients with alarm symptoms, GERD complications, a prolonged history of GERD symptoms, an uncertain diagnosis, or treatment-refractory symptoms to a gastroenterologist.⁶³ Patients with extraesophageal symptoms should be advised to see an otorhinolaryngologist, pulmonologist, or other specialist. Finally, a surgical consult may be indicated in patients with:

TABLE 4. OTC H2RAs AND PPI: DOSAGE AND COST

Medication	Dosage	Cost (\$)*
H2RAs		
Cimetidine (generic)	200 mg 1 or 2 times daily PRN	4.29
Tagamet HB 200®	200 mg 1 or 2 times daily PRN	8.59
Ranitidine (generic)	75 mg 1 or 2 times daily PRN	4.25
Zantac 75®	75 mg 1 or 2 times daily PRN	8.49
Famotidine (generic)	10 mg 1 or 2 times daily PRN	6.99
Pepcid® AC	10 mg 1 or 2 times daily PRN	7.97
Axid AR®	75 mg 1 or 2 times daily PRN	8.39
OTC PPI		
Prilosec OTC™ (omeprazole magnesium)	20.6 mg once daily	9.99
Prescription PPIs		
Omeprazole (Prilosec®)	20 mg daily	59.26
Lansoprazole (Prevacid®)	30 mg daily	71.96
Rabeprazole (Aciphex®)	20 mg daily	69.48
Pantoprazole (Protonix®)	40 mg daily	57.02
Esomeprazole (Nexium®)	40 mg daily	72.05

*Cost for 2 weeks' treatment with the highest dosage (discount pharmacy in New Jersey). The prescription PPIs are generally given for 4 to 8 weeks, depending on the indication. OTC = over-the-counter; H2RA = Histamine H₂-receptor antagonist; PRN = pro re nata (as needed); PPI = proton pump inhibitor.

- documented GERD symptoms that are responsive to medical therapy but who do not wish to continue long-term medical therapy;
- documented GERD symptoms that are unresponsive to medical therapy because of patient noncompliance, inability to afford medications, or relapse;
- complications of GERD such as Barrett's esophagus or grade III or IV esophagitis;
- peptic stricture;
- recurrent symptomatic aspiration;
- medical complications attributable to a large hiatal hernia such as bleeding or dysphagia;
- atypical symptoms such as asthma or chest pain with abnormal 24-hour pH monitoring study results; or
- severe symptoms that they would prefer to have treated surgically rather than medically.^{11,25}

CONCLUSION

Patients suffering from heartburn have a number of OTC treatments from which to choose. For those with episodic heartburn, antacids and H2RAs provide fast and reliable relief. For those with frequent episodes of heartburn, however, omeprazole magnesium, taken once daily for 14 days, is preferred. The recently intro-

duced OTC PPI does not act as quickly as antacids and H2RAs, but it is more effective and longer-lasting than the other two medication classes, and it will likely prove cost-effective in the long run because it prevents heartburn from occurring.

Although all of these medications are available OTC, it is optimal for NPs to guide patients in their use, and to make sure that patients do not have a more serious underlying condition or complications that warrant further attention. Finally, NPs should counsel patients in terms of lifestyle modifications that will mitigate, if not eliminate, FHB symptoms.

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DISCLOSURE STATEMENTS

Mary Knudtson has current consulting agreements with Procter & Gamble Pharmaceuticals, Eli Lilly and Company, and GlaxoSmithKline, and serves on the speaker

bureau for Procter & Gamble Pharmaceuticals and Abbott Laboratories, Inc. Rick H. Davis, Jr., serves on the speaker bureau for Procter & Gamble Pharmaceuticals and Astra Zeneca Pharmaceuticals.

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*Full references corresponding to the numbers in the text are available at www.npcentral.net/ce/heartburn