

# Expert Views<sup>®</sup>

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## optimizing the treatment of frequent heartburn in the primary care setting

Heartburn is a very prevalent condition with approximately 44% of all Americans experiencing heartburn at least once a month,<sup>1</sup> and nearly 70 million Americans are believed to experience frequent heartburn, which is defined as heartburn that occurs two or more days a week.<sup>2,3</sup> For the millions of frequent heartburn sufferers, over-the-counter (OTC) proton pump inhibitors (PPIs) may be appropriate therapies when antacids or histamine<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs) are not providing the needed efficacy. PPIs offer the potential for effective patient-directed management and substantial symptom improvement when used appropriately.

This publication features the insights of three practicing clinicians, Philip O. Katz, MD, Leonard Fromer, MD and Catherine Cone, PharmD, BCPS, PhC. Dr. Katz is Chairman of the Division of Gastroenterology at Albert Einstein Medical Center in Philadelphia, Pennsylvania. In addition to maintaining a clinical practice, he holds active teaching and editorial positions, and is recognized as a national authority on esophageal disease. Dr. Katz is the Past President of the American College of Gastroenterology (ACG, 2009-2010) and is a member of the American Gastroenterological Association (AGA). Dr. Cone is a Clinician Educator Assistant Professor at the University of New Mexico College of Pharmacy in Albuquerque, New Mexico. She completed a residency in pharmacy practice in 1998 and is a board certified pharmacotherapy specialist. Dr. Cone currently practices in a disease state management and an urgent care clinic. Dr. Fromer is the Executive Medical Director of the Group Practice Forum in Los Angeles, California and Assistant Clinical Professor in the Department of Family Medicine at the University of California at Los Angeles. He has been in private practice in Santa Monica, California, with Prairie Medical Group for 28 years. He lectures extensively on the topics of health-system reform, the patient-centered medical home and the accountable care organization.

## otc proton pump inhibitors for frequent heartburn

Heartburn, a burning sensation in the retrosternal area, occurs when acidic gastric contents flow backward from the stomach into the esophagus<sup>4-6</sup> irritating the delicate lining of the esophagus.<sup>7</sup> Heartburn symptoms can vary considerably, from occasional mild discomfort triggered by diet and lifestyle factors, to severe discomfort that regularly interferes with activities and impairs patients' quality of life.<sup>5,8</sup> Further, heartburn symptoms can be episodic or frequent in nature. Episodic heartburn, typically occurring one day or less per week, is generally mild in severity and is often triggered by dietary and lifestyle factors. In contrast, frequent heartburn, occurring two or more days per week, is considered bothersome by most patients.<sup>5</sup>

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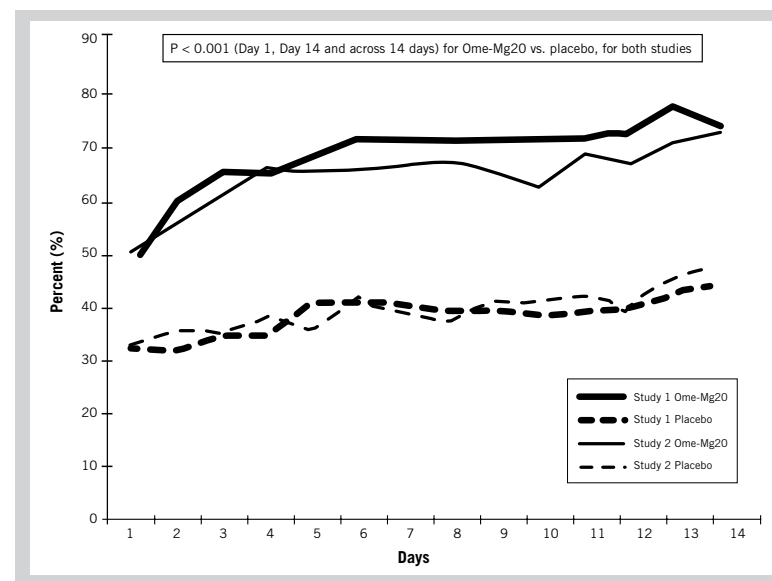
Evidence supports the efficacy of PPIs in treating frequent heartburn.<sup>9,10</sup> The switch of omeprazole from prescription-only status in 2003 (Prilosec OTC®, as omeprazole magnesium, AstraZeneca)<sup>11</sup> marked the first availability of OTC PPIs. Prilosec OTC contains the medicine equivalent of 20 mg of the prescription Prilosec (omeprazole) formulation.<sup>12,13</sup> OTC versions of lansoprazole (Prevacid® 24 HR, Novartis) and omeprazole/sodium bicarbonate (Zegerid™ OTC, MSD Consumer Care, Inc.) subsequently became available in 2009.<sup>11</sup>

OTC doses of PPIs have been found to achieve efficacy in patients with frequent heartburn within the first one to four days of a 14-day treatment regimen, with sustained efficacy for the remainder of the treatment regimen.<sup>3,14,15</sup> The approval of omeprazole magnesium 20.6 mg for the OTC treatment of frequent heartburn was based on the results of two multicenter, double-blind, randomized, double-dummy, parallel, placebo-controlled trials.<sup>3</sup> A total of 2,086 patients with frequent heartburn received omeprazole magnesium 20.6 mg (n=1,047) or placebo (n=1,039) for 14 consecutive mornings; patients reported an average of five days of mild-to-moderate heartburn per week at baseline. In both studies, significantly more patients receiving omeprazole magnesium 20.6 mg were heartburn-free for 24 hours on Day 1 after the first single morning dose than in the placebo group (p<0.001): omeprazole magnesium 20.6 mg (49.7%) vs. placebo (32.6%) p<0.001 (study 1); omeprazole magnesium 20.6 mg (46.8%) vs. placebo (32.1%) p<0.001 (study 2). Further, omeprazole magnesium 20.6 mg achieved a higher percentage of heartburn-free days compared to placebo across 14 consecutive days of dosing: omeprazole magnesium 20.6 mg (64.4%) vs. placebo (39.4%) p<0.001 (study 1); omeprazole magnesium 20.6 mg (67.8%) vs. placebo (37.9%) p<0.001 (study 2) with the degree of efficacy increasing over the first few days and being maintained over the entire 14 days (**Figure 1**).<sup>3</sup>

Similar results have been demonstrated with the nonprescription dose of lansoprazole.<sup>14,15</sup> In two identical multicenter, double-blind studies, adult patients experiencing frequent heartburn (≥2 days a week over the past month) were randomized to lansoprazole 15 mg or placebo once daily for 14 days.<sup>14</sup> Lansoprazole was associated with a greater mean percentage of 24-hour days without heartburn during 14 consecutive days of treatment compared with placebo (p<0.0001): in the treatment phase of the two studies, patients who were on lansoprazole were heartburn free on 60% of 24-hour days compared with approximately 45% of 24-hour days

for patients on placebo (p<0.0001). In addition, more patients treated with lansoprazole reported no nighttime heartburn during the 14-day treatment (study 1: lansoprazole, 79.5% vs. placebo, 76.3%, p=0.0003; study 2: lansoprazole, 81.6% vs. placebo, 77.0%, p<0.0001) and no heartburn during day one of the 14-day treatment compared with placebo (study 1: lansoprazole, 50.4% vs. placebo, 33.0% p<0.0001; study 2: lansoprazole 50.7% vs. placebo, 37.9% p<0.0011. In another large (n=864) randomized trial, lansoprazole 15 mg and 30 mg once daily were significantly more effective than placebo in decreasing the frequency of nighttime heartburn (p<0.0001 for both doses vs. placebo).<sup>15</sup> The percentages of patients with no nighttime heartburn were similar between lansoprazole groups and placebo.

The 20 mg nonprescription dose of omeprazole/sodium bicarbonate also demonstrated efficacy in the treatment of frequent heartburn. In a placebo-controlled study conducted in Scandinavia amongst gastroesophageal reflux disease (GERD) patients without erosive esophagitis treated with omeprazole 20 mg (n=205) once daily for up to 4 weeks, more patients experienced complete resolution of heartburn with omeprazole compared to placebo (n=105; p<0.005).<sup>16</sup>

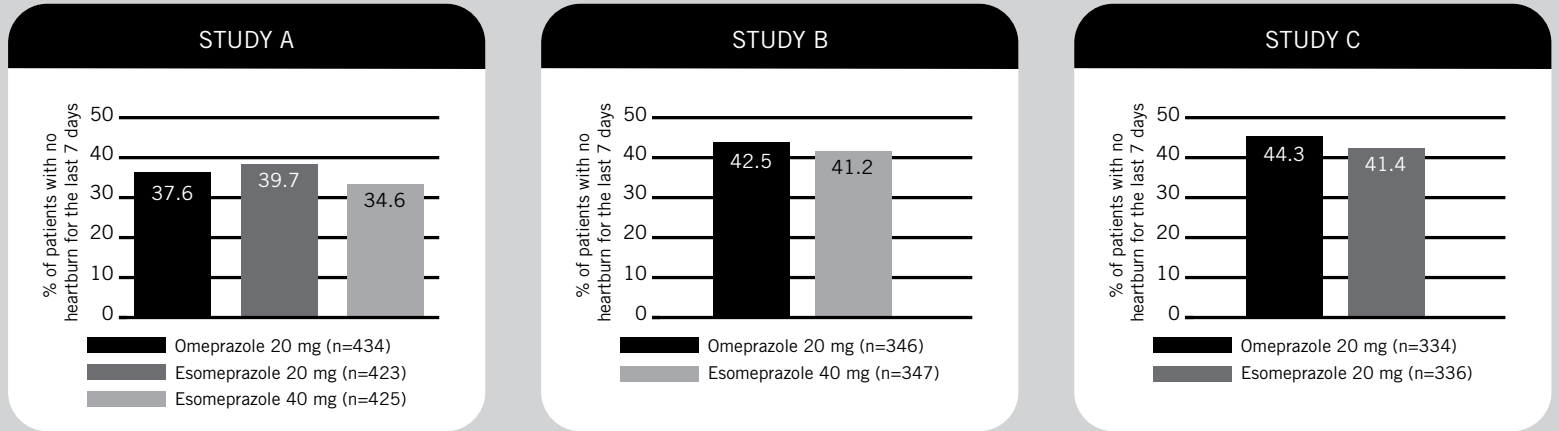


**Figure 1.** Percentage of patients heartburn-free over 14 consecutive days of therapy with omeprazole magnesium 20.6 mg compared with placebo.<sup>3</sup>

Allgood LD, Grender JM, Shaw MJ, Peura DA. Comparison of Prilosec OTC (omeprazole magnesium 20.6 mg) to placebo for 14 days in the treatment of frequent heartburn. *J Clin Pharm Ther.* 2005;30:105-112. Reprinted with permission from John Wiley & Sons, Ltd. via Copyright Clearance Center.

It is well established that higher prescription PPI doses result in more effective gastric acid suppression and are approved for healing of erosive esophagitis.<sup>13,17,18</sup> A review of current data suggests one cannot conclusively correlate higher PPI doses or intragastric pH control with more effective symptom

relief, as few studies evaluating gastric acidity also evaluated clinical outcomes.<sup>19</sup> Likewise, current data do not conclusively suggest that greater acid suppression correlates with more effective symptom relief in patients with endoscopy-negative reflux disease.<sup>20</sup>



**Figure 2.** Percentage of patients with complete resolution of heartburn at 14 days.<sup>20</sup>

Note: PPIs are not interchangeable. Prescription PPIs and OTC PPIs may differ in dose, indication, duration, efficacy and directions for use.

Armstrong et al. published results from three multinational, double-blind, randomized clinical trials investigating the efficacy of esomeprazole 20 mg and/or esomeprazole 40 mg in patients with endoscopy-negative reflux disease to that of omeprazole 20 mg.<sup>20</sup> The authors state: “The aim of the present studies was, therefore, to test the hypothesis that the greater acid suppression produced by esomeprazole would produce heartburn relief in a greater proportion of patients than omeprazole after four weeks of therapy.” Over 2,600 patients were enrolled (total of all three studies) if they experienced heartburn symptoms for the last six months or longer, and for four or more days in the week prior to enrollment. The primary end point was the complete resolution of heartburn at four weeks (defined as no episodes of heartburn during the last seven consecutive days of treatment). Among the secondary end points was the complete

resolution of heartburn at 14 days (defined similarly as above). Esomeprazole 20 mg was found to be comparable to esomeprazole 40 mg for the complete resolution of heartburn, and there were no significant differences found between both treatment groups in the complete resolution of heartburn at either 14 or 28 day end points (see Figure 2 above for 14 day results). In these studies, omeprazole 20 mg was used as an active control and it was shown that both esomeprazole 40 mg and 20 mg were comparable to omeprazole 20 mg in achieving complete resolution of heartburn (Figure 2).<sup>20</sup> In another study which looked at symptom relief of two doses of lansoprazole, once-daily lansoprazole 15 mg and lansoprazole 30 mg (61.7% and 61.3% respectively) were similar and significantly more effective than placebo (47.8%) ( $p < 0.0001$ ) in the treatment of frequent nighttime heartburn in a self-treating population.<sup>15</sup>

## minimal effective dose

Given the lack of demonstrated superiority with higher doses over lower doses of PPIs in the symptomatic relief of heartburn,<sup>20</sup> standard lower doses of these agents are appropriate for treatment of frequent heartburn. Consistent with this observation, clinical experts and professional organizations such as the ACG<sup>10</sup> and the AGA<sup>9</sup> recommend that once healing occurs, PPI dosage should be titrated down to the lowest effective dose based on symptom control.<sup>8,10,13,17,18,21,22</sup> Similarly, the Food and Drug Administration (FDA) advises health care professionals to consider whether a lower dose or shorter duration of therapy would adequately treat the patient's condition.<sup>23</sup>

Taking a lead from the World Health Organization's perspective on the rational use of medicines, and the FDA's "Safe use initiative fact sheet"<sup>24,25</sup> it is particularly important for health care professionals to play an active role in the management of frequent heartburn patients, even for those patients who suffer only from frequent heartburn.

To help guide treatment, physicians can:

- Screen patients periodically for response to therapy and adverse events
- Consider periodically whether reduction or discontinuation of therapy would be appropriate/tolerated

Indeed, as Dr. Cone noted, "it's important that we use the lowest dose that achieves the best response for the condition being treated, being cautious of contraindications..." She continued, "it's also important to follow up with patients to see how they're doing and, if they're doing well, to determine whether they need to continue the medication or if a lower dose can be used."

"When prescribing proton pump inhibitors, consider whether a lower dose or shorter duration of therapy would adequately treat the patient's condition."

- FDA Drug Safety Communication<sup>23</sup>

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## approach to managing frequent heartburn: a case study

A 36-year-old female patient presents to a primary care office complaining of burning pain in her chest. She is overweight and is currently taking several medications for various conditions. Physical examination and echocardiogram are unremarkable.

In order to characterize the nature of the patient's symptoms, the clinician obtains a dietary and medication history, and asks the following questions:

- When and how often does the pain occur?
- Where does the pain occur?
- Do certain foods exacerbate the pain?
- Does the pain worsen with physical activity?
- Are there any other symptoms associated with the pain?

Upon further questioning, the patient reveals that the pain is non-radiating and not associated with exertion or shortness of breath. The pain is frequent, occurring approximately two to three days a week unless the patient avoids specific foods, including spicy and tomato-based foods. The patient is then screened to rule out the presence of alarm signs and symptoms that may be suggestive of complications of GERD or an alternative diagnosis. Such signs and symptoms include gastrointestinal bleeding, nausea/vomiting,<sup>12</sup> dysphagia, odynophagia or weight loss.<sup>26</sup> Patients with these alarm features should be referred immediately for further evaluation.<sup>5,8</sup> Similarly,

patients with extraesophageal symptoms (such as chronic cough, laryngitis, asthma) should be referred for further diagnostic work-up.<sup>5,10</sup> In particular, ischemic heart disease must be ruled out in patients presenting with heartburn associated with chest pain.<sup>4,5,10</sup>

Upon questioning the patient about strategies she has tried to relieve the pain, the clinician learns that OTC antacids have been effective in relieving her symptoms. However, she is dissatisfied with the frequency of administration required to treat her recurring symptoms. Despite counseling on lifestyle and dietary modifications, she has difficulty remaining compliant with these changes.

Given the absence of alarm symptoms in this patient with frequent heartburn, the clinician further educates the patient regarding dietary/lifestyle modifications. Lifestyle modifications recommended in patients with heartburn include dietary modification, losing weight, elevating the head of the bed, avoiding late evening meals and smoking cessation.<sup>1,4,10</sup> These modifications may benefit some patients with frequent heartburn, but these changes alone are unlikely to control symptoms in the majority of patients.<sup>4,10</sup> Although some patients may find specific dietary modifications helpful (e.g., avoiding coffee, chocolate, fats), many patients continue to experience frequent heartburn.<sup>1,4,10</sup>

In addition to lifestyle/dietary modifications, OTC heartburn medications (H<sub>2</sub>RAs and PPIs) are appropriate options for this patient. These agents are considered by the ACG and AGA as appropriate first-line options for patients with uncomplicated frequent heartburn.<sup>4,9,10</sup> Nonprescription H<sub>2</sub>RAs are appropriate for on-demand therapy in patients with episodic and meal-provoked heartburn in which rapid relief of episodic heartburn associated with causative food or beverages is desired.<sup>5,27,28</sup>

In contrast to episodic use, the OTC PPIs are appropriate as initial treatment for frequent heartburn (i.e., heartburn that occurs two or more days a week).<sup>4,5,29</sup> PPIs may take one to four days for full effect although some people experience complete relief of symptoms within 24 hours.<sup>3,14,15</sup> These agents are intended for once daily use every day (every 24 hours) for 14 days. This course may be repeated every four months or used as directed by a doctor.<sup>12,16,30</sup> In order to achieve optimal acid-reducing efficacy, PPIs should be dosed before breakfast.<sup>4,10,30</sup>

Dr. Fromer added that health care providers should “provide instructions for patients so they understand why it is important to dose their medication before eating in the morning.”

Accordingly, the patient was instructed to begin a 14-day course of therapy with omeprazole magnesium 20.6 mg daily before breakfast. Heartburn resolved after three days of therapy; nearly 50% of patients experience complete relief of symptoms in the full day after taking the first dose although it may take one to four days for full effect.<sup>3,14</sup> The patient remained symptom-free during the rest of her 14-day course. Consistent with labeling for OTC PPIs,<sup>12,16,30</sup> treatment was discontinued at the end of 14 days. The patient was instructed to pursue lifestyle and dietary modifications and to consult her physician if her symptoms recur. Commenting on this approach, Dr. Fromer noted that “there has to be more of a secondary prevention approach: patient education, raising health literacy and helping patients understand what triggers their symptoms.”

The key primary care role in these patients involves early and accurate diagnosis, knowing when to refer, understanding the red flag symptoms, and understanding how PPIs work and the approach to dosing in the morning before eating.”

- Leonard Fromer, MD

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## conclusions

Frequent heartburn is very common in the U.S., affecting approximately 70 million Americans.<sup>2</sup> The availability of OTC heartburn medications allows for effective patient-directed management and can lead to significant improvement for heartburn sufferers. OTC-approved doses of PPIs are effective in relieving frequent heartburn symptoms in a majority of patients.<sup>3,14,15</sup> Further, OTC doses of these agents appear to be as effective as higher doses in relieving heartburn symptoms.<sup>15,20</sup> In keeping with these findings and with overall principles for rational drug use, practitioners and patients alike are encouraged to use the lowest effective dose of PPIs

in patients suffering only from frequent heartburn.<sup>9,10,13,17,18,21,22</sup> Finally, optimal self-management of patients with frequent heartburn requires that patients use OTC heartburn medications appropriately, recognizing that these agents are not intended to be used beyond the 14-day indication unless directed by a physician. In addition, those patients who do not respond to a 14-day course of therapy should be referred for further evaluation to rule out other conditions and/or assess the need for other therapies. Important directions for appropriate use, and safety information are found in corresponding full prescribing information and product labels.

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