

# Natural Approaches for Gastroesophageal Reflux Disease and Related Disorders

**Chris D. Meletis, N.D.,  
with Nieske Zabriskie, N.D.**

**G**astroesophageal reflux disease (GERD) is a chronic recurrent condition affecting millions of Americans. A recent study investigating the economic and social burden of gastrointestinal (GI) disease in the United States indicated that GERD was the most common GI-related diagnosis given at office visits in 2006. This study also showed that sales of proton pump inhibitors (PPIs) exceeded 10 billion dollars per year and the number of prescriptions for PPIs per year has doubled since 1999.<sup>1</sup>

Numerous environmental and genetic risk factors have been implicated in the pathogenesis of GERD. GERD commonly presents with heartburn and acid regurgitation, although there are numerous atypical presentations, such as chronic cough, noncardiac chest pain, laryngitis, and poor sleep quality.

This condition is associated with several other conditions, including Barrett's esophagus, esophageal carcinoma, gastritis, esophagitis, respiratory conditions, sleep disorders, and various ear-nose-throat (ENT) conditions. Conventional treatment often includes the use of PPIs and other acid blockers. Natural therapies and lifestyle interventions are important to consider owing to the chronic nature of GERD.

## Prevalence

Studies attempting to assess the prevalence of GERD widely vary in their results depending on criteria used for diagnosis. A large survey performed by the National Heartburn Alliance in 2000 estimated that 60 million American have GERD symptoms at least once per month, and 25 million adults have daily symptoms.

This survey revealed that 95 percent of these individuals have had symptoms for more than 1 year, and 54 percent have had symptoms for more than 5 years. Forty (40) percent of these individuals reported symptoms 2–4 times per week, and 33 percent reported symptoms 5 times per week or more.<sup>2</sup>

This survey also showed that GERD symptoms affect activities of daily living greatly, as more than 80 percent of the respondents reported decreased enjoyment of food, more than 60 percent reported that symptoms affected their ability to sleep well, and approximately 40 percent reported that their symptoms affect concentration at work and family activities.<sup>2</sup>

## Risk Factors

Both genetic and environmental factors appear to influence the presence of GERD. Numerous studies have shown that obesity, weight gain, and increasing body-mass index (BMI) are associated with GERD. Hiatal hernia is also a risk factor for GERD symptoms. Studies indicate that individuals with large hiatal hernias have shorter and weaker lower esophageal sphincters (LES), increased amount of reflux, less-efficient acid clearance, less effective peristalsis, and increased severity of esophagitis compared with individuals with small or no hiatal hernia.<sup>3</sup>

Research also indicates that smoking, excess alcohol consumption, irritable bowel syndrome, and a family history of upper GI disease are risk factors. Pharmaceutical usage such as anticholinergics, antidepressants, and inhaled bronchodilators are also related to the disease. This study also associated lack of education and manual work with the presence of GERD.<sup>4</sup>

Additional studies have suggested that increased intake of table salt, sweets, or white bread is also a risk factor. Exercise and diets high in fruit and dietary fiber appear to be protective against the condition.<sup>5,6</sup> However, high-intensity exercise has been shown to decrease LES pressure and induce GERD symptoms in otherwise asymptomatic individuals.<sup>7</sup> Caffeine ingestion also decreases LES pressure and decreases distal esophageal mean amplitude of contractions and peristaltic velocity, which can increase reflux.<sup>8</sup>

Ingestion of carbonated beverages has also been observed, in a study, to decrease the resting pressure, overall length, and abdominal length of the LES in healthy individuals temporarily.

ly. This study showed that 62 percent of individuals who drank carbonated beverages had significant decreases in these parameters to meet the criteria for incompetence of the LES.<sup>9</sup>

In addition, persistent wheezing, asthma, and airway hyper-responsiveness in childhood and adolescence have been shown to significantly increase risk for GERD symptoms at age 26 independent of BMI.<sup>10</sup> A study with a Spanish population indicated that long-term GERD symptoms of 10 years or longer are associated with obesity and having a direct family member with GERD symptoms. GERD symptoms of 1 year or less were more closely correlated with having a spouse with GERD symptoms or taking 1–5 aspirin per week.<sup>11</sup>

### Diagnosis

Diagnosis of GERD is often based on symptoms. It is characterized by chronic intermittent heartburn as a burning sensation in the chest and throat as well as acid regurgitation presenting as a sensation of acid in the throat or mouth. GERD may also present with atypical symptoms of esophageal and extraesophageal origin such as chronic cough, sleep disturbance, chest pain, asthma, and hoarseness.<sup>12</sup> In fact, one study showed that 50 percent of individuals with noncardiac chest pain had abnormal pH tests or positive endoscopy confirming the presence of GERD.<sup>13</sup>

A positive response to PPI therapy is frequently used to confirm the diagnosis of GERD. Additional diagnostic tests are performed for an individual with an atypical presentation, a high risk for complications, or a poor response to initial therapy.

Esophageal pH monitoring is an important diagnostic tool for GERD. Ambulatory pH monitoring detects abnormal levels of acid in the esophagus and can be used to correlate esophageal acid exposure with symptoms. The Bravo capsule is a wireless pH monitoring device that has been shown to be more tolerable, accurate, and sensitive than the catheter-based pH monitoring. The Bilitec system measures duodenogastroesophageal reflux; this system is useful particularly for the subset of patients that may be affected by duodenogastroesophageal reflux.

These patients report reflux symptoms with normal acid exposure in the esophagus on high-dose PPI therapy. Intraluminal impedance monitoring detects the composition, distribution, and clearing of both acid and nonacid esophageal reflux. Combined esophageal pH-impedance monitoring allows detection of nearly all gastroesophageal reflux episodes, acid as well as nonacid, which provides better diagnostics particularly with patients on acid-suppression therapy.<sup>14</sup> Esophageal manometry is also performed to measure the pressure at the LES. Esophagoscopy is used to diagnose esophagitis and a biopsy can differentiate esophageal strictures from cancer.

### Pathophysiology and Associated Conditions

Transient LES relaxation is the primary mechanism of GERD. It results from a vago–vagal reflex triggered by stretch receptors of the proximal stomach. Studies have indicated that most reflux episodes are acidic. However, according to one study, 28 percent of episodes were only weakly acidic and 10 percent of episodes were weakly alkaline.<sup>15</sup> Numerous factors may influence the symptoms of GERD. Delayed gastric emptying, volume of gastric content, quantity and acidity of refluxed contents, ability of the esophagus to clear this material, LES function, and the resistance of the esophageal tissue can influence reflux symptoms.<sup>16</sup> Some researchers have proposed that patients with GERD can be categorized further as having erosive esophagitis, nonerosive reflux disease, and Barrett's esophagus.<sup>17</sup>

---

*GERD may present with atypical symptoms of esophageal and extraesophageal origin.*

---

#### Gastritis

There is conflicting evidence regarding the role that *Helicobacter pylori* may play in GERD pathology. There are various studies that have looked at treatment of gastritis by eradicating *H. pylori* and the effects of treatment on concurrent GERD symptoms. The results of these studies vary from showing improvement to showing worsening of GERD symptoms.<sup>18</sup> Research regarding inflammation in the gastroesophageal junction, or cardia, has indicated that the presence of erosive GERD or *H. pylori* gastritis is associated with the inflammation.<sup>19</sup> In addition, GERD and carditis are associated with intestinal metaplasia at the gastroesophageal junction.<sup>20</sup>

#### Esophagitis

Esophagitis is common with GERD and may be classified as erosive or nonerosive with the severity based on the number and location of mucosal breaks. Other types of esophagitis, such as eosinophilic esophagitis, present with similar symptoms as GERD and are commonly misdiagnosed. The common presentation of eosinophilic esophagitis is dysphagia and food impaction. Additional symptoms may include epigastric pain, emesis, weight loss, and failure to thrive.<sup>21</sup>

The diagnosis is based on a histologic finding of greater than 20 eosinophils per high-powered field in the esophageal squamous mucosa. This condition also presents with motor disturbances that may cause food impaction in the absence of strictures. Manometry shows high amplitude long-duration waves in the distal esophagus particularly at night. The symptoms often respond to elimination or elemental dietary regimens and antiallergy treatment.<sup>22</sup> Standard skin-prick tests measure type 1 hypersensitivity reactions, which are typically mediated by immunoglobulin E (IgE). (It is possible to have a positive skin test but normal blood levels of IgE on a radioallergosorbent test [RAST].) However, these tests do not diagnose many food-allergy reactions, which are frequently IgG-mediated. Thus, IgG testing can offer additional insights that are frequently missed with standard skin-prick tests.

## Commonly Prescribed Pharmaceuticals for GERD

### Histamine H<sub>2</sub>-receptor antagonists

Cimetidine (Tagamet)  
Famotidine (Pepcid)  
Ranitidine (Zantac)  
Nizatidine (Axid)

### Proton pump inhibitors

Lansoprazole (Prevacid)  
Esomeprazole (Nexium)  
Omeprazole (Prilosec)  
Pantoprazole (Protonix)  
Rabeprazole (Aciphex)

GERD = gastroesophageal reflux disease.

### Respiratory conditions

GERD is associated with numerous respiratory conditions. Approximately 10 percent of patients presenting to ENT specialists have conditions that may be attributed to GERD.<sup>23</sup> One study revealed that GERD is present in 75 percent of individuals with refractory ENT symptoms and PPI therapy provided symptom relief or reduction in the majority of these individuals.<sup>24</sup>

Asthma is associated with the presence of GERD symptoms although the relationship has not been well-studied. It is estimated that prevalence of GERD in people with asthma is between 60 percent and 80 percent in adults and 50 percent and 60 percent in children. Although the direct correlation is unknown, researchers have suggested that reflux aggravates asthma, which in turn, induces further reflux.<sup>25</sup> GERD is associated with a chronic non-productive cough in some individuals; the cough occurs primarily during the day and while these patients are in an upright position. One study demonstrated that chronic cough was caused by reflux in 21 percent of cases. In addition, the researchers showed that chronic cough was the sole presenting symptom in GERD 43 percent of the time.<sup>26</sup>

Otitis media may also be linked to GERD. A study performed with otitis media with effusion in adults demonstrated that pepsinogen concentration was higher in middle-ear effusion in patients who reported GERD symptoms. In addition, treatment for GERD with PPIs provided some patients with GERD symptom relief as well as decreasing the concentration of pepsinogen in the effusion.<sup>27</sup>

What is more, research has indicated that patients with chronic rhinosinusitis have an increased prevalence of GERD. These chronic rhinosinusitis symptoms in many patients are reduced when their GERD is treated.<sup>28</sup>

Laryngeal symptoms may be associated with GERD. Often, they present as hoarseness, frequent throat clearing, a postnasal drip, excess phlegm, a sore throat, dysphagia, a globus sensation, or a cough. Chronic laryngitis and chronic sore throat are associated with GERD in as many as 60 percent of patients.<sup>29</sup>

In addition, one study showed that at least 50 percent of patients presenting with laryngeal and voice disorders had laryn-

gopharyngeal reflux.<sup>30</sup> Less-common GERD related laryngopharyngeal disorders include paroxysmal laryngospasm, subglottic stenosis, vocal-cord granuloma, and laryngeal and pharyngeal carcinoma.<sup>31</sup>

### Oral health

GERD has been shown to affect overall oral health. One study showed that children with GERD have increased dental erosion, salivary yeast, and salivary *Mutans streptococci* compared with healthy children.<sup>32</sup> In addition, research indicates that children with GERD have more dental caries and more severe erosion compared with healthy children.<sup>33</sup>

### Sleep Apnea

Sleep disturbance is common in individuals with GERD. Patients with obstructive sleep apnea (OSA) have GERD symptoms significantly higher than the general population.<sup>34</sup> What is more, studies have indicated that the severity of GERD symptoms is correlated positively to the severity of OSA.<sup>35</sup> One study showed that treatment with continuous positive airway pressure (CPAP) in individuals with GERD and OSA reduced supine esophageal-acid contact time to within normal levels in 81 percent of the study patients.<sup>36</sup> In addition, researchers have shown that treatment of GERD in patients who have OSA decreases the number of arousals during sleep.<sup>37</sup>

### Barrett's Esophagus and Cancer

Barrett's esophagus is a precancerous condition showing intestinal metaplasia of the lower esophagus and mucosecretory cells on histologic examination. It is the precursor to esophageal adenocarcinoma.

Approximately 8–10 percent of individuals with GERD have Barrett's esophagus.<sup>38</sup> In fact, the cancer risk for an individual with Barrett's esophagus is 30 times higher than in the general population. Risk factors for Barrett's esophagus include GERD for at least 5 years' duration, male gender, Caucasian race, and age over 50.<sup>39</sup> A study with U.S. veterans showed that GERD increases the risk of both laryngeal and pharyngeal cancers independent from other risk factors.<sup>40</sup>

## Conventional Treatment

### Pharmaceuticals

Pharmaceutical acid blockers are usually the initial recommendation for both diagnosis and treatment. Treatment recommendations are usually based on a step-up or step-down approach depending on the severity of symptoms.

Step-up treatment typically involves an 8-week trial of a histamine H<sub>2</sub>-receptor antagonist taken two times per day as needed, changing to a PPI if symptoms are not controlled. The step-down approach begins with an 8-week trial of a PPI taken 30–60 minutes before the first meal of the day and then decreasing to the lowest possible dosage that provides relief.

Studies have indicated that both PPI therapy and H<sub>2</sub> blockers provide symptom relief for the majority of patients. One study showed that 8 weeks of therapy with the PPI omeprazole

relieved symptoms in 74 percent and 8 weeks of the H<sub>2</sub> blocker ranitidine relieved symptoms in 50 percent of individuals with reflux esophagitis.<sup>41</sup> Low-dose antacids have also been shown to decrease reflux symptoms better than placebo.<sup>42</sup>

Long-term therapy with acid blockers has not been well-studied. Some research has indicated that nutrient deficiencies may arise with these treatments. Research has also suggested that long-term therapy with both PPI and H<sub>2</sub> blockers increases the risk of vitamin B<sub>12</sub> deficiency significantly in elderly adults.<sup>43</sup> In fact, one study demonstrated that therapy with H<sub>2</sub> blockers caused a 53 percent decrease in absorption of protein-bound vitamin B<sub>12</sub>.<sup>44</sup> H<sub>2</sub> blockers have also been associated with decreased absorption of folic acid, iron, and zinc.<sup>45–47</sup> Research has demonstrated that treatment with the H<sub>2</sub> blocker cimetidine significantly decreases intestinal calcium transport as well as altering vitamin D metabolism.<sup>48,49</sup> There is also evidence that long-term use of PPIs increases the risk of hip fracture significantly.<sup>50</sup>

Baclofen is a gamma-aminobutyric acid (GABA) receptor B agonist currently being investigated as a possible treatment for GERD symptoms. Studies have indicated that baclofen reduces the rate of transient LES relaxations significantly, reduces the rate of gastroesophageal acid-reflux episodes, increases basal LES pressure, and increases gastric pH. Studies have also suggested that the drug is well-tolerated by patients.<sup>51</sup>

Atropine has also been studied as a treatment for GERD symptoms. Evidence suggests that administration of atropine decreases transient relaxation in the LES and significantly decreases the number of reflux episodes.<sup>52</sup> However, atropine can only be administered short-term, via intramuscular injections or intravenously.

### Surgery

Surgery is considered based on severity of disease, response to pharmaceutical treatment, risk of complications, and individual patient needs. The most frequent antireflux procedure performed is laparoscopic fundoplication, although surgery can also be done to correct hiatal hernias and other anatomical causes of GERD.

Laparoscopic fundoplication places a gastric wrap around the gastroesophageal junction, strengthening the barrier function. Research has indicated that fundoplication relieves heartburn and typical symptoms in 93 percent of patients, yet only 56 percent of individuals had relief of their atypical symptoms.<sup>53</sup> This procedure does not appear to replace the use of acid-blocking medication or decrease the incidence of carcinoma over standard medication therapy.<sup>54</sup>

### Lifestyle Modification

Lifestyle modifications can have great impact on GERD symptoms. Diet recommendations include avoiding foods that trigger symptoms. Common culprits include acidic foods, such as tomatoes, coffee, tea, and citrus. Research has shown that diets high in the antioxidant vitamin C are associated with less risk of GERD symptoms, Barrett's esophagus, and esophageal adenocarcinoma.<sup>55</sup>

In addition, a small study showed that very-low-carbohydrate diets reduce GERD symptoms and decrease lower esophageal-acid exposure in obese individuals with GERD. In fact, this study

## Alternative Supplements for Treating GERD

Vitamin C  
Melatonin  
Fish oil  
D-limonene  
*Glycyrrhiza glabra* (licorice)  
Digestive enzymes  
*Atropa belladonna* (belladonna)  
Calcium  
Magnesium

GERD = gastroesophageal reflux disease.

showed that diets containing less than 20 g of carbohydrates per day significantly reduced symptoms in less than 6 days.<sup>56</sup> Another study demonstrated that chewing sugar-free gum for 1 half-hour after a meal reduced postprandial esophageal reflux possibly by increasing the frequency of swallowing.<sup>57</sup> A study with children who had GERD symptoms that were unresponsive to treatment showed that feeding an elemental formula reduced or resolved all patients' GERD symptoms as well as improving histologic changes in the esophagus.<sup>58</sup>

Commonly, it is suggested to patients to sleep with the head of the bed elevated as well as sleeping in the left-lateral decubitus position.<sup>59</sup> Numerous studies have investigated the effect of weight loss on GERD symptoms. Research has indicated that weight loss and decreased visceral fat mass correlated significantly with decreased esophageal-acid exposure.<sup>60</sup> Smoking cessation is also recommended.

## Alternative Treatment

### Antioxidants

Antioxidants have been shown to be protective in numerous diseases such as GERD, gastric ulcers, and GI cancers. Oxidative stress of the esophageal mucosa is a contributing factor in the pathology of GERD. A study was performed with individuals with both erosive and nonerosive GERD pre- and post-antireflux surgery measuring oxidative stress. This study showed that individuals with GERD have lower glutathione levels in the distal esophagus compared with controls. In addition, myeloperoxidase activity in the distal esophagus decreased after antireflux surgery but never returned to levels found in the control group.<sup>61</sup>

Supplementation to increase glutathione levels with the precursors N-acetyl-cysteine and selenium may be beneficial. Additional studies have shown that oxygen-free radicals measured by arachadonic acid peroxidation metabolites are significantly higher in patients with GERD compared with controls.<sup>62</sup> Studies have also indicated that free-radical oxidative damage plays a role in gastric and duodenal ulcers as well in as gastric carcinoma.<sup>63</sup>

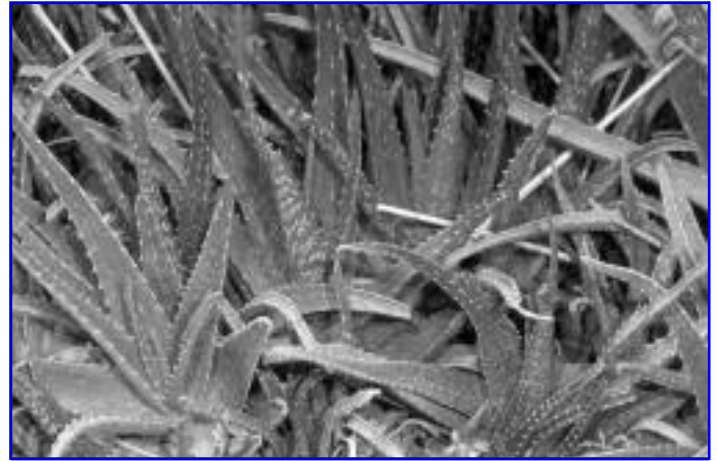
Although studies directly supporting antioxidant supplementation with GERD are lacking, substantial evidence supports using antioxidant therapy for patients with gastric ulcers and cancer, and shows that the therapy may also provide benefit for patients who have GERD. Research has shown that the hormone

## Tell Your Patients

### Lifestyle Modifications for GERD

- Lose weight.
- Avoid eating large meals.
- Avoid consuming acidic foods, such as citrus foods, tomatoes, coffee, and tea.
- Avoid caffeine and chocolate.
- Avoid consuming food allergens.
- Eat a diet high in fiber and antioxidants.
- Eat a low-carbohydrate diet.
- Avoid pharmaceuticals that aggravate GERD.
- Elevate the head of the bed 4–8 inches.
- Sleep in left lateral decubitus (lying down) position.
- Avoid lying down 2–3 hours after a meal.
- Stop smoking.

GERD = gastroesophageal reflux disease.



*Aloe vera* (aloe).

and potent antioxidant melatonin prevented gastric ulceration and reduced endogenous hydroxyl radicals by 88 percent. In fact, melatonin was shown to be more effective than ranitidine for preventing stress-related ulcers.<sup>64</sup>

Fish oil supplementation has also been shown to protect gastric mucosa and decrease the severity of gastric ulceration in animal studies. Fish oil increased antioxidant enzyme activity, decreased acid-pepsin secretion, increased mucin secretion, and decreased lipid peroxidation in the gastric mucosa.<sup>65</sup>

A study was performed with an antioxidant dietary supplement containing melatonin, L-tryptophan, vitamin B<sub>6</sub>, folic acid, vitamin B<sub>12</sub>, methionine, and betaine. The supplement or omeprazole was given to individuals with GERD. In this study, 100 percent of individuals who took the supplement had complete regression of their GERD symptoms within 40 days compared with less than 66 percent of individuals who had regression of symptoms treated with omeprazole.<sup>66</sup>

#### D-Limonene

D-limonene is a monoterpene in citrus oil. Numerous studies have shown that D-limonene exerts anticancer, antimicrobial, and anti-inflammatory effects. In particular, studies have shown that this constituent of citrus oil is protective against GI cancers, including cancers of the stomach and colon, decreasing both growth and metastasis.<sup>67</sup> Although direct evidence of D-limonene's effects on esophageal cancer is lacking, it is certainly possible that this monoterpene may be protective against Barrett's esophagus and esophageal adenocarcinoma.

#### Licorice

*Glycyrrhiza glabra* (licorice) root has historically been used as a demulcent and anti-inflammatory botanical for treating conditions such as gastric and duodenal ulcers. Studies have shown that ingestion of deglycyrrhizinated licorice (DGL) may increase mucous production and accelerate healing of duodenal and gastric ulcers.<sup>68,69</sup> In addition, a small study showed that DGL also accelerates healing of aphthous ulcers.<sup>70</sup> Although studies that correlate DGL with GERD directly are lacking, it is reasonable to

assume that DGL may provide symptom relief in patients with GERD. Clinically, alternative health care providers often prescribe additional demulcent herbs for their healing and soothing properties, including such herbs as *Aloe vera* (aloe), *Ulmus fulva* (slippery elm), and *Althaea officinalis* (marshmallow).

#### Mastic

*Pistacia lentiscus* (mastic) resin is used medicinally for treating duodenal and gastric ulcers. Animal studies show that it decreased *H. pylori* colonies thirtyfold.<sup>71</sup> Research has also indicated that mastic resin oral supplementation protects gastric mucosa from experimentally induced damage as well as decreasing free acidity.<sup>72</sup> In addition, a small study showed that mastic supplementation provided symptomatic relief of duodenal ulcers in 80 percent of individuals who were treated with the supplement, and 70 percent experienced healing with endoscopy.<sup>73</sup> The antisecretory and cytoprotective activity of mastic may provide benefit for individuals with GERD, although direct evidence is lacking.

#### Minerals

Calcium carbonate, magnesium, aluminum, and phosphate salts are frequently used in over-the-counter antacids. Studies have indicated that antacids are effective for treating GERD symptoms, reducing acid regurgitation, and relieving both daytime and nighttime heartburn.<sup>74</sup> Mineral supplementation, using calcium and magnesium, may reduce GERD symptoms, although direct evidence is lacking.

#### Digestive Enzymes

Supplemental digestive enzymes may reduce GERD symptoms. Delayed gastric emptying and a large volume of food in the stomach are associated with GERD symptoms, and supplementation using digestive enzymes may reduce these factors. Digestive enzymes are commonly included in combination products, including lipase, amylase, protease, maltase, lactase, sucrase, phytase, and cellulase. Clinically, some patients actually benefit from hydrochloric acid and pepsin supplementation, including individuals who have low levels of stomach acid and delayed gastric emptying.

### Allergy treatment

Eosinophilic esophagitis is frequently misdiagnosed as GERD. Allergy treatment may be indicated in individuals who are not responsive to typical GERD therapies. Allergy testing to measure both IgE and IgG antibodies is indicated. In addition, dietary supplementation, using products to treat allergic reactions directly may also be necessary. Quercetin is a bioflavonoid often used in allergies because it has antihistamine, anti-inflammatory, and antioxidant effects. Vitamin C has been shown to be protective against GERD and to have antioxidant and some antihistamine properties.

### Belladonna

*Atropa belladonna* (belladonna) is a botanical often used for its anticholinergic activity. One of the constituents of belladonna is atropine. Although anticholinergics have been shown to aggravate GERD, atropine has been shown to be beneficial. It is possible that belladonna may be useful for treating GERD owing to the herb's atropine component.

## Conclusions

GERD is a chronic recurring condition that makes a great impact on the quality of life of individuals who have this condition. As a result of the economic and social burdens of GERD in the United States, it is important for patients to have access to alternative therapies and lifestyle modifications. Currently, research in this area is minimal. □

### References

1. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. *Am J Gastroenterol* 2006;101:2128–2138.
2. National Heartburn Alliance. Survey 2000 Results: A Community Perspective. 2000. Online document at: [www.heartburnalliance.org/survey2000.pdf](http://www.heartburnalliance.org/survey2000.pdf) Accessed January 16, 2007.
3. Patti MG, Goldberg HI, Arcerito M, et al. Hiatal hernia size affects lower esophageal sphincter function, esophageal acid exposure, and the degree of mucosal injury. *Am J Surg* 1996;171:182–186.
4. Mohammed I, Nightingale P, Trudgill NJ. Risk factors for gastro-oesophageal reflux disease symptoms: A community study. *Aliment Pharmacol Ther* 2005;21:821–827.
5. Nocon M, Labenz J, Willich SN. Lifestyle factors and symptoms of gastro-oesophageal reflux—a population-based study. *Aliment Pharmacol Ther* 2006;23:169–174.
6. Nilsson M, Johnsen R, Ye W, et al. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux. *Gut* 2004;53:1730–1735.
7. Maddison KJ, Shepherd KL, Hillman DR, Eastwood PR. Function of the lower esophageal sphincter during and after high-intensity exercise. *Med Sci Sports Exerc* 2005;37:1728–1733.
8. Lohsiriwat S, Puengna N, Leelakusolvong S. Effect of caffeine on lower esophageal sphincter pressure in Thai healthy volunteers. *Dis Esophagus* 2006;19:183–188.
9. Hamoui N, Lord RV, Hagen JA, et al. Response of the lower esophageal sphincter to gastric distention by carbonated beverages. *J Gastrointest Surg* 2006;10:870–877.
10. Hancox RJ, Poulton R, Taylor DR, et al. Associations between respiratory symptoms, lung function and gastro-oesophageal reflux symptoms in a population-based birth cohort. *Respir Res* 2006;7:142.
11. Diaz-Rubio M, Moreno-Elola-Olaso C, Rey E, et al. Symptoms of gastro-oesophageal reflux: Prevalence, severity, duration and associated factors in a Spanish population. *Aliment Pharmacol Ther* 2004;19:95–105.
12. Hungin AP, Raghunath AS, Wiklund I. Beyond heartburn: A systematic review of the extra-oesophageal spectrum of reflux-induced disease. *Fam Pract* 2005;22:591–603.
13. Dekel R, Martinez-Hawthorne SD, Guillen RJ, Fass R. Evaluation of symptom index in identifying gastroesophageal reflux disease-related noncardiac chest pain. *J Clin Gastroenterol* 2004;38:24–29.
14. Hirano I. Review article: Modern technology in the diagnosis of gastro-oesophageal reflux disease—Bilitec, intraluminal impedance and Bravo capsule pH monitoring. *Aliment Pharmacol Ther* 2006;23(suppl1):12–24.
15. Zerbib F, des Varannes SB, Roman S, et al. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. *Aliment Pharmacol Ther* 2005;22:1011–1021.
16. Castell DO, Murray JA, Tutuian R, et al. Review article: The pathophysiology of gastro-oesophageal reflux disease—oesophageal manifestations. *Aliment Pharmacol Ther* 2004;20(suppl9):14–25.
17. Fass R, Ofman JJ. Gastroesophageal reflux disease—should we adopt a new conceptual framework? *Am J Gastroenterol* 2002;97:1901–1909.
18. Malfertheiner P, Peitz U. The interplay between *Helicobacter pylori*, gastro-oesophageal reflux disease, and intestinal metaplasia. *Gut* 2005;54(suppl1):i13–i20.
19. Voutilainen M, Farkkila M, Mecklin JP, et al. Chronic inflammation at the gastroesophageal junction (carditis) appears to be a specific finding related to *Helicobacter pylori* infection and gastroesophageal reflux disease. The Central Finland Endoscopy Study Group. *Am J Gastroenterol* 1999;94:3175–3180.
20. Voutilainen M, Farkkila M, Juhola M, et al. Complete and incomplete intestinal metaplasia at the oesophagogastric junction: Prevalences and associations with endoscopic erosive oesophagitis and gastritis. *Gut* 1999;45:644–648.
21. Pasha SF, Sharma VK, Crowell MD. Current concepts and treatment options in eosinophilic esophagitis. *Curr Opin Investig Drugs* 2006;7:992–996.
22. Luis AL, Rinon C, Encinas JL, et al. Non stenotic food impaction due to eosinophilic esophagitis: A potential surgical emergency. *Eur J Pediatr Surg* 2006;16:399–402.
23. Drug VL, Cobzeanu D, Papaghiuc C, et al. Gastroesophageal reflux involvement in ENT disorders [in Romanian]. *Rev Med Chir Soc Med Nat Iasi* 2005;109:220–222.
24. Poelmans J, Feenstra L, Tack J. Determinants of long-term outcome of patients with reflux-related ear, nose, and throat symptoms. *Dig Dis Sci* 2006;51:282–288.
25. Sontag SJ. Gastroesophageal reflux disease and asthma. *J Clin Gastroenterol* 2000;30(3suppl):S9–S30.
26. Irwin RS, Curley FJ, French CL. Chronic cough. *Am Rev Respir Dis* 1990;141:640–647.
27. Sone M, Yamamuro Y, Hayashi H, et al. Otitis media in adults as a symptom of gastroesophageal reflux. *Otolaryngol Head Neck Surg* 2007;136:19–22.
28. Loehrl TA, Smith TL. Chronic sinusitis and gastroesophageal reflux: Are they related? *Curr Opin Otolaryngol Head Neck Surg* 2004;12:18–20.
29. Poelmans J, Tack J. Extraoesophageal manifestations of gastro-oesophageal reflux. *Gut* 2005;54:1492–1499.
30. Koufman JA, Amin MR, Panetti M. Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders. *Otolaryngol Head Neck Surg* 2000;123:385–388.
31. Franco RA Jr. Laryngopharyngeal reflux. *Allergy Asthma Proc* 2006;27:21–25.
32. Ersin NK, Oncag O, Tumgor G, et al. Oral and dental manifestations of gastroesophageal reflux disease in children: A preliminary study. *Pediatr Dent* 2006;28:279–284.
33. Linnett V, Seow WK, Connor F, Shepherd R. Oral health of children with gastro-oesophageal reflux disease: A controlled study. *Aust Dent J* 2002;47:156–162.
34. Ing AJ, Ngu MC, Breslin AB. Obstructive sleep apnea and gastro-oesophageal reflux. *Am J Med* 2000;108(suppl4a):120S–125S.

35. Demeter P, Visy KV, Magyar P. Correlation between severity of endoscopic findings and apnea-hypopnea index in patients with gastroesophageal reflux disease and obstructive sleep apnea. *World J Gastroenterol* 2005;11:839–841.
36. Tawk M, Goodrich S, Kinasewitz G, Orr W. The effect of 1 week of continuous positive airway pressure treatment in obstructive sleep apnea patients with concomitant gastroesophageal reflux. *Chest* 2006;130:1003–1008.
37. Zanation AM, Senior BA. The relationship between extraesophageal reflux (EER) and obstructive sleep apnea (OSA). *Sleep Med Rev* 2005;9:453–458.
38. Stoltey J, Reeba H, Ullah N, et al. Does Barrett's oesophagus develop over time in patients with chronic gastro-oesophageal reflux disease? *Aliment Pharmacol Ther* 2007;25:83–91.
39. Pascu O, Lencu M. Barrett's esophagus. *Rom J Gastroenterol* 2004;13:219–222.
40. El-Serag HB, Hepworth EJ, Lee P, Sonnenberg A. Gastroesophageal reflux disease is a risk factor for laryngeal and pharyngeal cancer. *Am J Gastroenterol* 2001;96:2013–2018.
41. Festen HP, Schenk E, Tan G, et al. Omeprazole versus high-dose ranitidine in mild gastroesophageal reflux disease: Short- and long-term treatment. The Dutch Reflux Study Group. *Am J Gastroenterol* 1999;94:931–936.
42. Weberg R, Berstad A. Symptomatic effect of a low-dose antacid regimen in reflux oesophagitis. *Scand J Gastroenterol* 1989;24:401–406.
43. Valuck RJ, Ruscin JM. A case-control study on adverse effects: H<sub>2</sub> blocker or proton pump inhibitor use and risk of vitamin B<sub>12</sub> deficiency in older adults. *J Clin Epidemiol* 2004;57:422–428.
44. Salom IL, Silvis SE, Doscherholmen A. Effect of cimetidine on the absorption of vitamin B<sub>12</sub>. *Scand J Gastroenterol* 1982;17:129–131.
45. Russell RM, Golner BB, Krasinski SD, et al. Effect of antacid and H<sub>2</sub> receptor antagonists on the intestinal absorption of folic acid. *J Lab Clin Med* 1988;112:458–463.
46. Sturniolo GC, Montino MC, Rossetto L, et al. Inhibition of gastric acid secretion reduces zinc absorption in man. *J Am Coll Nutr* 1991;10:372–375.
47. Aymard JP, Aymard B, Netter P, et al. Haematological adverse effects of histamine H<sub>2</sub>-receptor antagonists. *Med Toxicol Adverse Drug Exp* 1988;3:430–448.
48. Ghishan FK, Walker F, Meneely R, et al. Intestinal calcium transport: Effect of cimetidine. *J Nutr* 1981;111:2157–2161.
49. Odes HS, Fraser GM, Krugliak P, et al. Effect of cimetidine on hepatic vitamin D metabolism in humans. *Digestion* 1990;46:61–64.
50. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006;296:2947–2953.
51. Ciccaglione AF, Marzio L. Effect of acute and chronic administration of the GABA B agonist baclofen on 24 hour pH metry and symptoms in control subjects and in patients with gastro-oesophageal reflux disease. *Gut* 2003;52:464–470.
52. Lidums I, Checklin H, Mittal RK, Holloway RH. Effect of atropine on gastro-oesophageal reflux and transient lower oesophageal sphincter relaxations in patients with gastro-oesophageal reflux disease. *Gut* 1998;43:12–16.
53. So JB, Zeitels SM, Rattner DW. Outcomes of atypical symptoms attributed to gastroesophageal reflux treated by laparoscopic fundoplication. *Surgery* 1998;124:28–32.
54. Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: Follow-up of a randomized controlled trial. *JAMA* 2001;285:2331–2338.
55. Veugelers PJ, Porter GA, Guernsey DL, Casson AG. Obesity and lifestyle risk factors for gastroesophageal reflux disease, Barrett esophagus and esophageal adenocarcinoma. *Dis Esophagus* 2006;19:321–328.
56. Austin GL, Thiny MT, Westman EC, et al. A very low-carbohydrate diet improves gastroesophageal reflux and its symptoms. *Dig Dis Sci* 2006;51:1307–1312.
57. Moazzez R, Bartlett D, Anggiansah A. The effect of chewing sugar-free gum on gastro-esophageal reflux. *J Dent Res* 2005;84:1062–1065.
58. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: Improvement with an amino acid-based formula. *Gastroenterology* 1995;109:1503–1512.
59. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med* 2006;166:965–971.
60. Mathus-Vliegen EM, Tytgat GN. Gastro-oesophageal reflux in obese subjects: Influence of overweight, weight loss and chronic gastric balloon distension. *Scand J Gastroenterol* 2002;37:1246–1252.
61. Rantanen TK, Rasanen JV, Sihvo EI, et al. The impact of antireflux surgery on oxidative stress of esophageal mucosa caused by gastroesophageal reflux disease: 4-yr follow-up study. *Am J Gastroenterol* 2006;101:222–228.
62. Modzelewski B. Effect of arachidonic acid peroxidation products on the development of gastroesophageal reflux disease [in Polish]. *Pol Merk Lekarski* 2004;16:532–535.
63. Tandon R, Khanna HD, Dorababu M, Goel RK. Oxidative stress and antioxidants status in peptic ulcer and gastric carcinoma. *Indian J Physiol Pharmacol* 2004;48:115–118.
64. Bandyopadhyay D, Bandyopadhyay A, Das PK, Reiter RJ. Melatonin protects against gastric ulceration and increases the efficacy of ranitidine and omeprazole in reducing gastric damage. *J Pineal Res* 2002;33:1–7.
65. Bhattacharya A, Ghosal S, Bhattacharya SK. Effect of fish oil on offensive and defensive factors in gastric ulceration in rats. *Prostaglandins Leukot Essent Fatty Acids* 2006;74:109–116.
66. Pereira R de S. Regression of gastroesophageal reflux disease symptoms using dietary supplementation with melatonin, vitamins and amino acids: Comparison with omeprazole. *J Pineal Res* 2006;41:195–200.
67. Lu XG, Zhan LB, Feng BA, et al. Inhibition of growth and metastasis of human gastric cancer implanted in nude mice by D-limonene. *World J Gastroenterol* 2004;15:2140–2144.
68. Larkworthy W, Holgate PF. Deglycyrrhizinized liquorice in the treatment of chronic duodenal ulcer: A retrospective endoscopic survey of 32 patients. *Practitioner* 1975;215:787–792.
69. Khayyal MT, el-Ghazaly MA, Kenawy SA, et al. Antilulcerogenic effect of some gastrointestinally acting plant extracts and their combination. *Arzneimittelforschung* 2001;51:545–553.
70. Das SK, Das V, Gulati AK, Singh VP. Deglycyrrhizinized liquorice in aphthous ulcers. *J Assoc Physicians India* 1989;37:647.
71. Paraschos S, Magiatis P, Mitakou S, et al. In vitro and in vivo activities of Chios mastic gum extracts and constituents against *Helicobacter pylori*. *Antimicrob Agents Chemother* 2007;51:551–559.
72. Al-Said MS, Ageel AM, Parmar NS, Tariq M. Evaluation of mastic, a crude drug obtained from *Pistacia lentiscus* for gastric and duodenal anti-ulcer activity. *J Ethnopharmacol* 1986;15:271–278.
73. Al-Habbal MJ, Al-Habbal Z, Huwez FU. A double-blind controlled clinical trial of mastic and placebo in the treatment of duodenal ulcer. *Clin Exp Pharmacol Physiol* 1984;11:541–554.
74. Weberg R, Berstad A. Symptomatic effect of a low-dose antacid regimen in reflux oesophagitis. *Scand J Gastroenterol* 1989;24:401–406.

---

**Chris D. Meletis, N.D.**, is the executive director of the Institute for Healthy Aging, in Carson City, Nevada, and is an associate professor of natural pharmacology at the National College of Naturopathic Medicine, in Portland, Oregon. **Nieske Zabriskie, N.D.**, is a naturopathic doctor in Beaverton, Oregon.

---

To order reprints of this article, write to or call: Karen Ballen, *ALTERNATIVE & COMPLEMENTARY THERAPIES*, Mary Ann Liebert, Inc., 140 Huguenot Street, 3rd Floor, New Rochelle NY 10801, (914) 740-2100.