CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Functional Heartburn: Expert Review

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BEST PRACTICE ADVICE 1: A diagnosis of functional heartburn should be considered when retrosternal burning pain or discomfort persists despite maximal (double-dose) proton pump inhibitor (PPI) therapy taken appropriately before meals during a 3-month period. **BEST PRACTICE ADVICE 2:** A diagnosis of functional heartburn requires upper endoscopy with esophageal biopsies to rule out anatomic and mucosal abnormalities, esophageal high-resolution manometry to rule out major motor disorders, and pH monitoring off PPI therapy (or pH-impedance monitoring on therapy in patients with proven gastroesophageal reflux disease [GERD]), to document physiologic levels of esophageal acid exposure in the distal esophagus with absence of reflux–symptom association (ie, negative symptom index and symptom association probability). **BEST PRACTICE ADVICE 3:** Overlap of functional heartburn with proven GERD is diagnosed according to Rome IV criteria when heartburn persists despite maximal PPI therapy in patients with history of proven GERD (ie, positive pH study, erosive esophagitis, Barrett's esophagus, or esophageal ulcer), and pH impedance testing on PPI therapy demonstrates physiologic acid exposure without reflux–symptom association (ie, negative symptom index and symptom association probability). **BEST PRACTICE ADVICE 4:** PPIs have no therapeutic value in functional heartburn, the exception being proven GERD that overlaps with functional heartburn. **BEST PRACTICE ADVICE 5:** Neuromodulators, including tricyclic antidepressants, selective serotonin reuptake inhibitors, tegaserod, and histamine-2 receptor antagonists have benefit as either primary therapy in functional heartburn or as add-on therapy in functional heartburn that overlaps with proven GERD. **BEST PRACTICE ADVICE 6:** Based on available evidence, acupuncture and hypnotherapy may have benefit as monotherapy in functional heartburn, or as adjunctive therapy combined with other therapeutic modalities. **BEST PRACTICE ADVICE 7:** Based on available evidence, anti-reflux surgery and endoscopic GERD treatment modalities have no therapeutic benefit in functional heartburn and should not be recommended.

Keywords: Functional Heartburn; Nonerosive Reflux Disease; Ambulatory Reflux Monitoring; High-Resolution Manometry.

Functional heartburn consists of retrosternal burning similar to that experienced in gastroesophageal reflux disease (GERD), but without evidence of abnormal esophageal acid exposure on ambulatory reflux monitoring, major esophageal motor disorders on high-resolution manometry, or esophageal mucosal pathology (such as erosive esophagitis, Barrett's esophagus, or eosinophilic esophagitis) on endoscopy with esophageal biopsies.[1] In contrast, despite identical clinical presentation, a diagnosis of nonerosive reflux disease (NERD) requires the presence of abnormal esophageal acid exposure on ambulatory reflux monitoring.[1,2] The prevalence of functional heartburn in the community is difficult to determine, but as many as 21%–39% of patients with heartburn refractory to proton pump inhibitor (PPI) undergoing pH-impedance monitoring fulfill criteria for functional heartburn.[3–6] Functional heartburn is important to recognize because without investigation, this condition might be considered equivalent with GERD, and treating physicians could continue acid suppressive therapy unnecessarily or escalate antireflux treatments, which might even lead to harm. Importantly, acid suppressive therapies are typically not effective, and antireflux surgery or other invasive antireflux modalities should be avoided. This is primarily because acid does not trigger functional heartburn symptoms, as evident from acid perfusion studies comparing functional heartburn to NERD patients.[7]

There have been advances in esophageal testing to differentiate functional heartburn from refractory reflux disease. Studies of afferent nerves in esophageal mucosa have demonstrated that functional heartburn patients have deep localization of nerves similar to that of healthy volunteers rather than superficial localization seen in NERD, supporting a nociceptive pathophysiologic mechanism in functional heartburn similar to other functional gastrointestinal disorders.[8] Furthermore, balloon distension studies have demonstrated a similar degree of visceral hypersensitivity in the esophagus and the rectum in patients with functional heartburn, supporting a generalized increase in perception of visceral stimuli.[9] There is also a high likelihood of anxiety and other affective disorders in patients with functional heartburn.[10] These etiological factors indicate that functional heartburn is a separate entity that warrants multimodal management distinct from GERD

patients because patients with functional heartburn, either alone or overlapping with GERD, will likely not improve unless esophageal perception and underlying affective disorders are managed adequately.

This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Gastroenterology*. This review highlights clinical presentation, modern diagnosis, and management of functional heartburn.

Clinical Presentation

Many patients with GERD-like symptoms who fail PPI therapy may, in fact, have a functional disorder, including functional heartburn,[5,11,12] diagnosed in as many as one-quarter of patients with persistent heartburn on PPI therapy, either by itself or overlapping with established GERD.[13] Heartburn is defined as a burning sensation with pain or discomfort that starts from the epigastrium and radiates retrosternally. While patients may use various terms to describe GERD-like symptoms, including reflux, heartburn, regurgitation, chest pain, chest discomfort, fullness, throat burning, mouth burning, epigastric burning, water brash, belching, and sour and bitter taste in the mouth, their association with gastroesophageal reflux needs to be determined by careful history.[14] The clinical presentation of functional heartburn is similar to heartburn due to GERD, but the diagnosis of functional heartburn is commonly considered only in patients with persistent heartburn symptoms, typically without improvement (or even worsening) while on PPI therapy. Diagnostic criteria for NERD, reflux hypersensitivity (heartburn triggered by physiologic reflux episodes) and functional heartburn were redefined by Rome IV criteria,[1] leading to stricter diagnostic criteria and less confusion between true GERD/NERD and functional heartburn.[15]

Clinical description of heartburn, whether obtained in the office by a primary care provider/gastroenterologist, or from validated symptom questionnaires, has only modest sensitivity and specificity compared to objective reflux evidence on testing, or to symptom relief with PPI therapy.[16–18] Furthermore, the Montreal Consensus heartburn-related definitions encompass not just true GERD, but also functional esophageal disorders, both reflux hypersensitivity and functional heartburn, as well as various degrees of overlap between GERD and functional esophageal disorders.[19,20] This overlap with functional disorders, as well as other non-GERD mechanisms for heartburn, may be partly responsible for the 40% dissatisfaction rate with PPI therapy in patients with heartburn.[21] In a prospective study of 366 patients with refractory heartburn who were enrolled in a Veterans Affairs study, 99 (27%) had functional heartburn on the basis of negative esophageal testing, including pH-impedance monitoring off acid suppression,

while 23 (6%) had non-GERD esophageal disorders, and 7 (2%) had esophageal motility disorders.

The lack of, or partial, symptom relief despite optimal therapy is an important starting point for consideration of the diagnosis of functional heartburn.[1] The impact of heartburn symptoms on quality of life needs to be factored into clinical decision-making and the degree of invasive investigation needed for evaluation and management.[22,23] The purpose of invasive investigation is to make a conclusive diagnosis in order to provide precision, personalized management of esophageal symptoms targeted toward the mechanisms of symptom generation.[2,20] In functional heartburn, this involves not just initiation of neuromodulators, but potentially, discontinuation of ineffective approaches, such as acid suppressive therapy. Thus, functional heartburn should be considered only in patients who report troublesome heartburn symptoms at least 2 times per week for the previous 3 months despite double-dose PPI taken appropriately before meals.[1] The presence of concurrent functional gastrointestinal disorders and somatization disorder should also be considered.[24] Indeed, both functional dyspepsia and irritable bowel syndrome are frequently associated with functional heartburn[10,25] and negatively impact symptom response to therapies.[26–28]

Diagnosis

Endoscopy is indicated in patients with heartburn who fail an adequate trial of empirical PPI therapy in order to rule out other esophageal or gastric diseases, including structural abnormalities, such as strictures or webs, eosinophilic esophagitis, pill-induced esophagitis, Barrett's esophagus, and neoplasia (Figure 1). The prevalence of erosive esophagitis is <10% in patients refractory to PPI therapy[29,30]; when identified, this indicates poorly controlled persistent acid reflux or true refractory GERD according to Rome IV criteria.[1] Although the prevalence of eosinophilic esophagitis does not exceed 8% in patients presenting with refractory heartburn,[30–32] eosinophilic esophagitis should be ruled out by adequate biopsy sampling to comply with the current definition of functional heartburn.

Because most patients with refractory heartburn unresponsive to PPIs have normal endoscopy and esophageal biopsies, ambulatory reflux monitoring is performed to evaluate for evidence for gastroesophageal reflux (Figure 1). By definition, there should be no link between reflux and symptoms in functional heartburn. According to recent consensus statements,[1,33] patients without previous evidence of pathologic gastroesophageal reflux (ie, significant peptic esophagitis, Barrett's esophagus, or positive pH study) should be investigated using pH or pH-impedance monitoring off anti-secretory medications to document the level of baseline reflux. High-resolution manometry is typically performed for localizing the proximal border of the lower esophageal sphincter for placement of pH and pH-impedance catheters, which should be evaluated for the presence of major esophageal motor disorders, which can be
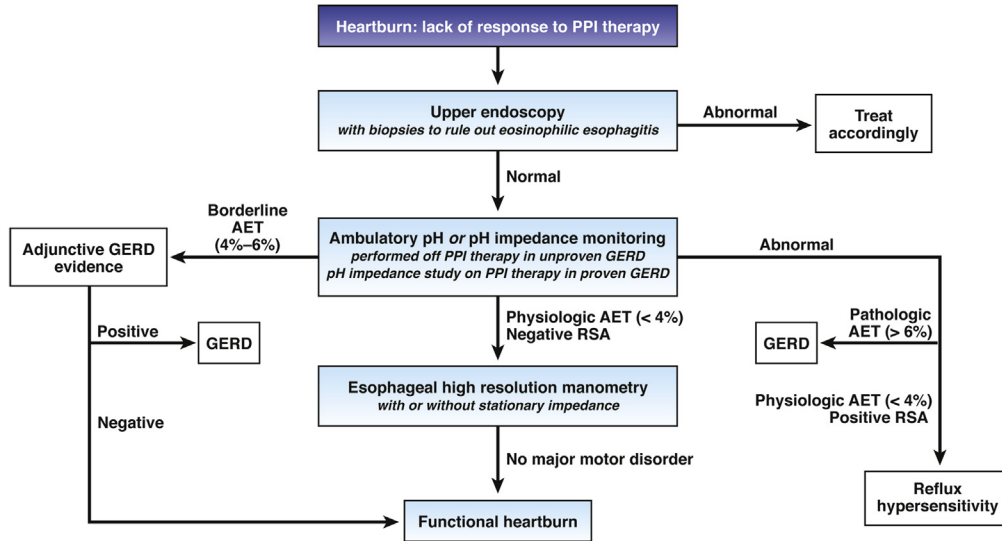
AET, acid exposure time; RSA, reflux-symptom association; GERD, gastroesophageal reflux disease

Figure 1. Flow diagram demonstrating evaluation of persisting heartburn symptoms despite maximal acid suppression. Endoscopy with biopsies to rule out eosinophilic esophagitis is the first step.[1] Ambulatory reflux monitoring (either pH alone or pH-impedance monitoring) is performed off acid suppression in unproven GERD[2] (no prior esophagitis, Barrett's esophagus, or peptic stricture, and no prior positive pH study), and on therapy in proven GERD. Functional heartburn is diagnosed when esophageal acid burden is physiologic (acid exposure time <4%), in the absence of esophageal mucosal disorders on endoscopy and major motor disorders on esophageal high-resolution manometry.[1] When acid exposure time is borderline (4%–6%), absence of adjunctive reflux evidence (ie, normal esophageal biopsies, normal baseline impedance >2292 ohms, normal PSPW index >0.61, negative reflux-symptom association, <40 reflux episodes, normal esophagogastric junction, and esophageal body motor profile on high-resolution manometry)[2] indicates the possibility of functional heartburn. Functional heartburn coexists with GERD in patients with proven GERD otherwise fulfilling criteria for functional heartburn.

associated with esophageal perceptive symptoms, including heartburn and chest pain (Figure 1).[34] The prevalence of heartburn has been reported to be as high as 35% in achalasia[35,36]; while this diagnosis can be suspected on upper endoscopy, diagnosis requires esophageal high-resolution manometry. The presence of a minor motor disorder, such as ineffective esophageal motility, does not preclude the diagnosis of functional heartburn, provided reflux disease has been excluded.

The most relevant and reliable parameter on ambulatory reflux monitoring is the percent time pH is <4 in the distal esophagus, termed the *acid exposure time* (AET). AET is considered to be reliably normal below 4% and abnormal above 6%.[33] Abnormal AET has been reported in 26.3%–72% of patients in refractory heartburn.[25,28,37–39] Extending recording time to 48 or 96 hours with the wireless pH monitoring system increases the likelihood of detecting reflux disease; several studies have shown a highest diagnostic yield when the worst day is considered for the diagnosis of GERD, thus reducing the proportion of patients with functional heartburn.[39–41]

Adding impedance to pH monitoring is helpful for the characterization of reflux episodes, as it allows detection of weakly acidic reflux episodes, thereby increasing the likelihood of a temporal correlation between symptoms and reflux episodes.[42] Overall, studies performed with 24-hour pH-impedance monitoring report that between 21% and 40% of patients with refractory reflux symptoms have functional heartburn.[25,28,38,43] However, in patients studied

off therapy, the added value of pH impedance compared to pH alone monitoring is relatively limited.[43,44]

Both pH alone and pH-impedance monitoring provide analysis of the temporal relationship between reflux events and symptoms. In patients with normal AET, symptom index (SI), and symptom association probability (SAP) are used to distinguish between functional heartburn and reflux hypersensitivity. These indices reflect the occurrence of symptoms (ie, activation of the event marker by the patient) and reflux events during the same 2-minute time window. SI is a simple parameter that determines the proportion of symptoms that are reflux-related (positive if >50%). SAP uses a statistical formula, Fisher exact test, which determines the probability that the observed temporal relationship between symptoms and reflux has not occurred by chance (positive if ≥95%). The 2 indices are complementary, but neither SI nor SAP are 100% reliable, and their relevance has been challenged by some authors, depending on frequency of symptoms and reflux occurrence.[45] Functional heartburn can be reliably diagnosed in a patient with refractory heartburn, normal endoscopy, and AET, and negative SI and SAP. Reflux hypersensitivity can be diagnosed if both SI and SAP are positive, but there is currently no consensus as to which should be taken into account if a discrepancy exists between SI and SAP.[33] The reflux–symptom association analysis is closely related to proper performance of the reflux monitoring procedure and meticulous analysis protocols, including careful selection of symptoms of interest. Patients must be instructed on how to

use the event marker and accurately fill in the symptom diary. A modification of the reflux–symptom association involves administration of acidic juice of known pH during pH monitoring to determine whether symptoms can be elicited, and to evaluate pH recovery patterns that can distinguish between NERD and functional esophageal syndromes, including functional heartburn.[46]

Patients with proven GERD (evidenced by previous reflux esophagitis, Barrett's esophagus, or abnormal pH monitoring) and persistent symptoms should be investigated on double-dose PPI therapy with pH-impedance monitoring, which allows the detection of weakly acidic reflux events. Overall, pH-impedance monitoring on therapy can establish a relationship between symptoms and acid reflux or weakly acidic reflux in 10% and 30%–40% of patients, respectively,[38,44,47] while negative studies are found in 50%–60% of patients. Of note, some patients may have an overlap between GERD and functional heartburn. In these patients with an abnormal baseline AET, reflux monitoring should be performed on PPI therapy with pH-impedance monitoring. Diagnosis of functional heartburn overlapping with GERD is established if AET is normal and both SI and SAP are negative for both acid and weakly acidic reflux events, according to criteria introduced for the first time in Rome IV.[1] Because this concept of overlapping GERD and functional disorders has been introduced recently,[1,11] little is known about the clinical and psychological characteristics of these patients.

Additional metrics may be useful when the results of ambulatory reflux monitoring is borderline or inconclusive, for example, if AET is between 4% and 6%, or if discrepancies exist between SI and SAP. Mean nocturnal baseline impedance (MNBI) measured by pH-impedance tracings has been linked to mucosal damage.[48] Some studies suggest that low MNBI (<2292 ohms), which functions as a surrogate marker of reflux-induced altered mucosal integrity, may help to differentiate patients with reflux-related symptoms from patients with functional heartburn.[49–52] The post-reflux swallow-induced peristaltic wave (PSPW) index, that is, the proportion of reflux episodes on pH impedance monitoring followed by a swallow, reflects the integrity of primary peristalsis stimulated by reflux episodes.[50] A normal PSPW index (>0.61) may help to distinguish patients with functional heartburn from those with GERD.[10] Considering the day-to-day variability and the lack of sensitivity of pH/pH-impedance studies, both MNBI and PSPW index may prove to be helpful for the management of patients with refractory heartburn, but more data are needed to recommend the use of these metrics, including inter-observer reproducibility, normal values, and relevant cutoff values in clinical practice.

Treatment

Although functional heartburn does not have long-term pathologic consequences, the impact on patient quality of life can be substantial and very limiting. The treatment goals of functional heartburn are 3-fold: symptom improvement and, ideally, symptom resolution; prevention of symptom recurrence; and improvement of health-related quality of life. The main therapeutic modalities include lifestyle modifications, pharmacotherapy with neuromodulators, alternative and complementary medicine, and psychological intervention (Table 1). A subset of patients may require more than one therapeutic modality for acceptable symptom control.

Lifestyle Modifications

There is limited evidence that improvement in quality of night-time sleep can positively impact functional heartburn,[5] as an increase in stressful activities, including loud noise and sleep deprivation, can increase perception of esophageal symptoms.[53,54] Sleep disturbances have been identified as particularly common as heartburn and regurgitation symptoms increase in severity and frequency.[55] Additionally, patients who report predictable and repetitive triggering of heartburn symptoms with certain food items or physical activities may benefit from avoiding these.[56] However, there is no conclusive evidence that further lifestyle modifications have a role in functional heartburn in contrast to GERD.

Pharmacotherapy

Antireflux medications, specifically PPIs, have no therapeutic role in functional heartburn, unless there is an overlap between GERD and functional heartburn.[11,57] If such overlap is demonstrated on upper endoscopy and/or ambulatory reflux monitoring, PPI therapy can be maintained while targeted therapy for functional heartburn is initiated.[58] If workup demonstrates no conclusive evidence of GERD,[2] an attempt to discontinue PPI therapy is warranted. An exception to this rule is histamine 2 receptor antagonists, which may have an independent benefit in functional heartburn from an esophageal pain modulatory effect.[59]

Neuromodulators have established value in the treatment of functional esophageal disorders, based on experience with noncardiac chest pain. Commonly used neuromodulators fall into the following categories: tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin modulators (agonists and antagonists), and serotonin-norepinephrine reuptake inhibitors.[58,60] Neuromodulators alter neuronal function without acting as neurotransmitters, with a primary central action and a minor secondary peripheral action on esophageal pain.[58]

Several neuromodulators have been studied in functional heartburn (Table 2). In a double-blind, placebo-controlled trial, 83 functional heartburn and reflux hypersensitivity patients were randomized to either placebo or imipramine 25 mg daily for a period of 8 weeks.[61] Although there was no difference in improvement of heartburn between imipramine and placebo, there was significant improvement in quality of life with imipramine using per-protocol analysis ($P = .045$). Fluoxetine is the only selective serotonin reuptake inhibitor studied in functional heartburn, where patients with persisting heartburn and

Table 1. Therapeutic Options for Functional Heartburn

Therapeutic options
Lifestyle modifications
Improved sleep experience
Pharmacotherapy
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Tegaserod
Histamine 2 receptor antagonists
Melatonin
Alternative/complementary medicine
Acupuncture
Psychological intervention
Hypnotherapy

negative endoscopy who failed standard-dose, once-daily omeprazole were randomized to double-dose omeprazole, add-on fluoxetine 20 mg daily, or add-on placebo.[62] Those receiving fluoxetine demonstrated a significantly greater improvement in proportion of heartburn-free days (median, 35.7 days) compared with those receiving double-dose PPI (median, 7.14 days; $P < .001$) and placebo (median, 7.14 days; $P < .001$). This superior therapeutic effect of fluoxetine was seen only in the subset of patients with normal pH test.

In a double-blind, placebo-controlled trial, patients with functional heartburn were randomized to receive tegaserod (a 5-HT4 receptor partial agonist) at a 6-mg twice-daily dose vs placebo for 14 days.[63] Those receiving tegaserod tolerated higher balloon pressures ($P = .04$) and maximum wall tension ($P = .0004$) compared with placebo during balloon distension studies. Further, tegaserod significantly decreased the frequency of heartburn ($P = .004$), regurgitation ($P = .048$), and distress from regurgitation ($P = .039$) compared with placebo, and with a higher global preference for tegaserod over placebo among the patients in the study.

The histamine 2 receptor antagonists ranitidine has been shown to have a pain modulatory effect by decreasing chemoreceptor sensitivity to esophageal acid perfusion at a dose of 150 mg daily in functional heartburn.[59] However, certain brands of this medication are now subject to a US Food and Drug Administration recall due to contamination with agents that may have a carcinogenic effect. Melatonin, which also has a pain modulatory effect in the gastrointestinal tract, has demonstrated efficacy in various functional pain syndromes. In one study, functional heartburn patients randomized to receive melatonin 6 mg demonstrated a significant improvement in GERD health-related quality of life compared with nortriptyline 25 mg ($P = .0015$) and placebo ($P < .0001$) taken at bedtime for a period of 3 months.[64]

Despite the limited numbers of trials assessing the value of neuromodulators in functional heartburn, these medications appear to have a therapeutic role, especially as first-line therapy.[65] Treatment with tricyclic antidepressants should follow the "low and slow" approach, where the lowest dose of tricyclic antidepressant is initially used and is increased by weekly increments of the same dose to a goal of 50–75 mg daily.[60] These medications are commonly administered at bedtime because of somnolence, which, in turn, can improve patients sleep experience and augment their analgesic effect.[54]

Alternative and Complementary Medicine

There are currently no studies that evaluated the primary role of various alternative and complementary medicine techniques in functional heartburn. However, in one small sample study of 30 heartburn patients who failed standard-dose PPI and were randomized to add-on acupuncture or double-dose PPI, 10 acupuncture sessions over 4 weeks provided a significant decrease in the mean daytime heartburn, night-time heartburn, and acid regurgitation scores compared with those receiving double-dose PPI.[66] Mean general health score was significantly improved only in those receiving acupuncture. However, it is unclear what proportion of the study participants had functional heartburn, either solely or overlapping with GERD.

Table 2. Neuromodulator Trials in Functional Heartburn

Class	Drug	Dose	No. of subjects	Outcome	Study type
TCA	Imipramine	25 mg/d	83	No difference than placebo in symptom relief Improved QOL	RCT
SSRI	Fluoxetine	20 mg/d	144	Improvement in percentage of heartburn-free days	RCT
Serotonin agonist (5-HT4)	Tegaserod	6 mg bid	42	Decreased frequency of heartburn, regurgitation, and distress	RCT
H2RA	Ranitidine	150 mg	18	Decrease in esophageal sensitivity	RCT
Miscellaneous anxiolytics, sedatives, and hypnotics	Melatonin	6 mg bid	60	Improved GERD-HRQOL	RCT

bid, twice per day; H2RA, histamine 2 receptor antagonist; HRQOL, health-related quality of life; QOL, quality of life; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Psychological Intervention

Only hypnotherapy has been evaluated in patients with functional heartburn. In a very small study that included 9 patients with functional heartburn, 7 weekly sessions of esophageal-directed hypnotherapy were tolerated very well, with significant improvement in heartburn symptoms, visceral anxiety, quality of life, and a trend toward improvement in catastrophizing.[67]

Anti-Reflux Surgery or Endoscopic Treatment

Both anti-reflux surgery and endoscopic treatment for GERD should be avoided in patients with functional heartburn. Normal preoperative esophageal acid exposure has been shown to be a risk factor for poor outcomes after surgical fundoplication.[68,69]

Prognosis

Similar to other functional disorders, functional heartburn does not carry potential long-term complications, but is associated with reduced quality of life.[22] Because there can be overlap between true GERD and functional heartburn, and because a 24-hour ambulatory reflux monitoring study can miss abnormal esophageal acid exposure because of day-to-day variation,[70] long-term complications of GERD (eg, Barrett's esophagus and peptic stricture) can potentially be identified in patients thought to have functional heartburn. However, this is anticipated to be rare, and the vast majority of patients with functional heartburn will have compromised quality of life rather than organic complications over time.

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Conflicts of interest

The authors disclose the following: Ronnie Fass: Ironwood, Takeda, Chinoin (consulting); AstraZeneca, Takeda, Horizon, Diversitek, Eisai Pharmaceuticals (speaking); and Ironwood, Salix (research). Frank Zerbib: Reckitt Benckiser (consulting). C. Prakash Gyawali: Medtronic, Diversatek (teaching and consulting) and Ironwood, Quintiles (consulting).