Reflux hypersensitivity - what is in the name?

Takahisa Yamasaki and Ronnie Fass
Division of Gastroenterology and Hepatology, Esophageal and Swallowing Center, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, USA

REVIEW ARTICLE

RESUMEN

La hipersensibilidad al reflujo, que Roma IV introdujo recientemente como un nuevo trastorno funcional del esófago, se define por la presencia de síntomas típicos de acidez estomacal en presencia de biopsias y endoscopia superior normales, exposición normal al ácido esofágico y una correlación positiva entre los síntomas del paciente y eventos de reflujo. La hipersensibilidad al reflujo es muy común y generalmente se superpone con otros trastornos gastrointestinales funcionales y a menudo se asocia con algún tipo de comorbilidad psicológica. La hipersensibilidad esofágica debida a la sensibilización periférica y/o central se ha considerado como el principal mecanismo subyacente para la aparición de síntomas en pacientes con hipersensibilidad al reflujo. Además, los factores centrales como el estrés, los trastornos psicológicos por hipervigilancia y la falta de sueño, desempeñan un papel importante en la mejora de la percepción de los estímulos intraesofágicos. El diagnóstico se realiza mediante el uso de una combinación de endoscopia con biopsias, pruebas de pH inalámbricas o pruebas de impedancia de pH y manometría esofágica de alta resolución. La hipersensibilidad al reflujo se trata con neuromoduladores, como los antidepresivos tricíclicos (ATC), los inhibidores selectivos de la recaptación de serotonina (ISRS). Sin embargo, en algunos casos, se debe considerar un mejor control del reflujo gastroesofágico ya sea medicamente, endoscópicamente o incluso quirúrgicamente. La intervención psicológica y la medicina alternativa/complementaria también deben ser asimismo consideradas. (GastroLatam Rev. 2018;2:5-17)

Corresponding author: Ronnie Fass, ronnie.fass@gmail.com

INTRODUCTION

The recently published Rome IV criteria have introduced two functional esophageal disorders with heartburn as their predominant symptom, functional heartburn, and reflux hypersensitivity. What differentiate between functional heartburn and reflux hypersensitivity is the presence of heartburn symptoms that correlate with gastroesophageal reflux events in the latter group. The main impact of Rome IV on functional esophageal disorders was the recognition that reflux hypersensitivity, previously known as the hypersensitive esophagus, should be a separate disorder.

The position of reflux hypersensitivity within functional esophageal disorders has evolved through the different Rome criteria. Rome II suggested that patients with heartburn and normal upper endoscopy are divided into those with non-erosive reflux disease (NERD) and those with functional heartburn. The functional heartburn group was composed from patients with hypersensitive esophagus (those with reflux-related symptoms) and patients with non-reflux-related heartburn. Similarly, Rome III proposed that patients with heartburn and normal endoscopy are divided into those with NERD and those with functional heartburn. However, unlike Rome II, Rome III divided the NERD group into patients with abnormal esophageal acid exposure, the hypersensitive esophagus, and patients with non-reflux-related symptoms who are responsive to proton-pump inhibitor (PPI) treatment. Subsequently, Rome IV criteria proposed the separation of the reflux hypersensitivity group.

ABSTRACT

Reflux hypersensitivity, which was recently introduced by Rome IV as a new functional esophageal disorder, is defined by the presence of typical heartburn symptoms in the presence of normal upper endoscopy and biopsies, normal esophageal acid exposure, and a positive correlation between patient’s symptoms and reflux events. Reflux hypersensitivity is very common, generally overlaps with other functional gastrointestinal disorders and is often associated with some type of psychological comorbidity. Esophageal hypersensitivity due to peripheral and/or central sensitization has been considered as the main underlying mechanism for the occurrence of symptoms in reflux hypersensitivity patients. In addition, central factors, including stress, hypervigilance psychological disorders, and sleep deprivation, play an important role in enhancing perception of intraesophageal stimuli. Diagnosis is made using a combination of endoscopy with biopsies, wireless pH testing or pH-impedance testing, and high-resolution esophageal manometry. Reflux hypersensitivity is treated with neuromodulators such as tricyclic antidepressants and selective serotonin reuptake inhibitors. In some cases, however, better gastroesophageal reflux control should be considered either medically, endoscopically, or even surgically. Psychological intervention and alternative/complementary medicine should be entertained as well.

Key words: Reflux hypersensitivity. Functional esophageal disorders. Rome IV. Neuromodulators.
from the gastroesophageal reflux disease (GERD) groups and heartburn-related functional esophageal disorders, presenting it as a new functional esophageal disorder. In addition, Rome IV suggested for the 1st time that functional esophageal disorders can overlap with GERD, including reflux hypersensitivity. The use of high-dose PPI (twice daily) may unmask the presence of functional esophageal disorders such as reflux hypersensitivity, which is responsible for patients’ persistent heartburn symptoms.

Reflux hypersensitivity is one of the five functional esophageal disorders (Fig. 1). The others include functional heartburn, functional chest pain, functional dysphagia, and globus. Functional esophageal disorders have been defined as “chronic esophageal symptoms in the absence of identifiable structural, inflammatory, motor, or metabolic mechanisms as the etiology”. While functional esophageal disorders have been recognized to be chronic and with a considerable impact on patients’ quality of life and thus health-care utilization, the included patient population may alter overtime as new diagnostic tools are incorporated into our clinical armamentarium. Rome IV included new diagnostic techniques in its proposed workup of patients suspected of having functional esophageal disorders such as impedance+pH, high-resolution esophageal manometry (HERM), and the wireless pH capsule. With the introduction of new and more accurate diagnostic tools, it is likely that functional esophageal disorders such as reflux hypersensitivity will evolve again. Some investigators believe that these tools will diagnose new organic disorders that have not been recognized before or will identify patients with currently known disorders. Regardless, we believe that even with the development of new diagnostic tools, there is always going to be a considerable group of patients with functional esophageal disorders.

**DEFINITION**

According to Rome IV, the definition of reflux hypersensitivity include presence of retrosternal symptoms of heartburn and chest pain, normal endoscopy, and absence of evidence that eosinophilic esophagitis is the cause of the symptoms, absence of major esophageal motor disorders (achalasia, esophagogastric junction outflow obstruction, distal esophageal spasm, jackhammer esophagus, and absent contractility), and evidence of triggering of symptoms by reflux events despite normal esophageal acid exposure on pH or pH-impedance monitoring (response to antisecretory therapy does not exclude the diagnosis) (Table 1). Criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least twice a week. Furthermore, overlap could exist between GERD and reflux hypersensitivity.

The most important component of the definition of reflux hypersensitivity is the presence of positive correlation between symptoms and gastroesophageal reflux events (acidic, weakly acidic, and/or weakly alkaline), using symptom index (SI) and/or symptom association probability (SAP).

Comparison with the Rome III criteria is unavailable because reflux hypersensitivity was not part of functional esophageal
TABLE 1. ROME IV DEFINITION OF REFLUX HYPERSENSITIVITY

Must include all of the following:

1. Retrosternal symptoms including heartburn and chest pain*

2. Normal endoscopy and absence of evidence that eosinophilic esophagitis is the cause of the symptoms

3. Absence of major esophageal motor disorders**

4. Evidence of triggering of symptoms by reflux events despite normal acid exposure on pH or pH-impedance monitoring†

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least twice a week.

**Achalasia/EGJ outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent contractility.

†Response to antisecretory therapy does not exclude the diagnosis.

---

FIGURE 1. Functional esophageal disorders (Rome IV).

- **Functional esophageal disorders**
  - Absence of major esophageal motor disorders (achalasia/EGJ outflow obstruction, distal esophageal spasm, jackhammer esophagus, absent peristalsis).
  - Absence of evidence that gastroesophageal reflux disease or eosinophilic esophagitis are the cause of the symptom.

- **Functional dysphagia**
  - Sense of solid and/or liquid foods sticking, lodging, or passing abnormally through the esophagus.
  - Absence of evidence that esophageal mucosal or structural abnormality is the cause of the symptom.

- **Functional chest pain**
  - Retrosternal chest pain or discomfort; cardiac causes should be ruled out.
  - Absence of associated esophageal symptoms, such as heartburn and dysphagia.

- **Functional heartburn**
  - Burning retrosternal discomfort or pain.
  - No symptom relief despite optimal antisecretory therapy.

- **Globus**
  - Persistent or intermittent, nonpainful, sensation of a lump or foreign body in the throat with no structural lesion identified on physical examination, laryngoscopy, or endoscopy.
    a. Occurrence of the sensation between meals.
    b. Absence of dysphagia or odynophagia.
    c. Absence of a gastric inlet patch in the proximal esophagus.

- **Reflux hypersensitivity**
  - Retrosternal symptoms including heartburn and chest pain.
  - Evidence of triggering of symptoms by reflux events despite normal acid exposure on pH or pH-impedance monitoring (response to antisecretory therapy does not exclude the diagnosis).
disorders. However, the definition of hypersensitive esophagus has been consistent with the current definition of reflux hypersensitivity⁴.

THE NAME

The term reflux hypersensitivity was proposed by the Rome IV committee for functional esophageal disorders⁴. Originally, the reflux hypersensitivity patient population was named the hypersensitive esophagus, which was defined as heartburn patients with normal upper endoscopy and esophageal acid exposure but with positive correlation between symptoms and acid reflux events⁴. However, the committee felt that the term hypersensitive esophagus is too close to the term esophageal hypersensitivity, which describes the main underlying mechanism of all functional esophageal disorders. Due to the clear correlation between symptoms and reflux events in the context of normal esophageal acid exposure, the name reflux hypersensitivity was proposed. In addition, because these patients demonstrate increased esophageal sensitivity to any type of gastroesophageal reflux, a more generic term was chosen. Furthermore, there was also an attempt to avoid the addition of the term “functional” into the name, which still provides a clear indication of what the disorder is all about.

It was evident to the committee from the get go that the main criticism that will be leveled at this disorder is the reliance on SIs for the diagnosis³. Queries, of which of the SIs to use for the diagnosis and which functional esophageal testing, are the most reliable in generating accurate SIs, would likely be raised.

The hypersensitive esophagus group has been studied for almost 4 decades and has been extensively reviewed by all Rome committees, including Rome III and II³. In none of these evaluations, the presence of this group was questioned. What was debated if this group of patients is a functional esophageal disorder or has a low-intensity GERD. All Rome committees recognized the limitations of SIs but at the same time understood that there is a significant subset of heartburn patients who appear to develop reflux-related symptoms in the background of physiological range of esophageal acid exposure.

What the Rome IV committee for functional esophageal disorders did was to put to rest the decades-long debate where these patients with reflux hypersensitivity belong to. It was decided that they represent a unique type of functional esophageal disorder which is different from functional heartburn or other functional esophageal disorders. It was the committee’s opinion that by now there are sufficient data to support having reflux hypersensitivity as a separate functional esophageal disorder.

EPIDEMIOLOGY

The prevalence of reflux hypersensitivity in the general population and in those with heartburn is unknown. A recent study that evaluated 82 heartburn patients with normal endoscopy demonstrated using impedance+pH that 14.6% had reflux hypersensitivity (normal esophageal acid exposure but positive SI and
SAP). The authors also demonstrated that 21.9% had functional heartburn (normal esophageal acid exposure and negative SI and SAP)\(^5\). In this small study, both functional esophageal disorders accounted for 36.5% of the heartburn patients who presented with normal endoscopy. Savarino et al. evaluated 329 endoscopy-negative patients with a pH-impedance monitoring off PPI treatment. The authors demonstrated that 130 (40%) of the patients had NERD, 120 (36%) reflux hypersensitivity, and 79 (24%) functional heartburn\(^6\). In this study, the two functional esophageal disorders counted for 60% of the heartburn patients with normal endoscopy. As compared with pH testing, pH-impedance allows also the association between non-acidic (weakly acidic + weakly alkaline) reflux and symptoms, expanding on the sensitivity of pH test that can correlate only acidic reflux with symptoms\(^7\).

The presence of reflux hypersensitivity in refractory heartburn patients has also been scarcely studied. Patel et al. reported that 77 (28.9%) of 266 refractory heartburn patients were found to have positive SAP with acidic and/or weakly acidic reflux in the context of normal esophageal acid exposure. Of those, 5 (6.5%) had positive SAP for acid only, 39 (50.6%) for weakly acidic reflux, and 33 (42.9%) for both acidic and weakly acidic reflux\(^8\). In another study, the authors assessed 78 PPI non-responders (failed PPI twice daily) patients with heartburn who underwent 24 h pH-impedance monitoring while on PPI. The authors demonstrated that 28 (36%) of the patients had reflux hypersensitivity and 43 (55%) patients had functional heartburn\(^9\). These results suggest that both functional heartburn and reflux hypersensitivity account for more than 90% of the heartburn patients who failed PPI twice daily.

Another study examined 111 patients with PPI-refractory NERD using esophageal manometry and pH-impedance off PPI treatment. The authors excluded 33 (29.7%) patients with esophageal motility disorders. Of the remaining 78 subjects, 22 (19.8%) patients were found to have functional heartburn, 34 (30.6%) patients had reflux hypersensitivity, and 22 (19.8%) patients had NERD\(^10\).

Overall, it appears that reflux hypersensitivity is less common than functional heartburn in both non-treated heartburn patients or those who failed PPI treatment.

**PATHOPHYSIOLOGY**

Esophageal hypersensitivity due to peripheral and/or central sensitization has been considered as the main underlying mechanism for the occurrence of symptoms in patients with reflux hypersensitivity. This is the same mechanism responsible for symptoms in the other functional esophageal disorders. Central neural mechanisms\(^11\), such as psychological comorbidity (anxiety and depression), stress, hypervigilance, and sleep deprivation, play an important role in modulating esophageal perception and cause patients to perceive low-intensity esophageal stimuli as being painful\(^12\). However, it is still unclear what role these central factors play in symptom generation of patients with reflux hypersensitivity.

Martinez et al. evaluated patients with predominant heartburn and normal endoscopy\(^13\). It was demonstrated that patients with NERD
were significantly more likely to show a SI > 75% compared to patients with normal acid exposure (either functional heartburn or reflux hypersensitivity). Patients with reflux hypersensitivity reported having heartburn at pH < 4 in 70.7% of the time compared with 12.7% of the time in those with functional heartburn, despite experiencing a similar mean number of heartburn episodes. This study supports the hypothesis that esophageal hypersensitivity is likely an important underlying mechanism for the generation of symptoms in patients with reflux hypersensitivity. In another study, the authors showed that the reflux hypersensitivity group had the highest number of patients demonstrating increased chemo- and mechanoreceptor sensitivity to acid perfusion and balloon distension, respectively, as compared with healthy subjects, patients with NERD and those with functional heartburn.

Reflux hypersensitivity patients demonstrated increased esophageal hypersensitivity to physiologic amounts of acid reflux. However, several studies also evaluated the role of non-acidic reflux or proximal esophageal migration of gastroesophageal reflux in patients with reflux hypersensitivity. One study, using impedance+pH, demonstrated that patients with reflux hypersensitivity have a significantly higher number of weakly acidic reflux episodes as well as a higher rate of proximal migration of reflux events compared to functional heartburn patients. This study suggested that increased number of weakly acidic reflux and proximal migration of gastroesophageal reflux are important underlying mechanisms for symptoms in reflux hypersensitivity patients.

Another study compared HREM and impedance+pH results between NERD and reflux hypersensitivity patients. The authors demonstrated that NERD and reflux hypersensitivity patients showed similar HREM findings. However, NERD patients had a significantly higher acid exposure time, total bolus exposure time, and proximal/distal acid reflux events as compared with reflux hypersensitivity patients. The authors showed that distal non-acidic reflux events were significantly more common in reflux hypersensitivity than in NERD patients. In this study, the authors emphasized the role of non-acidic reflux in symptom generation of reflux hypersensitivity patients and the need not to only focus on acidic reflux.

Recently, two pH-impedance parameters, post-reflux swallow-induced peristaltic wave (PSPW) index and mean nocturnal baseline impedance (MNBI), have been proposed to evaluate esophageal chemical clearance and mucosal integrity, respectively. These parameters have been proposed to increase the accuracy of diagnosing patients with gastroesophageal reflux disease and thus separating them from those with functional esophageal disorders like reflux hypersensitivity. Frazzoni et al. demonstrated that both PSPW index and MNBI were significantly lower in NERD patients as compared to those with reflux hypersensitivity and in both NERD and reflux hypersensitivity as compared to patients with functional heartburn. However, the study did not follow the diagnostic criteria of Rome IV for the reflux hypersensitivity group. In addition, PSPW assessment requires highly experienced individuals and a very detailed evaluation of the impedance strip. Another recent study, using the Rome...
IV criteria, demonstrated that both PSPW index and MNBI were significantly lower in NERD patients as compared with reflux hypersensitivity\textsuperscript{15}. Subsequently, the same authors demonstrated that both PSPW index and MNBI were significantly lower in reflux hypersensitivity patients as compared with functional heartburn and healthy controls\textsuperscript{18}.

Transient receptor potential vanilloid 1 (TRPV-1), a non-selective cation channel expressed by epithelial cells and sensory nerves, has been shown to be upregulated in patients with erosive esophagitis and NERD\textsuperscript{19}. Yoshida et al. reported that esophageal hypersensitivity in NERD patients is related to neurogenic inflammation with an increase in both releases of substance P and neurokinin 1 receptor expression. The latter may be associated with an activation of TRPV-1 and protease-activated receptor 2 (PAR2)\textsuperscript{20}. Furthermore, one study demonstrated that the activation of PAR2 mediates the sensitization of TRPV-1 and acid-sensing ion channels (ASICs) and enhances weak acid-induced ATP release from esophageal epithelial cells\textsuperscript{21}. These findings suggested that the pathogenesis of heartburn sensation in patients with reflux hypersensitivity or the esophageal hypersensitivity to physiologic amounts of acid exposure is the activation of PAR2, TRPV-1, and ASICs.

Psychological disorders have been shown to be an important factor in the generation and exacerbation of symptoms in functional esophageal disorders\textsuperscript{22}. A recent study demonstrated that anxiety, in particular, is associated with the severity of reflux symptoms in GERD patients\textsuperscript{23}. Bilgi et al. reported that general anxiety disorder was significantly more common in reflux hypersensitivity patients compared to NERD and functional heartburn patients. In addition, reflux hypersensitivity showed significantly lower quality of life as compared with NERD patients. The authors concluded that the lower quality of life in reflux hypersensitivity might be related to the severity of their comorbid psychopathology\textsuperscript{24}.

**CLINICAL PRESENTATION**

Symptom presentation of reflux hypersensitivity is similar to any of the other GERD phenotypes or functional heartburn. Duration, frequency, and severity or symptom intensity are similar among GERD phenotypes and functional esophageal disorders with heartburn as the predominant symptom\textsuperscript{25}. Thus, identifying the exact disorder leading to patient’s heartburn is not feasible based on clinical presentation only.

In a recent study by de Bortoli et al., the authors demonstrated that 66.5% of reflux hypersensitivity patients were woman, 15.1% smokers, 39% alcohol consumers, 47.7% with hiatal hernia, 4.1% with Helicobacter pylori infection, 48.2% with IBS diagnosis, 35.8% with anxiety, and 6% with depression, and the mean BMI was 24.1\textsuperscript{26}. Using multivariate logistic regression analysis as compared with GERD, the authors found that female sex, lower BMI, IBS diagnosis, hiatal hernia, H. pylori status, and anxiety are associated with reflux hypersensitivity. However, more studies are needed to evaluate these clinical characteristics in patients with reflux hypersensitivity.
As previously mentioned overlap of reflux hypersensitivity with psychological comorbidity is not uncommon, especially depression and anxiety. There is also a significant overlap with GERD, although the degree of this phenomenon is unknown. In addition, reflux hypersensitivity showed a significantly lower quality of life when compared with NERD patients.

**DIAGNOSIS**

The diagnosis of reflux hypersensitivity is focused on demonstrating a negative esophageal function workup but at the same time the presence of positive association with reflux events. Rome IV criteria proposed two diagnostic pathways for reflux hypersensitivity, one in patients on PPI treatment and the other in patients off PPI treatment (Fig. 2). In patients on PPI treatment, assessment should start with an upper endoscopy to exclude mucosal abnormalities and biopsies to rule out eosinophilic esophagitis. If the test is normal, then patient’s GERD history will determine the next step. If the patient has a positive history of GERD (abnormal endoscopy and/or pH testing), then pH impedance on PPI treatment should be performed. If the patient has no history of GERD, then a wireless pH capsule off PPI treatment should be done. In case, any of the aforementioned tests are normal, then SIs (SI and SAP) should be assessed and if positive, then the diagnosis is reflux hypersensitivity (Fig. 3). The identification of reflux events (either acidic or nonacidic) triggering symptoms in the context of normal esophageal acid exposure is key to the diagnosis of reflux hypersensitivity. If patients have a history of GERD (abnormal upper

**Figure 2.** The evolution of reflux hypersensitivity in Rome IV.
endoscopy and/or abnormal pH test), then diagnosis would be reflux hypersensitivity overlapping with GERD.

Figure 3 shows the diagnostic algorithm of reflux hypersensitivity in patients with heartburn and no treatment.

While SIs have been used for decades and treatment was provided accordingly, a few investigators have pointed out to some of their limitations and questioned their sensitivity. However, SIs are the best tool we have to identify the patients who are highly sensitive to physiologic amounts of reflux.

**TREATMENT**

Due to the limited understanding of the pathophysiologic basis of functional esophageal disorders including reflux hypersensitivity, therapy is commonly empiric and in many cases of limited value. However, antireflux therapeutic modalities have been considered as the first line of therapy in patients with reflux hypersensitivity because symptoms are triggered by gastroesophageal reflux events. They include the same medical, endoscopic, and surgical interventions that are used to also treat GERD. However, one has to recognize that there are less than handful studies in reflux hypersensitivity that assesses the value of the aforementioned therapies. Moreover, thus far, there are no studies assessing the value of antireflux endoscopic techniques in reflux hypersensitivity.

Patients with reflux hypersensitivity have been shown to respond successfully to standard or double-dose PPI. In a randomized, placebo-controlled, double-blind, cross-over study,
treatment with PPI twice daily for 1 month, significantly improved symptom frequency and severity in patients with reflux hypersensitivity. This study suggests that further suppression of gastric acid and thus minimization of esophageal acid exposure may improve symptoms in patients with reflux hypersensitivity. However, it is still unclear if standard dose PPI, given twice daily, provides the maximum effect in reflux hypersensitivity, as it is in GERD patients, or higher doses may be required to provide the best symptomatic control.

Interestingly, antireflux surgery has been especially studied in this patient population with good response. Broeders et al. demonstrated that patients with reflux hypersensitivity benefit from laparoscopic Nissen fundoplication (LNF) as much as those with NERD. The authors also reported that LNF drastically reduced the incidence of acid and weakly acidic reflux as well as liquid and mixed reflux episodes in reflux hypersensitivity patients. Another study reported that 94% (N = 18) of refractory heartburn patients (failed PPI twice daily) with normal esophageal acid exposure but a positive SI to non-acid or acid reflux was successfully treated with LNF. Recently, Patel et al. demonstrated that antireflux surgery can provide good reflux control in reflux hypersensitivity patients with structural disruption of the esophagogastric junction.

Overall, the preferred approach to the use of antireflux treatment in reflux hypersensitivity is to start with at least double dose PPI for up to 2 months. Surgery should be considered in a very carefully selected patient population. While there are no clear guidelines who are the best reflux hypersensitivity candidates for antireflux surgery, they should demonstrate some response to PPI treatment and clear association of their symptoms with reflux events.

As was mentioned above, neuromodulators such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-noradrenalin reuptake inhibitors are commonly used to treat visceral hypersensitivity and also specifically functional esophageal disorders. These medications may be considered as the first-line therapy or used in addition or after antireflux treatment has been employed. However, it should be emphasized that till now, there are very few studies assessing their value in reflux hypersensitivity.

TCAs have been demonstrated to be efficacious in controlling esophageal pain in patients with functional esophageal disorders. In a recent trial, patients with reflux hypersensitivity and functional heartburn were randomized to a fixed dose of 25 mg imipramine once daily versus placebo for 8 weeks. The authors failed to demonstrate superiority of imipramine over placebo in improving heartburn symptoms in both patient’s groups. However, in this study, 70% of the patients treated with low-dose imipramine reported improvement in quality of life. In general, when treating functional esophageal disorders, TCAs should not be given in a fixed dose. Instead, TCAs dose should be carefully titrated upward in each individual patient based on symptomatic response and development of side effects. In our practice, we start with a very low dose, 5–10 mg daily at bedtime and increase by 5–10 mg increments to a goal of 30–50 mg.

SSRIs have demonstrated clinical efficacy in patients with a variety of esophageal disorders such as functional chest pain,
esophageal hypersensitivity, NERD, and PPI non-responders heartburn patients. A recent study in healthy volunteers demonstrated that 20 mg citalopram given intravenously in a single dose, reduced chemical and mechanical esophageal sensitivity without altering esophageal motility. In a randomized, double-blind, placebo-controlled trial, 75 patients with reflux hypersensitivity were randomized to receive citalopram 20 mg or placebo. At the end of a 6-month follow-up period, 38.5% of the patients receiving citalopram and 66.7% of those receiving placebo continued to report heartburn symptoms ($p = 0.021$). The study suggested that citalopram was effective in controlling heartburn in patients with reflux hypersensitivity.

Histamine-2 receptor antagonists (H2RAs) have been shown to reduce esophageal chemoreceptor sensitivity to acid. Ranitidine (single 150 mg dose) significantly decreased esophageal sensitivity to acid infusion compared with placebo in patients with Rome II defined functional heartburn. These studies suggest that patients with reflux hypersensitivity may benefit from a trial of H2RAs.

Other esophageal neuromodulators such as adenosine antagonists (theophylline), ondansetron, tegaserod, octreotide, gabapentin, and pregabalin have been scarcely studied in functional esophageal disorders, and specifically, none of these compounds was evaluated in patients with reflux hypersensitivity.

Psychological interventions, alternative and complementary medicine, as well as other non-traditional approaches may have a role as sole therapy or part of comprehensive therapeutic approaches toward reflux hypersensitivity. However, currently, we are still devoid of any studies evaluating their therapeutic value in this patient population.

**CONCLUSIONS**

Reflux hypersensitivity was introduced by Rome IV as a new functional esophageal disorder and is currently defined as the presence of heartburn symptoms in patients with normal upper endoscopy and biopsies, normal esophageal acid exposure, normal HREM, and a positive association between symptoms and reflux events. Diagnosis of this disorder is made using endoscopy with biopsies, pH impedance while patient on PPI treatment, wireless pH capsule while patient off PPI treatment, and HREM.

Antireflux therapeutic modalities (primarily medical and surgical interventions) can be used as first-line therapy. In patients, who are PPI non-responders, neuromodulators are the main strategy of treatment of reflux hypersensitivity. However, due to the recent introduction of reflux hypersensitivity as a new disorder, it is likely that more studies evaluating its pathophysiology, epidemiology, natural course, and treatment will be carried out.

**REFERENCES**

5. Chu C, Du Q, Li C, et al. Ambulatory 24-hour multichannel intraluminal impedance-pH monitoring and high resolution endoscopy distinguish