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Patients with refractory reflux symptoms: What do they have and how should they be managed?

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Abstract

With the widespread use of PPIs, the frontier of treating reflux disease has shifted from refractory esophagitis to PPI-refractory symptoms. However, symptoms are inherently less specific than mucosal disease and, as noted by Herregods et al in their contribution appearing in this issue of *Neurogastroenterology and Motility*, patients with refractory GERD symptoms often do not have GERD. This review discusses potential etiologies for PPI-refractory symptoms. Three major concepts are explored: subendoscopic esophagitis, weakly acidic reflux events, and alternative explanations for persistent symptoms. With respect to subendoscopic esophagitis and unsuppressed reflux, ample evidence exists that these are present in PPI-refractory patients. The problem is that these findings are also often present in substantial numbers of individuals with a satisfactory response to PPI therapy. Hence, the emphasis shifts to determinants of symptom perception. The major conclusion of the review is that psychogenic factors such as hyperalgesia, allodynia, hypervigilance, and heightened anxiety are the most plausible explanations as the dominant determinants of PPI-refractory symptoms.

INTRODUCTION

It is remarkable how improvements in therapeutics shift the sands of disease presentation... and the expectations of therapy. In 1990, omeprazole was invincible. Not only were proton pump inhibitors (PPIs) game-changers in GERD management, but ‘PPI response’ became a cornerstone of GERD diagnosis. Remember the “PPI test” [1]? If it didn’t work, it wasn’t GERD; or so the thinking went. No wonder that twenty-five years later, as noted by Herregods et al in their analysis of “refractory GERD patients” appearing in this issue of *Neurogastroenterology and Motility*, “several studies have shown that the use of the standard PPI dose once daily results in either a partial or complete lack of response of

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symptoms in up to 40% of GERD patients after a 4-week course” [2]. What has changed? For one thing, our concept of GERD.

Prior to the advent of PPIs, there was general skepticism of a GERD diagnosis without the endoscopic demonstration of esophagitis. Non-erosive reflux disease (NERD) eventually gained acceptance, although even now, there are corners of the world in which only esophagitis is deemed worthy of PPI therapy. That issue aside, the widespread use of PPIs amongst gastroenterologists, cardiologists, otolaryngologists, and pulmonologists led to recognition of reflux as a cause or contributing factor to a spectrum of disorders, both esophageal and extra-esophageal. This was codified with The Montreal Definition of GERD, defining the entity as an array of disorders unified only by the common umbrella of being caused by the reflux of gastric content into the esophagus [3]. Hence, a GERD diagnosis can be based on either tissue damage attributable to gastroesophageal reflux or ‘troublesome’ symptoms attributable to reflux and, in either case, the target organ can be esophageal or extra-esophageal. Needless to say that while this definition may be intellectually satisfying, it presents a challenging task to the clinician now faced with an array of nonspecific symptoms, *potentially* related to GERD. No wonder that GERD or ‘refractory GERD’ has become the most common diagnosis in referral GI practices [4].

Examining the reaction to the dilemma of refractory reflux symptoms, three major approaches have been pursued. First, there are the acid enthusiasts. Whatever residual symptom exists, it is attributable to that last hydrogen ion that was not suppressed by a (too-weak) PPI. We just need more potent drugs or higher doses of existing drugs. Second, there are the technology enthusiasts. Persistent reflux symptoms are from reflux, just not necessarily *acid* reflux. This thinking spawned impedance testing (and prior to that, Biletec monitoring). No doubt these are elegant technologies, but it is equally clear that they have not solved the puzzle. Twenty-four years after Silny’s original report on impedance monitoring [5], we are still arguing over what findings are abnormal and just what ‘abnormal’ means. Third, there is the emerging camp exploring alternative explanations for ‘refractory reflux symptoms’. Perhaps, these are related to hypersensitivity to reflux, or to psychological comorbidities, or simply unrelated to reflux altogether. Reviewing these alternative scenarios provokes the familiar refrain that this is, indeed, a heterogeneous condition. Each explanation is likely correct in some instances, but as always, GERD defies generalizations.

Greater acid suppression

From the pharmaceutical perspective, the most successful strategy for treating reflux disease has been acid inhibition, evident by a series of blockbuster drugs, most impressively the PPIs. There is strong evidence that this strategy works with respect to healing reflux esophagitis [6] to the point that refractory esophagitis is a distinctly rare clinical scenario. Rather, the therapeutic frontier has moved on to refractory reflux symptoms and, here, the story is much less clear. Depending on the specific symptom in question, complete response of putative GERD symptoms varies widely from as much as about 50% for heartburn to nil for ‘reflux laryngitis’ [7]. Furthermore, it has proven very difficult to demonstrate a dose-response relationship for symptom relief with any of the PPIs. Hence, when two doses of a

PPI were marketed, it was always the lower dose for the indication for symptomatic GERD. Why then the push for more intensive acid inhibition? Ultimately, it lies in the hypothesis that residual symptoms are a manifestation of a compromised esophageal mucosa and that if that could be healed by better acid suppression, symptoms would resolve.

There is an abundance of evidence that specialized techniques can demonstrate an injured esophageal epithelium not evident endoscopically. Histologic evaluation of biopsy samples from normal appearing mucosa have identified basal cell hyperplasia, papillary elongation, intraepithelial eosinophilia, neutrophilia, mononuclear cell proliferation, and dilated intercellular spaces (DIS) as microscopic features of NERD [8, 9]. Mechanistically, the integrity of the esophageal epithelium is vital in maintaining a barrier to noxious constituents of refluxate (acid, pepsin, bile acids, etc.). The relative impermeability of the esophageal epithelium is a function of cell-to-cell connections (tight junctions, adherens junctions, and desmosomes) providing a structural framework and the disruption of this framework causes DIS [10]. The demonstration of DIS, either by light or electron microscopy, has the potential to discriminate between patients with reflux syndromes (non-erosive disease and hypersensitive esophagus) and those with functional heartburn, who are histopathologically indistinguishable from healthy controls [11]. An interesting offshoot of this is the potential to utilize the serological detection of a degradation product of one of these junctional proteins, e-cadherins, as an indicator of reflux injury [12]. Yet another indicator of a 'leaky' epithelium is its baseline impedance. First measured in conjunction with impedance monitoring as done for reflux testing, this concept is now being applied using a single-channel mucosal impedance catheter with sensors that traverse the working channel of the upper endoscope. Recently published data report that impedance measurements using this novel technology can distinguish among normal subjects, GERD patients, and disease controls [13].

Evident from the preceding discussion, there are clearly more sensitive methods than endoscopy for the detection of acid injury to the esophageal mucosa. However, when applying these in the context of 'PPI failures' one must also consider their specificity for that entity. Consider the example of endoscopy. The Los Angeles Classification of esophagitis was devised to maximize specificity for reflux esophagitis [14]. However, erosive esophagitis, mainly Los Angeles A, was found in conjunction with no reflux symptoms in 5% of a 1000-person population-based endoscopy study conducted in Kalixanda [15]. In all likelihood, these individuals also had histological esophagitis, DIS, and low baseline impedance. In fact, those findings would probably be present in a considerably greater fraction of the asymptomatic individuals studied as DIS is not specific to acid-induced injury, having also been described with emotional stress [16] and eosinophilic esophagitis [17], among other conditions. Regardless, the Kalixanda findings are consistent with the generality that there is a poor parallel between symptom severity and mucosal erosions in reflux disease; patients with non-erosive disease and reflux esophagitis exhibit very similar spectra of symptom severity [18]. Hence, while reversal of DIS can be demonstrated with PPI therapy, a corresponding elimination of symptoms is far less consistent, especially in NERD patients [19]. Then, there is also the observation that many patients with a satisfactory symptomatic response to PPI therapy nonetheless show persistently abnormal esophageal acid exposure on pH monitoring [20]. Hence, the missing

links in the ‘more is better’ argument regarding acid suppression for PPI refractory symptoms are confirmatory treatment data and the demonstration that sub-endoscopic injuries to the mucosa are not present in individuals with a satisfactory symptom response. Increasing potency of acid suppression beyond that achieved with currently available PPIs has been tested, but it has not been shown superior for symptom-defined outcomes [21, 22]. In summary, although it is clearly possible to demonstrate sub-endoscopic abnormalities of the esophageal mucosa, there is little clinical evidence supporting the hypothesis that these are an important cause of ‘PPI failure’. Rather, the likely utility of these techniques lies in their utility as biomarkers of reflux injury to the esophageal mucosa.

Improved reflux detection

It is possible that PPI-refractory reflux symptoms are attributable to persistent reflux not detected by pH monitoring. This became an attractive hypothesis with the development of multichannel impedance monitoring given the ability of this elegant technology to detect reflux events irrespective of their content or acidity [23]. Early on, there was the demonstration that PPIs had negligible effect on the occurrence of reflux, only on its acidity [24]. Acid reflux became ‘non-acid’ or, more precisely, weakly acidic reflux. Subsequently, a multicenter study of 168 refractory GERD patients reported that 11% of them had symptom-association for acid reflux and 37% had symptom-association with non-acid reflux while on PPI therapy [25]. Since then, several variables of conducting and analyzing pH-impedance studies have been extensively investigated in attempts to improve the clinical utility of pH-impedance studies. These include the proximal extent of reflux, refluxate gas content, and conducting studies ‘on’ or ‘off’ PPIs. From this, some general principles have emerged regarding pH-impedance monitoring vs pH monitoring alone: 1) impedance monitoring is much more sensitive in detecting rumination and belching disorders [26], 2) when done while withholding PPI therapy, the diagnostic yield of impedance monitoring is only modestly better than that of pH monitoring alone [27], and 3) when done while taking PPIs the yield of impedance monitoring is substantially better than that of pH monitoring alone at demonstrating symptom-reflux correlation [27]... but, this is of unproven clinical significance.

From the preceding discussion, it is evident that impedance monitoring represents a technological advance that has improved our understanding of reflux physiology and of the effects of PPI therapy on that physiology. However, similar to the discussion of sub-endoscopic mucosal injury, one must also consider the specificity of these findings in the context of PPI-refractory symptoms. After all, everyone with reflux disease who takes PPIs converts their acid reflux to weakly acidic reflux. Is this any different in a PPI-responder than it is in a PPI non-responder? Although that question has not really been the object of clinical experimentation, the presumed answer is no. Rather, the differentiating feature is hyperalgesia (increased sensation of noxious stimuli) among the non-responders [28]. Although heightened esophageal sensitivity in NERD patients can be shown with balloon distention or evoked potentials to electrical stimulation, it is also self-evident by the observation that NERD patients have a similar profile of symptom severity despite having numerically fewer reflux events and less esophageal acid exposure than erosive esophagitis patients. Mechanistically, accumulating evidence suggests both peripheral and central

sensitization by up-regulation of acid-sensing ion channels and the associated central pathways [28].

In summary, pH-impedance technology allows for the detection and characterization of reflux events in ways not previously possible, clearly demonstrating that ongoing reflux in the face of PPI therapy for GERD is the norm rather than the exception. With regard to PPI-refractory symptoms, pH-impedance studies show that a substantial fraction of these are reflux-related. Whether the association is with acidic reflux events or weakly acidic events is mainly a function of whether or not the patient was taking a PPI in the course of the study. It is also clear that only 5-15% of reflux events are associated with symptoms calling into question the logic of treatment with reflux inhibitors that reduce the number of reflux events by about 40%; you would really have to eliminate essentially all reflux events to have a significant effect. However, the major paradigm shift that has gained traction with widespread pH-impedance testing is the concept of hypersensitivity as an important co-factor in treatment-resistant disease.

Alternative explanations for persistent symptoms

The current clinical management strategy for refractory GERD patients utilizes the combination of endoscopy and reflux testing to categorize patients as typical reflux, hypersensitive, or functional heartburn, a condition in which, though the symptom profile may be typical, there is no demonstrable correlation between those symptoms and the occurrence of reflux [7]. Functional heartburn patients have also been described as having allodynia, the painful perception of what is normally an innocuous stimulus. The magnitude of the functional heartburn group will vary with the specifics of the referral population and the reflux testing methodology applied; in this issue of NGM, Herregods et al found it to be 30%, nearly a third, in their referral practice [2]. Recognize though, that at the fringe, there is only a subtle distinction between hypersensitivity and functional heartburn and given that the two end up with a similar management strategy, one could argue that making that distinction is not vital. In the Herregods study, the major treatment approach to both was with imipramine and they report that 4/8 patients with functional heartburn achieved >50% symptom reduction compared to 6/8 (75%) of patients with hypersensitivity treated with the same drug. Clearly, it is the strategy of choice either way. Recognize also that the hypersensitive group has been variably assigned to GERD or functional heartburn depending on the iteration of the Rome classification. Whereas Rome II classified hypersensitivity as functional [29], Rome III classified it as GERD [30] and, rumor has it that Rome IV wants to abolish the 'functional' terminology altogether.

So what then is the explanation of symptom genesis in functional heartburn if not from reflux? Psychological co-morbidities have been invoked as one explanation. Anxiety and depression were found to increase GERD-related symptoms in a population-based study [31]. Patients categorized as functional on the basis of poor reflux-symptom correlation reportedly exhibit a high level of anxiety and hysteria compared with patients exhibiting good reflux-symptom correlation [32]. Also supportive of this, a recent study showed that increased levels of anxiety were associated with more severe retrosternal pain and retrosternal burning in GERD patients along with increased levels of anxiety, depression,

and diminished scores of the mental component of quality of life questionnaire [32]. The functional heartburn patients in that study exhibited increased levels of anxiety. However, again, one must consider the issue of specificity and realize that minimal data support the contention that patients with PPI-refractory symptoms have more severe psychiatric illnesses than reflux patients with a satisfactory PPI response.

An alternative explanation to refractory acid exposure or psychiatric comorbidity fueling PPI-refractory symptoms is esophageal hypervigilance, which has been recently defined by Keefer, Pandolfino and colleagues as the cognitive-affective process that stems from hyperawareness of discomfort. The heightened awareness (or sensitivity) is coupled with behavior that is out of proportion to the prior symptom experience, serving to amplify the ‘threat level’ of symptoms and their potential consequences. Hypervigilant behavior is further reinforced when symptoms do not occur as predicted because the individual falsely attributes the lack of, or disappearance of, symptoms to his/her careful attempt to avoid their perceived triggers. Hypervigilance begets hypervigilance and also results in an inability to enjoy symptom-free periods, negatively impacting quality of life [33]. A recent analysis of 70 patients with PPI-refractory symptoms studied with pH-impedance monitoring and psychometric testing came to the surprising conclusion that, regardless of patient phenotype in terms of positive or negative symptom correlation and normal or abnormal esophageal acid exposure, the unifying characteristic of all phenotypes was hypervigilance [34]. In fact, hypervigilance accounted for 50% of patient-reported symptom severity. Psychological distress (depression, anxiety, somatization) on the other hand, was found to be within normal limits in all phenotypes.

Conclusions

So, one has to conclude that multiple elements, either alone or in combination, are potentially at play in the genesis of PPI-refractory symptoms: persistent acid reflux, an impaired esophageal mucosa, weakly-acidic reflux, hypersensitivity, and hypervigilance. Not a simple answer to be sure. Nonetheless, this is the current landscape that the clinician must navigate.

The first step in management of refractory reflux symptoms is to optimize PPI therapy. Debate continues as to whether this should be with once daily or twice daily dosing, but realistically, the clinical community has long since decided this one. Regardless of the absence of appropriate RCTs proving the point, there is little question that a subset of patients benefit from twice daily dosage and when that is the case, this is by far the simplest management strategy. On the other hand, not everyone benefits from twice daily PPI therapy and if there is no convincing incremental benefit achieved from twice daily dosing, reduce it to the standard dose. Then also, there are the important issues of timing PPI dosing to before meals, encouraging observance of sensible lifestyle modifications (avoiding late meals and trigger foods), and encouraging weight loss [6]. Finally, reinforce that 100% symptom resolution is neither necessary nor the norm; some degree of residual symptoms are OK.

When tweaking the PPI dosing is insufficient, the consensus is that diagnostic testing should then be undertaken to guide further management [6]. As demonstrated in the Herregods series [2], potential diagnoses include GERD, hypersensitivity, functional heartburn,

functional chest pain, achalasia, and distal esophageal spasm. To that we would add eosinophilic esophagitis from our own, otherwise similar, clinical experience. Depending on the nuances of the history, every test is probably not necessary in every individual, but the combination of endoscopy (with mucosal biopsies when dysphagia is among the reported symptoms), high-resolution manometry, and pH monitoring (done off of PPI therapy) should suffice to establish a working diagnosis. Some centers prefer pH-impedance monitoring, but the extended recording period and superior patient tolerance of wireless pH monitoring have made this the preferred test at our institution.

After evaluation, the most intriguing question of all is, who gets what therapy? Clearly, the achalasics get specific therapy, those with refractory GERD can consider antireflux surgery, and those with no evidence of esophageal disease should be redirected. However, a substantial fraction of patients will end up with the diagnosis of either GERD with hypersensitivity or functional heartburn and these are challenging patients because there is no sure-fire treatment. Hence, all roads lead to Rome. A multitude of observations suggest this to be the issue: hyperalgesia, allodynia, hypervigilance, heightened anxiety. Right now, our pharmacological tools for these conditions are limited to low-dose antidepressants, but hopefully new drugs will soon be found that modify the process of, or the reaction to, sensitization [35]. Beyond psychopharmacology, we have cognitive-behavioral therapy [36] and esophageal-directed hypnotherapy [33, 37], promising concepts for further research and treatment.

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Abbreviations

BI	baseline impedance
DIS	dilated intercellular spaces
EGJ	esophagogastric junction
GERD	gastroesophageal reflux disease
LPR	laryngopharyngeal reflux
NERD	non-erosive reflux disease
PPI	proton pump inhibitor

REFERENCES

1. Kahrilas PJ. Treatment vs management of gastroesophageal reflux disease. *Am J Gastroenterol*. 1997; 92:1959–1960. editorial. [PubMed: 9362172]
2. Herregods TVK, Troelstra M, Weijenberg PW, Bredenoord AJ, Smout AJPM. Patients with refractory symptoms often do not have GERD. *Neurogastroenterol Motil*. 2015 In Press.
3. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006; 101(8):1900–20. [PubMed: 16928254]

4. Fass R, Sifrim D. Management of heartburn not responding to proton pump inhibitors. *Gut*. 2009; 58(2):295–309. [PubMed: 19136523]
5. Silny J. Intraluminal multiple electric impedance procedure for measurement of gastrointestinal motility. *J Gastrointest Motil*. 1991; 3:151–162.
6. Kahrilas PJ, Shaheen NJ, Vaezi M, collaboration with the AGAI Medical Position Panel on GERD management. American Gastroenterological Association Institute medical position statement: management of gastroesophageal reflux disease. *Gastroenterology*. 2008; 135:1383–1391. [PubMed: 18789939]
7. Boeckxstaens G, El-Serag HB, Smout AJPM, Kahrilas PJ. Symptomatic reflux disease: the present, the past, and the future. *Gut*. 2014; 63:1185–1193. [PubMed: 24607936]
8. Fiocca R, Mastracci L, Riddell R, et al. Development of consensus guidelines for the histologic recognition of microscopic esophagitis in patients with gastroesophageal reflux disease: the Esohisto project. *Hum Pathol*. 2010; 41(2):223–31. [PubMed: 19800099]
9. Yeran L, Fiocca R, Mastracci L, et al. Refinement and reproducibility of histologic criteria for the assessment of microscopic lesions in patients with gastroesophageal reflux disease: the Esohisto Project. *Dig Dis Sci*. 2011; 56(9):2656–65. [PubMed: 21365241]
10. Tobey NA, Hosseini SS, Argote CM, et al. Dilated intercellular spaces and shunt permeability in nonerosive acid-damaged esophageal epithelium. *Am J Gastroenterol*. 2004; 99(1):13–22. [PubMed: 14687135]
11. Savarino E, Zentilin P, Mastracci L, et al. Microscopic esophagitis distinguishes patients with non-erosive reflux disease from those with functional heartburn. *J Gastroenterol*. 2013; 48(4):473–82. [PubMed: 23001252]
12. Jovov B, Que J, Tobey NA, et al. Role of E-cadherin in the pathogenesis of gastroesophageal reflux disease. *Am J Gastroenterol*. 2011; 106(6):1039–47. [PubMed: 21448147]
13. Ates F, Yuksel ES, Higginbotham T, et al. Mucosal impedance discriminates GERD from non-GERD conditions. *Gastroenterology*. 2015; 148(2):334–43. [PubMed: 25448923]
14. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut*. 1999; 45(2):172–80. [PubMed: 10403727]
15. Ronkainen J, Aro P, Storskrub T, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand J Gastroenterol*. 2005; 40(3):275–85. [PubMed: 15932168]
16. Farre R, De Vos R, Geboes K, et al. Critical role of stress in increased oesophageal mucosa permeability and dilated intercellular spaces. *Gut*. 2007; 56(9):1191–7. [PubMed: 17272649]
17. Katzka DA, Ravi K, Geno DM, et al. Endoscopic Mucosal Impedance Measurements Correlate with Eosinophilia and Dilation of Intercellular Spaces in Patients with Eosinophilic Esophagitis. *Clin Gastroenterol Hepatol*. 2015 [epub ahead of print].
18. Carlsson R, Dent J, Watts R, et al. International GORD Study Group. Gastro-oesophageal reflux disease in primary care: an international study of different treatment strategies with omeprazole. *Eur J Gastroenterol Hepatol*. 1998; 10:119–24. [PubMed: 9581986]
19. Farre R, Fornari F, Blondeau K, et al. Acid and weakly acidic solutions impair mucosal integrity of distal exposed and proximal non-exposed human oesophagus. *Gut*. 2010; 59(2):164–9. [PubMed: 19880965]
20. Milkes D, Gerson LB, Triadafilopoulos G. Complete elimination of reflux symptoms does not guarantee normalization of intraesophageal and intragastric pH in patients with gastroesophageal reflux disease (GERD). *Am J Gastroenterol*. 2004; 99:991–6. [PubMed: 15180715]
21. Dent J, Kahrilas PJ, Hatlebakk J, et al. A randomized, comparative trial of a potassium-competitive acid blocker (AZD 0865) and esomeprazole for the treatment of patients with nonerosive reflux disease. *Am J Gastroenterol*. 2008; 103:20–26. [PubMed: 18184117]
22. Kahrilas PJ, Dent J, Lauritsen K, et al. A randomized, comparative study of three doses of AZD0865 and esomeprazole for healing of reflux esophagitis. *Clin Gastroenterol Hepatol*. 2007:1385–1391. [PubMed: 17950677]

23. Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut*. 2004; 53(7): 1024–31. [PubMed: 15194656]
24. Vela MF, Camacho-Lobato L, Srinivasan R, et al. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. *Gastroenterology*. 2001; 120:1599–606. [PubMed: 11375942]
25. Mainie I, Tutuian R, Shay S, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance–pH monitoring. *Gut*. 2006; 55:1398–402. [PubMed: 16556669]
26. Kessing BF, Bredenoord AJ, Smout AJ. The pathophysiology, diagnosis, and treatments of excessive belching. *Am J Gastroenterol*. Aug; 2014 109(8):1196–203. [PubMed: 25001253]
27. Zerbib F, Roman S, Ropert A, et al. Esophageal pH–impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. *Am J Gastroenterol*. 2006; 101:1956–63. [PubMed: 16848801]
28. Knowles CH, Aziz Q. Visceral hypersensitivity in non-erosive reflux disease. *Gut*. 2008; 57:674–83. [PubMed: 18079285]
29. Clouse RE, Richter JE, Heading RC, Janssens J, Wilson JA. Functional esophageal disorders. *Gut*. 1999; 45(Suppl. II):II31–6. [PubMed: 10457042]
30. Galmiche JP, Clouse RE, Bálint A, et al. Functional esophageal disorders. *Gastroenterology*. 2006; 130:1459–65. [PubMed: 16678559]
31. Jansson C, Nordenstedt H, Wallander MA, et al. Severe gastro-oesophageal reflux symptoms in relation to anxiety, depression and coping in a population based study. *Aliment Pharmacol Ther*. 2007; 26(5):683–91. [PubMed: 17697202]
32. Rubenstein JH, Nojkov B, Korsnes S, et al. Oesophageal hypersensitivity is associated with features of psychiatric disorders and the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2007; 26:443–53. [PubMed: 17635379]
33. Riehl ME, Keefer L. Hypnotherapy for esophageal disorders. *Am J Clin Hypn*. 2015; 58(1):22–33. [PubMed: 26046715]
34. Keefer L, Eident K, Kahrilas I, Roman S, Pandolfino JE. Symptom reporting among PPI non responders may be driven by esophageal hypervigilance and not reflux phenotype. *Gastroenterology*. 2015; 148((4) Supplement):S-147.
35. Kessing BF, Bredenoord AJ, Saleh CM, Smout AJ. Effects of anxiety and depression in patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2015; 13(6):1089–1095. [PubMed: 25496817]
36. Riehl ME, Kinsinger S, Kahrilas PJ, Pandolfino JE, Keefer L. Role of a health psychologist in the management of functional esophageal complaints. *Dis Esoph*. Apr 3.2014 2014 DOI: 10.1111/dote.12219 [Epub ahead of print].
37. Riehl ME, Pandolfino JE, Palsson OS, Keefer L. Feasibility and acceptability of esophageal-directed hypnotherapy for functional heartburn. *Dis Esoph*. Mar 30.2015 doi: 10.1111/dote.12353. [Epub ahead of print].

KEY MESSAGES

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