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Review Article: Individualised Management of Reflux-Like Symptoms—Strategies Beyond Acid Suppression

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ABSTRACT

Background: Reflux-like symptoms and reflux oesophagitis are often perceived as having the same acid-related aetiology and responsiveness to antisecretory therapy. However, the frequency of residual symptom reporting on proton pump inhibitor (PPI) therapy suggests the two entities have some differential pathophysiological determinants requiring distinct management approaches.

Aims: To examine the complexities of reflux-like symptom pathophysiology and strategies that may be used to target contributing factors beyond acid reflux.

Methods: A panel of ten expert clinicians (primary care, gastroenterology and psychology) held a series of online meetings to share perspectives on the underlying contributors to, and management of, reflux-like symptoms when PPIs are ineffective or provide partial relief. This review summarises the agreed key themes that emerged from the expert discussions.

Results: While degradation of the anti-reflux barrier dominates in reflux oesophagitis, cognitive-affective, behavioural, and other psychosocial factors can play a major role in symptom persistence. These require individualised management strategies, beginning with education on the gut-brain connection and expectation setting with regard to PPI therapy. A detailed clinical history and patient-reported outcome tools that measure symptom burden and associated anxiety/hypervigilance can help guide management using brain-gut behavioural therapies, supported diet/lifestyle modification, diaphragmatic breathing, weight loss, and/or on-demand symptom control measures according to a patient's specific needs.

Conclusions: A paradigm shift in reflux-like symptom management is required such that acid suppression is viewed as one of several interventions that can be utilised as part of a phenotype-driven, individualised approach to care that acknowledges the multiple contributors to symptom burden.

1 | Introduction

Reflux-like symptoms are a frequent reason for proton pump inhibitor (PPI) prescribing, with patients often treated long term and at high doses [1–4]. In essence, reflux-like symptoms are conflated with reflux oesophagitis and assumed to have the same excellent responsiveness to potent inhibition of gastric acid secretion. However, this reductionist approach often proves ineffective, with a substantial proportion of patients reporting persistent symptoms despite optimised PPI therapy [5, 6]. This differential clinical responsiveness between reflux oesophagitis and persistent reflux-like symptoms calls into question whether they really do have a shared pathophysiology and should be managed with the same strategy.

Comprehensive published reviews and consensus statements provide recommendations for the specialist diagnosis, medical management (including the evolving role of potassium-competitive acid blockers [PCABs]) and surgical procedures for patients with refractory reflux-like symptoms [7–11]. The aim of the current review was to examine the issue of persistently symptomatic patients with non-erosive disease from a primary care and generalist perspective. Both acid and non-acid-targeted interventions such as education, expectation setting, lifestyle, and psychological interventions should be considered based on the individual's clinical presentation and personal circumstances.

2 | Methods

A panel of ten expert clinicians from primary and secondary care (gastroenterology and psychology) held a series of three online meetings to share perspectives on the pathophysiology and management of reflux-like symptoms when a PPI is ineffective or provides only partial relief. The focus was to determine how care of symptomatic patients could be enhanced through personalised strategies from a primary care/generalist perspective. During the first meeting, key themes for exploration were agreed, including potential underlying contributors of reflux-like symptoms/non-acid-mediated symptoms and alternative (non-acid suppressive) management strategies. Each member chose a topic for detailed review and presented their findings during the second meeting for wider group analysis and discussion. In the final meeting, content gaps were identified and discussed. The output of these meetings, summarised herein, examines the complexities of reflux-like symptom pathophysiology and management strategies that may be used to target them.

3 | Pathophysiology

3.1 | Reflux Oesophagitis

Reflux oesophagitis is characterised by endoscopically visible mucosal breaks in the distal oesophageal mucosa stratified by the Los Angeles Classification as mild (A, B) or severe (C, D) based on the extent and confluence of the mucosal breaks [12]. The pathophysiology of reflux oesophagitis centres on incompetence of the anti-reflux barrier at the oesophagogastric junction manifested by a hypotensive lower oesophageal sphincter, dilatation of the diaphragmatic hiatus, and hiatal hernia leading to excessive gastro-oesophageal acid reflux into the distal oesophagus and poor oesophageal clearance of the refluxed acid [12]. This results in greatly increased distal oesophageal acid exposure causing inflammation and mucosal erosions. Reflux oesophagitis can almost uniformly be healed with potent antisecretory therapy (PPIs or PCABs) and the healing rates observed in clinical trials parallel the antisecretory potency of the treatments [13]. However, the irreversible nature of the physiological defects, especially evident with severe oesophagitis, mandates open-ended maintenance antisecretory therapy unless these physiological defects are addressed with alternative strategies such as intensive weight loss or surgery [12].

3.2 | 'Typical' Reflux-Like Symptoms

According to the Montreal Consensus on the definition of gastro-oesophageal reflux disease (GERD), defining typical oesophageal symptoms are heartburn, chest pain, and regurgitation [14]. However, early on, it was recognised that most individuals with typical reflux-like symptoms do not have reflux (erosive) oesophagitis leading to the concept of non-erosive reflux disease (NERD) [12, 15]. When these individuals were evaluated further by physiological testing (either pH-metry or pH-impedance testing) they were found to be heterogeneous, some with excessive oesophageal acid exposure, as is typical in reflux oesophagitis, and some with normal values of oesophageal acid exposure, the latter then labelled as 'functional'. This was subsequently further refined by the Rome Foundation and the Lyon Consensus into 'true NERD' characterised by abnormal oesophageal acid exposure, 'reflux hypersensitivity' characterised by normal oesophageal acid exposure, but a significant correlation between reported symptoms and reflux events, and 'functional heartburn' characterised by normal oesophageal acid exposure without a significant correlation between reported symptoms and reflux events [12].

An overwhelming problem with the stated classifications is that, while these defining symptoms can be related to reflux events, there is a very poor correlation between the two, with most reflux events being asymptomatic and most symptoms not temporally linked to reflux events. There is also a huge disconnect between patient-reported symptom severity and the degree of physiological abnormality as demonstrable by oesophageal pH-metry [16]. The explanation for this disconnect is probably related to the complex process of how oesophageal events are perceived, which is dependent on both peripherally and centrally mediated neurologic processes. Although the details of these processes remain elusive, the result is that psychological stressors, cognitive–affective factors, and aberrant coping behaviours are important modulators of the symptom experience. Fortunately, many of these modulators are modifiable, as evident by the inherent neural plasticity that leads to the development of hypersensitivity (the perception of stimuli not normally perceived or the experience of symptoms at greater intensity than is typical). The gut microbiome, shaped by an individual's environment, life experiences, and social

factors (e.g., poverty, ethnicity, discrimination, food insecurity) may also impact visceral sensitivity and central nervous system (CNS) processing [17, 18].

The Oesophageal Hypervigilance and Anxiety Scale (EHAS) was developed as an instrument to quantify an individual's level of oesophagus-focused anxiety and symptom vigilance [16]. The EHAS is a 15-item questionnaire with each item such as *"I have a difficult time enjoying myself because I cannot get my mind off the discomfort in my throat/chest/oesophagus*" rated on a 5-point Likert scale ranging from 'strongly disagree' to 'strongly agree' resulting in an overall score of 0–60. The relevance of the EHAS score was demonstrated in a study of 105 patients with reflux-like symptoms but without reflux oesophagitis that compared physiological variables derived from pH-impedance studies to EHAS scores as potential symptom determinants [19]. Among the variables tested (oesophageal acid exposure time, number of reflux events, mean nocturnal baseline impedance and EHAS score), only the EHAS score correlated with symptom severity as gauged by the GERDQ questionnaire. Furthermore, this was true regardless of whether the individuals were classified as 'true NERD', reflux hypersensitivity, or functional heartburn by pH-impedance testing [19]. A shorter 7-item version, EHAS-7, has been shown to perform as well as the original version and may be easier to implement in clinical practice when time is limited [16].

Further exploring the concept that psychosocial processes often dominate over physiological determinants in the persistence of reflux-like symptoms, was a detailed evaluation of 393 consecutive patients with 'PPI-refractory' symptoms evaluated with pH-impedance monitoring and a battery of psychometric testing (13 questionnaires on psychosocial functioning) [20]. A data-driven machine-learning approach was used to assess the performance of variables in predicting total reflux severity score measured by the ReQuest Questionnaire. The machine-learning model with the best predictive performance (88% of the observed variance in symptom severity scores) included 24 variables, each ranked according to their predictive 'worth'. The first 11 most important variables were all psychological with a total worth of 1.164 and included depressive symptoms (worth = 0.210), illness behaviour (worth = 0.165), post-traumatic stress disorder symptoms (worth = 0.128), GI-specific anxiety (worth = 0.117), and pain catastrophizing (worth = 0.114). Reflux-related variables had lower predictive worth totalling only 0.109, including 0.046 for total number of reflux episodes (ranked 12th), 0.033 for Lyon classification (ranked 17th), 0.026 for total reflux exposure (ranked 22nd) and 0.004 for PPI intake (ranked 24th) [20].

Still further emphasising the impact of psychosocial factors in the perception and burden of reflux-like symptoms is a study that explored such variables in 123 patients with abnormal oesophageal acid exposure on pH-metry and 116 with normal acid exposure but positive symptom correlation on pH-metry [21]. The major finding was that oesophageal hypervigilance was persistent across patients with reflux, irrespective of pH-metry results, and significantly predicted symptom severity. Hence, the evolving model of the pathogenesis of typical reflux-like symptoms is that psychosocial factors are important across the entire spectrum of GERD, including reflux oesophagitis (Figure 1) [21].

The recognition that psychological comorbidities and visceral hypersensitivity play a dominant role in symptom perception has led to the disease concept of 'disorders of gut-brain interaction' (DGBIs, previously known as functional gastrointestinal disorders) [22, 23]. DGBIs including functional heartburn, functional dyspepsia, and irritable bowel syndrome (IBS) commonly overlap and frequently coexist with somatic symptoms such as headache, backache, insomnia, fibromyalgia, stiffness and dizziness [24]. A study in the UK found that DGBIs were extremely common, affecting 1 in 3 adults, but were sparsely recognised or taught within the British medical education system [23], a problem that is likely to exist globally. Patient's adaptation responses also influence their symptom experience. Patients who are able to rationalise persistent symptoms cope better than those with flight-or-fight, fear, and/or a stress response (Figure 2). Quality of life is further impaired when the perception of symptoms as threatening leads to avoidance behaviour, which drives the reinforcement of fear and restricts life activities. These processes contribute to oesophageal hypervigilance, a behavioural reaction whereby increased attention is paid to the oesophageal symptoms and the settings in which they occur leading patients to 'expect' and/or engage in maladaptive coping behaviours to avoid symptoms in those settings [25].

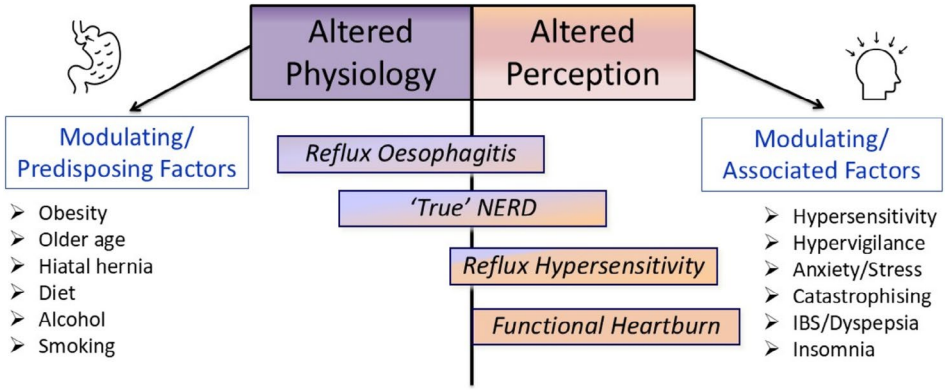

FIGURE 1 | Pathogenesis of reflux-like symptoms: A complex interaction of body and mind. Across the spectrum of symptomatic 'GERD' syndromes, patients with reflux oesophagitis and 'true NERD' may have both abnormal physiology and abnormal perception contributing to symptom pathogenesis while the pathogenesis is almost entirely attributable to altered perception in reflux hypersensitivity and functional heartburn. IBS, irritable bowel syndrome; NERD, non-erosive reflux disease.

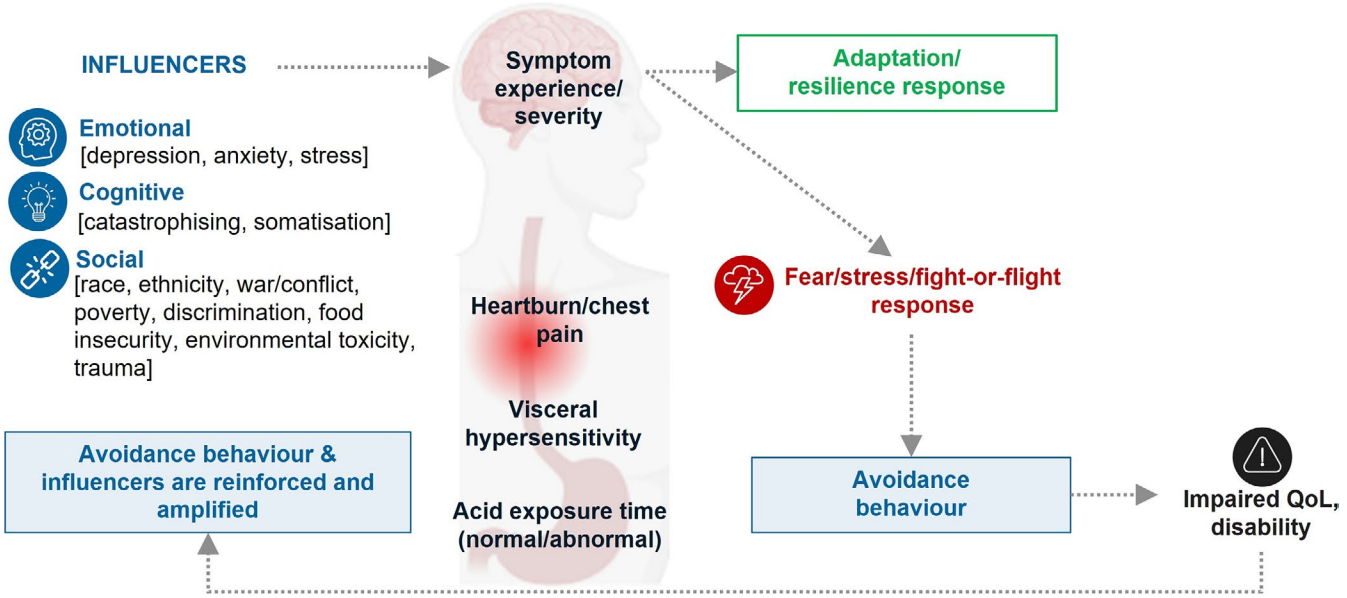

FIGURE 2 | Oesophageal hypervigilance: A complex but modifiable driver of refractory heartburn. Oesophageal hypervigilance develops when a heightened state of awareness or sensitivity to symptoms is coupled with behaviours that serve to detect and avoid future threats. QoL, quality of life.

3.3 | 'Atypical' Reflux Symptoms

A multitude of 'atypical' or extra-oesophageal GERD syndromes have been proposed including laryngitis, pharyngitis, post-nasal drip, otitis and asthma. However, since affected patients rarely have reflux oesophagitis on endoscopy, establishing a causative role of reflux in these syndromes presents vexing problems. Oesophageal pH-metry or pH-impedance metry have become the mainstays of evaluation, but there is little consensus on how to interpret the studies in this context. Clearly there are examples of patients with reflux leading to extra-oesophageal syndromes [14], but establishing gastro-oesophageal reflux as a dominant contributor to these atypical syndromes in a clinical setting remains problematic [26]. Furthermore, the current paradigm for persistent throat symptom management is another scenario where the role of psychosocial factors on symptom burden has received inadequate attention. A study in patients with laryngeal symptoms demonstrated elevated levels of hypervigilance and anxiety (assessed by EHAS) in those with and without abnormal oesophageal pH-metry (oesophageal acid exposure time $>6\%$), highlighting the need to integrate approaches beyond acid reduction [27]. There is also substantial heterogeneity in this group of patients, much like the spectrum of GERD, with some phenotypes driven by abnormal reflux physiology and some predominantly driven by hypersensitivity and behavioural factors [28].

General principles that have emerged from the collective experience with atypical reflux symptoms are: (1) it is uncommon for reflux to be the dominant cause of extra-oesophageal syndromes in patients who are not also experiencing typical oesophageal symptoms; (2) even when reflux is involved, it is usually one of multiple contributors and often not the dominant one; (3) diagnostics (pH-metry or pH-impedance metry) are more helpful in ruling out GERD in these patients than ruling it in; and (4) there is a strong tendency to over-treat these patients with PPIs.

3.4 | Overlapping Gastrointestinal Symptoms

Dyspeptic symptoms frequently overlap with reflux-like symptoms and are often present in PPI 'non-responders', a term that remains inconsistently defined [29]. Clinical evidence suggests that patients with functional heartburn have more in common with those with functional dyspepsia than reflux disease, and experience more postprandial fullness, bloating, early satiety and nausea than patients with 'true NERD' and reflux hypersensitivity [30]. Irritable bowel syndrome, another DGBI, has also been shown to overlap more frequently with functional heartburn than true NERD and reflux hypersensitivity, suggesting common pathophysiological pathways [31]. Hence, patients should be questioned to differentiate between dyspeptic and reflux-like symptoms. Medical jargon should be avoided during these patient consultations as there are major cultural differences in the terminology used to describe upper GI symptoms [32]. Easy-to-understand tools using pictogram-like drawings simplify communication with patients [33, 34]. Also, as a point of differentiation, *Helicobacter pylori* (*H. pylori*) testing is important in dyspepsia management but is generally unnecessary and not indicated in patients who only have typical reflux-like symptoms.

4 | Potential Lifestyle Contributors to Reflux-Like Symptoms

4.1 | Dietary Habits

Poor dietary habits, especially eating past satiety and eating close to bedtime, are associated with gastro-oesophageal reflux [35]. Eating large meals causes gastric distention, promotes greater acid secretion, triggers transient lower oesophageal sphincter relaxations, and makes reflux from the postprandial acid pocket more likely [35, 36]. As for specific foods to avoid, the dominance of dietary triggers varies widely among patients. Frequently invoked potential triggers include

coffee, alcohol, chocolate, diets rich in fat or carbohydrate, fried foods, and highly processed foods (high levels of sugar, salt and saturated fats) [37–39]. Consuming carbonated beverages has also been shown to increase the risk of heartburn during sleep [40].

4.2 | Weight Gain, Obesity and Hiatal Hernia

Large-scale cohort and population-based studies show that reflux-like symptoms increase progressively with increases in body mass index (BMI), even among normal weight individuals [41, 42]. Epidemiological research also indicates that obesity is an important risk factor for reflux complications, including reflux oesophagitis, Barrett's oesophagus, and oesophageal adenocarcinoma [43–46]. Hiatal hernia and increased intra-abdominal pressure are probably the most important physiological risk factors for gastro-oesophageal reflux, and both are also linked to obesity [47]. The spectrum of disruption of the diaphragmatic hiatus culminating in hiatal hernia is age-related and is the likely dominant pathophysiological factor linking advancing age to reflux. However, excessive abdominal straining (e.g., through weight training) can also cause hiatal hernia in normal weight and younger individuals [48].

5 | Individualised Management Strategies

5.1 | Expectation Setting and Counselling

Reflux-like symptoms have a multifactorial pathophysiology and wax and wane over time. The decision whether to continue PPI long-term will be individualised, based on the level of symptomatic benefit and patient preference. Management should be patient-centred, with a personalised strategy that is reflective of the relative dominance of physiological, behavioural and dietary factors at play in their specific case. However, this complex pathophysiology is often oversimplified as a problem of excessive oesophageal acid exposure. The acid-related concept is so deep-rooted that the concept of 'PPI failure' may be more a problem of unrealistic expectations rather than one of PPI efficacy. The availability of over-the-counter products and, in some countries, direct-to-consumer advertising, can further boost expectations and when these expectations are not met it can generate fear among patients about alternative reasons for refractory symptoms, such as cancer or heart disease.

Identification of specific contributing factors requires an understanding of a patient's personal circumstances and perceptions, as well as a clear elucidation of their symptom type, severity, comorbidities, treatment history, and potential alarm features requiring investigation (e.g., weight loss, anaemia or dysphagia). Counselling patients on the multi-factorial aetiology of reflux-like symptoms, including the gut-brain connection, is critical for them to understand that a single intervention is unlikely to be a perfect solution. A better understanding of symptom pathophysiology may reduce fear and increase adherence to strategies which address suspected underlying contributors other than gastric acid.

The gut-brain axis should be explained in patient-friendly language as a two-way communication pathway by which certain thoughts, feelings and behaviours can increase the perception of and response to symptoms in the gastrointestinal tract, including the oesophagus and throat. Care is required so that patients understand that they are not being told that their symptoms are 'all in the mind'. Clinicians should reassure patients that the sensory pathways that are triggering symptoms can be modified, and that treatment aims to achieve steady and continued improvement rather than immediate resolution [49].

The doctor-patient relationship is key to achieving a more holistic approach to management that is based on the patient experience. Patients want their concerns to be taken seriously and are more satisfied when consultations are interactive [50]. Clinicians should use active listening, show compassion, and build rapport with patients to help elicit information such as current life stressors, anxiety around symptoms, or any history of trauma [49]. Patient-reported outcome (PRO) tools, such as the EHAS, GERDQ, the GERD Impact Scale (GIS) or Quality of Life in Reflux and Dyspepsia (QOLRAD) can make consultations more interactive, effective, and efficient.

Some patients may also need to be specifically reassured that the risk of developing oesophageal cancer is extremely low [49]. Data from the UK National Endoscopy Database highlights the low diagnostic yield from gastroscopy for symptom evaluation [51]. Nearly half of gastroscopies performed to investigate upper GI symptoms were conducted to investigate symptoms of reflux or dyspepsia (47.9%), but the adjusted positive predictive values for identifying cancer in these patients were only 0.3% for dyspepsia and 0.2% for reflux-like symptoms [51]. These compare to an adjusted positive predictive value of 6.8% for identifying cancer in men aged 50 or over with dysphagia [51]. Nevertheless, investigation is often required to provide reassurance for the clinician, patient, and patient's family.

5.2 | Diet and Lifestyle Changes

Diet and lifestyle intervention is a key element of care for all patients with reflux-like symptoms. While rigorous evidence from randomised controlled trials (RCTs) is scarce, the concept that dietary and lifestyle changes can lower the risk of reflux-related symptoms is well established. However, relevant dietary and lifestyle contributors are highly individualised. Patients need to identify their specific risk factors and develop practical strategies to address them [52]. Expert consensus statements around diet and lifestyle advice for patients with reflux-like symptoms included avoidance of high-fat foods and potential dietary triggers (e.g., citrus, tomatoes, highly spiced or fried foods, chocolate, alcohol, coffee, carbonated drinks, etc.), overeating, and recumbency after meals [35]. Simple strategies, such as using plates of smaller size, deciding on a cut-off time for that last meal of the day (leaving a minimum 3-h interval before bedtime) or raising the head of the bed using blocks or a wedged pillow, are easy to implement and may help those who experience breakthrough acid reflux after meals or during the night [35, 52]. There are also lessons

to be learned from the Japanese practice of 'mindful eating', which aims to promote a heightened awareness of satiety cues by paying attention to flavours, textures, and the act of chewing, rather than eating distractedly [53]. The pre-meal mantra 'hara hachi bu' or "eat until you are 80% full" serves as a reminder to stop eating when comfortably satisfied, rather than overly full [53].

5.3 | Weight Management

Weight reduction is recommended for patients with reflux-like symptoms who are overweight or obese, and for those in the normal weight range who have recently gained weight [54]. Large-scale cohort and population-based studies show that weight loss reduces symptoms dose-dependently and increases the chance of treatment success with acid-reducing/neutralising medicines [41, 42]. Furthermore, a comparative study of symptomatic overweight patients with reflux oesophagitis showed that when PPI was prescribed with a tailored dietetic/aerobic exercise program to reduce body weight, there was not only greater symptom improvement, but more than half of patients were able to completely discontinue PPI (27/50) versus no patients who received PPI alone (0/51) [55].

The specific weight management intervention will depend on the services available locally. Use of an approved glucagon-like peptide-1 receptor agonist (GLP-1RA) may also be available to support weight loss as an adjunct to a calorie-restricted diet and exercise [56]. However, specific clinical data for these drugs for overweight patients with reflux-like symptoms is not yet available. Furthermore, some short-acting GLP-1RAs may increase the risk of oesophagitis and Barrett's oesophagus (with and without dysplasia) in patients with type 2 diabetes [57].

5.4 | Atypical (Laryngopharyngeal) Symptoms

PPI treatment is a common approach to the management of atypical reflux symptoms, but evidence from RCTs demonstrates little, if any, benefit over placebo [58, 59]. Furthermore, similar to the case of typical GERD symptoms, there is a huge disconnect between objective findings and symptom severity. For example, in a small study where patients with 'PPI-refractory' laryngopharyngeal symptoms underwent anti-reflux surgery, laryngeal signs improved in 80% of patients but only 10% showed symptomatic improvement [60]. Consequently, the paradigm is shifting away from the historic approach that largely focused on empiric, acid suppression with high-dose PPIs, and moving toward a phenotype-driven, personalised approach where the role of psychosocial factors on symptom perception and burden is acknowledged. Even if the original symptoms were caused by reflux or an upper respiratory tract infection, the vehicle of chronicity is laryngeal hypersensitivity that becomes further amplified by anxiety, hypervigilance, and learned detrimental behaviours such as throat clearing and chronic cough that can become habitual and self-perpetuating [61, 62]. The Laryngeal Cognitive-Affective Tool (LCAT), a 15-item questionnaire, has been validated specifically for the measurement of laryngeal hypervigilance and symptom-specific anxiety in patients with chronic laryngeal symptoms [62].

5.5 | Psychological Interventions

Brain-gut behaviour therapies (BGBT) may be beneficial in several circumstances, including in patients who identify a link between stress and their symptoms, those with difficulty coping with symptoms, and those who exhibit avoidance behaviours [63, 64]. BGBTs reduce both reflux symptom severity and psychological symptoms (e.g., GI-specific anxiety) resulting in improved quality of life [65–67]. The EHAS tool can be useful to gauge levels of symptom-associated anxiety and hypervigilance [16]. Good candidates for BGBT are those who accept and show an interest in the gut-brain connection, who acknowledge that coping could be improved, and who are willing to invest time in behaviour change [63, 64]. BGBT techniques may be combined with pharmacological approaches using agents that modulate both peripheral and central hyperalgesia, such as tricyclic antidepressants and selective serotonin/norepinephrine reuptake inhibitors [49].

BGBTs include nurse-led GI self-management skills training, GI-focused cognitive-behavioural therapy (CBT), gut-directed hypnotherapy, and mindfulness-based interventions (Figure 3) [63, 68]. A study investigating oesophageal-directed hypnotherapy in nine consecutive patients with functional heartburn demonstrated consistent and significant improvement in the impact of heartburn symptoms (assessed by QOLRAD, $p=0.01$), visceral anxiety ($p=0.01$), and emotional quality of life ($p=0.05$) [67]. A combination of techniques can be used to individualise therapy to a patient's specific needs or therapeutic targets (e.g., avoidance behaviour, visceral hypersensitivity, or trait anxiety; Figure 3) [63, 68]. While most of these techniques require specialist referral, primary care is ideally placed to implement nurse-led self-management skills training. Stress management and relaxation techniques may be key components of self-management programmes, as well as the implementation of the diet and lifestyle changes mentioned previously [63]. Programmes can be delivered remotely, often using self-help workbooks with the support of trained nurses [63].

BGBT may also be relevant for patients with chronic atypical symptoms who have developed laryngeal-specific anxiety and hypervigilance. In a study of patients referred for laryngopharyngeal symptoms who were treated with 'laryngeal recalibration therapy' involving a cognitive behavioural element, 85% had a symptomatic response, whether or not they had proven underlying reflux disease [69, 70].

5.6 | Diaphragmatic Breathing

Diaphragmatic breathing may be effective for reducing reflux-like symptoms [35]. In addition to its activation of the parasympathetic nervous system during high stress or symptom-triggering situations [71], it increases lower oesophageal sphincter pressure and crural diaphragm tension and may be especially useful for patients with regurgitation [35, 63]. Diaphragmatic breathing can also help relaxation by increasing vagal tone, which is disrupted in DGBIs [63].

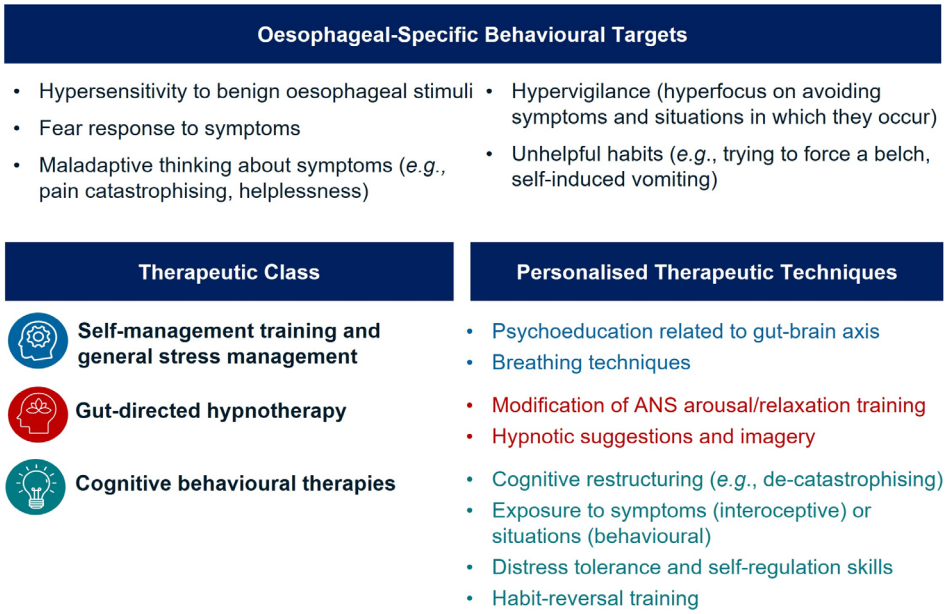

FIGURE 3 | Brain-gut behavioural interventions and targets. ANS, autonomic nervous system. Brain-gut behaviour therapies (BGBTs) target the specific and modifiable cognitive, emotional, and behavioural mediators underlying disorders of gut-brain interaction (DGBIs). More information on the evidence behind existing and emerging classes of BGBTs and their application as part of integrated care can be found in the Rome Working Team Report [63].

5.7 | On-Demand Symptom Control Measures

The growing resistance of patients and providers to maintenance PPI therapy in circumstances without a clear indication has led to broad PPI deprescribing initiatives in several countries [72]. An alternative to continuous maintenance treatment with a PPI is an on-demand symptom control strategy. Antacid or alginate-antacid products are a useful on-demand strategy for patients with postprandial acid reflux and regurgitation and for those with a hiatal hernia [73–75]. Alginate-antacid forms a viscous pH-neutral raft on contact with the postprandial acid pocket. It reduces the proximal migration of acid reflux episodes and displaces the acid pocket below the diaphragm in patients with a hiatal hernia [75, 76]. Meta-analyses show efficacy for symptom control versus placebo and non-inferiority to some PPIs [74, 77, 78]. In addition to targeting the acid pocket, alginates and other bioadhesive treatments that coat the oesophagus may reduce symptoms through protecting the mucosa [79]. A hyaluronic acid–chondroitin sulphate-based bioadhesive formulation has demonstrated superior reduction in reflux-like symptoms compared with placebo in patients with NERD [80].

On-demand therapy can also be useful as an alternative to dose escalation in patients being maintained on acid suppressive therapy for control of reflux-like symptoms. There is evidence of benefit when topical mucosal preparations containing alginate [81], or protective bioadhesive agents [82] are added to a PPI in patients with residual symptoms. The addition of an alginate preparation to a PPI significantly reduced the number of nights with reflux-like symptoms compared with a PPI alone [81].

6 | Summary

PPIs are extremely effective for healing reflux oesophagitis, but less so for resolving persistent reflux-like symptoms and even less for atypical reflux symptoms. This discrepancy is largely related to differences in the pathophysiological determinants of these entities. Whereas anatomical and physiological degradation of the anti-reflux barrier dominates in reflux oesophagitis, cognitive-affective and behavioural processes increase symptom burden by driving symptom generation and amplifying symptom perception. Hypersensitivity, hypervigilance, and anxiety are important contributors that correlate closely with symptom severity and persistence. It follows that management strategies should be individualised for patients, beginning with expectation setting and counselling. Rather than focusing solely on acid inhibition, effective management should utilise behaviour modification (e.g., diet and lifestyle changes, weight control) education regarding brain-gut interactions, psychological interventions, and on-demand symptom control measures as either a substitute or adjunct. A fundamental change in management approach is required such that acid suppression is viewed as just one of several interventions that can be utilised as part of an individualised approach to care.

Author Contributions

Peter J. Kahrilas: writing – original draft, conceptualization, writing – review and editing. **Laurie Keefer:** writing – review and editing. **Rena Yadlapati:** writing – review and editing. **Foteini Anastasiou:** writing – review and editing. **Joel J. Heidelbaugh:** writing – review and editing. **Colin W. Howden:** writing – review and editing. **Juan M. Mendive:** writing – review and editing. **Edoardo Vincenzo Savarino:** writing – review and editing. **Mihaela Udrescu:** writing – review and editing. **A. Pali S. Hungin:** conceptualization, writing – original draft, writing – review and editing.

Conflicts of Interest

All authors attended the online meetings funded by Reckitt Benckiser Healthcare Ltd., which formed the basis for this work.

Foteini Anastasiou has served as an advisory board member for Reckitt.

Joel J. Heidelbaugh has no further conflicts of interest.

Colin W. Howden has served as a speaker for Phathom Pharmaceuticals and RedHill Biopharma, a consultant, and an advisory board member for Phathom Pharmaceuticals, Braintree Laboratories, RedHill Biopharma, Meridian Diagnostics, and ISOThrive.

A. Pali S. Hungin has served as a consultant and an advisory board member and has been involved in the development of educational materials for Reckitt and the Primary Care Society for Gastroenterology (UK).

Peter J. Kahrilas has served as a consultant and an advisory board member for Reckitt and Implantica, as a speaker for Phathom Pharmaceuticals, and owns the patent for Medtronic FLIP panometry methods and technology.

Laurie Keefer has served as a consultant and an advisory board member for AbbVie, Ardelyx, Coprata Health, Eli Lilly, Janssen, Pfizer, and Reckitt; is co-founder and equity owner for Trellus Health; serves on the board of directors of the Rome Foundation; and receives royalties from Routledge and Northwestern University.

Juan M. Mendive has served as a consultant, an advisory board member, and has been involved in the development of educational materials for Reckitt.

Edoardo Vincenzo Savarino has served as speaker for Abbvie, Abivax, Agave, AGPharma, Alfasigma, Apoteca, Biosline, CaDiGroup, Celltrion, Dr. Falk, EG Stada Group, Fenix Pharma, Galapagos, Johnson & Johnson, JB Pharmaceuticals, Innovamedica/Adacyte, Eli Lilly, Malesci, Mayoly Biohealth, Montefarco, Novartis, Omega Pharma, Pfizer, Rafa, Reckitt Benckiser, Sandoz, Sanofi/Regeneron, SILA, Sofar, Takeda, Tillots, Unifarco; has served as consultant for Abbvie, Agave, Alfasigma, Biogen, Bristol-Myers Squibb, Celltrion, Dr. Falk, Eli Lilly, Fenix Pharma, Ferring, Giuliani, Grunenthal, Johnson & Johnson, JB Pharmaceuticals, Merck & Co, Nestlé, Pfizer, Reckitt Benckiser, Sanofi/Regeneron, SILA, Sofar, Takeda, Unifarco; he received research support from Bonollo, Difass, Pfizer, Reckitt Benckiser Healthcare Ltd., Sanofi/Regeneron, SILA, Sofar, Unifarco, Zeta Farmaceutici.

Mihaela Udrescu has served as a consultant and an advisory board member and has been involved in the development of educational materials for Reckitt and Astra Zeneca.

Rena Yadlapati has served as a consultant for Phathom Pharmaceuticals and Sebella, and has served on the advisory board for RJS Mediagnostix.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

1. L. G. T. Shanika, A. Reynolds, S. Pattison, and R. Braund, "Proton Pump Inhibitor Use: Systematic Review of Global Trends and Practices," *European Journal of Clinical Pharmacology* 79, no. 9 (2023): 1159–1172.

2. B. Farrell, E. Lass, P. Moayyedi, D. Ward, and W. Thompson, "Reduce Unnecessary Use of Proton Pump Inhibitors," *BMJ* 379 (2022): e069211.

3. L. E. Targownik, D. A. Fisher, and S. D. Saini, "AGA Clinical Practice Update on De-Prescribing of Proton Pump Inhibitors: Expert Review," *Gastroenterology* 162, no. 4 (2022): 1334–1342.

4. K. Plehhova, J. Wray, P. Aluko, et al., "Prescribing Practices for Proton Pump Inhibitors Among Primary Care Physicians in England," *BJGP Open* (2024), https://doi.org/10.3399/bjgpo.2024.0059. Online ahead of print.

5. H. El-Serag, A. Becher, and R. Jones, "Systematic Review: Persistent Reflux Symptoms on Proton Pump Inhibitor Therapy in Primary Care and Community Studies," *Alimentary Pharmacology & Therapeutics* 32, no. 6 (2010): 720–737.

6. S. D. Delshad, C. V. Almario, W. D. Chey, and B. M. R. Spiegel, "Prevalence of Gastroesophageal Reflux Disease and Proton Pump Inhibitor-Refractory Symptoms," *Gastroenterology* 158, no. 5 (2020): 1250–1261.

7. D. Armstrong, A. P. Hungin, P. J. Kahrilas, et al., "Management of Patients With Refractory Reflux-Like Symptoms Despite Proton Pump Inhibitor Therapy: Evidence-Based Consensus Statements," *Alimentary Pharmacology & Therapeutics* 61, no. 4 (2025): 636–650.

8. F. Zerbib, A. J. Bredenoord, R. Fass, et al., "ESNM/ANMS Consensus Paper: Diagnosis and Management of Refractory Gastro-Esophageal Reflux Disease," *Neurogastroenterology and Motility* 33, no. 4 (2021): e14075.

9. A. Patel, L. Laine, P. Moayyedi, and J. Wu, "AGA Clinical Practice Update on Integrating Potassium-Competitive Acid Blockers Into Clinical Practice: Expert Review," *Gastroenterology* 167, no. 6 (2024): 1228–1238.

10. A. Patel and R. Yadlapati, "Diagnosis and Management of Refractory Gastroesophageal Reflux Disease," *Gastroenterology and Hepatology* 17, no. 7 (2021): 305–315.

11. T. A. Davis and C. P. Gyawali, "Refractory Gastroesophageal Reflux Disease: Diagnosis and Management," *Journal of Neurogastroenterology and Motility* 30, no. 1 (2024): 17–28.

12. D. A. Katzka, J. E. Pandolfino, and P. J. Kahrilas, "Phenotypes of Gastroesophageal Reflux Disease: Where Rome, Lyon, and Montreal Meet," *Clinical Gastroenterology and Hepatology* 18, no. 4 (2020): 767–776.

13. C. W. Howden, C. Scarpignato, E. Leifke, et al., "Mathematical Model of the Relationship Between pH Holding Time and Erosive Esophagitis Healing Rates," *CPT: Pharmacometrics & Systems Pharmacology* 14, no. 1 (2024): 28–41, https://doi.org/10.1002/psp4.13235.

14. N. Vakil, S. V. van Zanten, P. Kahrilas, et al., "The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus," *American Journal of Gastroenterology* 101, no. 8 (2006): 1900–1920; quiz 1943.

15. E. Savarino, P. Zentilin, and V. Savarino, "NERD: An Umbrella Term Including Heterogeneous Subpopulations," *Nature Reviews. Gastroenterology & Hepatology* 10, no. 6 (2013): 371–380.

16. T. H. Taft, L. Guadagnoli, D. A. Carlson, W. Kou, L. Keefer, and J. Pandolfino, "Validation of the Short-Form Esophageal Hypervigilance and Anxiety Scale," *Clinical Gastroenterology and Hepatology* 20, no. 2 (2022): e64–e73, https://doi.org/10.1016/j.cgh.2020.12.021.

17. B. J. Gawey, R. A. Mars, and P. C. Kashyap, "The Role of the Gut Microbiome in Disorders of Gut-Brain Interaction," *FEBS Journal* 292, no. 6 (2024): 1357–1377, https://doi.org/10.1111/febs.17200.

18. K. R. Amato, M. C. Arrieta, M. B. Azad, et al., "The Human Gut Microbiome and Health Inequities," *Proceedings of the National Academy of Sciences of the United States of America* 118, no. 25 (2021): e2017947118, https://doi.org/10.1073/pnas.2017947118.

19. M. W. Wong, T. T. Liu, C. H. Yi, et al., "Oesophageal Hypervigilance and Visceral Anxiety Relate to Reflux Symptom Severity and Psychological Distress but Not to Acid Reflux Parameters," *Alimentary Pharmacology & Therapeutics* 54, no. 7 (2021): 923–930.

20. L. Guadagnoli, A. Geeraerts, H. Geysen, et al., "Psychological Processes, Not Physiological Parameters, Are Most Important Contributors to Symptom Severity in Patients With Refractory Heartburn/Regurgitation Symptoms," *Gastroenterology* 165, no. 4 (2023): 848–860.

21. L. Guadagnoli, R. Yadlapati, T. Taft, J. E. Pandolfino, M. Tye, and L. Keefer, "Esophageal Hypervigilance is Prevalent Across Gastroesophageal Reflux Disease Presentations," *Neurogastroenterology and Motility* 33 (2021): e14081.

22. Q. Aziz, R. Fass, C. P. Gyawali, H. Miwa, J. E. Pandolfino, and F. Zerbib, "Esophageal Disorders," *Gastroenterology* 150, no. 6 (2016): 1368–1379, https://doi.org/10.1053/j.gastro.2016.02.012.

23. J. Simons, U. Shajee, O. Palsson, et al., "Disorders of Gut-Brain Interaction: Highly Prevalent and Burdensome Yet Under-Taught Within Medical Education," *United European Gastroenterology Journal* 10, no. 7 (2022): 736–744.

24. R. S. Choung, R. G. Locke, 3rd, C. D. Schleck, G. Richard Locke, III, A. R. Zinsmeister, and N. J. Talley, "Multiple Functional Gastrointestinal Disorders Linked to Gastroesophageal Reflux and Somatization: A Population-Based Study," *Neurogastroenterology and Motility* 29, no. 7 (2017): e13041, https://doi.org/10.1111/nmo.13041.

25. L. Guadagnoli and R. Yadlapati, "The Role of Hypervigilance in Chronic Esophageal Diseases: A Scoping Review," *Translational Gastroenterology and Hepatology* 9 (2024): 44.

26. S. Roman and F. Mion, "Editorial: Diagnosis of GERD in Patients With Extra-Oesophageal Symptoms-Still a Long Way to Go...," *Alimentary Pharmacology & Therapeutics* 59, no. 9 (2024): 1148–1149.

27. A. J. Krause, M. Greytak, Z. C. Burger, et al., "Hypervigilance and Anxiety Are Elevated Among Patients With Laryngeal Symptoms With and Without Laryngopharyngeal Reflux," *Clinical Gastroenterology and Hepatology* 21, no. 11 (2023): 2965–2967.

28. R. Yadlapati, A. M. Kaizer, D. R. Sikavi, et al., "Distinct Clinical Physiologic Phenotypes of Patients With Laryngeal Symptoms Referred for Reflux Evaluation," *Clinical Gastroenterology and Hepatology* 20, no. 4 (2022): 776–786.

29. A. D'Alessandro, F. P. Zito, M. Pesce, et al., "Specific Dyspeptic Symptoms Are Associated With Poor Response to Therapy in Patients With Gastroesophageal Reflux Disease," *United European Gastroenterology Journal* 5, no. 1 (2017): 54–59.

30. E. Savarino, D. Pohl, P. Zentilin, et al., "Functional Heartburn Has More in Common With Functional Dyspepsia Than With Non-Erosive Reflux Disease," *Gut* 58, no. 9 (2009): 1185–1191.

31. N. de Bortoli, L. Frazzoni, E. V. Savarino, et al., "Functional Heartburn Overlaps With Irritable Bowel Syndrome More Often Than GERD," *American Journal of Gastroenterology* 111, no. 12 (2016): 1711–1717.

32. R. C. Heading, E. C. Thomas, P. Sandy, et al., "Discrepancies Between Upper GI Symptoms Described by Those Who Have Them and Their Identification by Conventional Medical Terminology: A Survey of Sufferers in Four Countries," *European Journal of Gastroenterology & Hepatology* 28, no. 4 (2016): 455–462.

33. S. Bösner, K. Bönisch, J. Haasenritter, P. Schlegel, E. Hüllermeier, and N. Donner-Banzhoff, "Chest Pain in Primary Care: Is the Localization of Pain Diagnostically Helpful in the Critical Evaluation of Patients? A Cross Sectional Study," *BMC Family Practice* 14 (2013): 154.

34. G. Holtmann, O. Chassany, K. R. Devault, et al., "International Validation of a Health-Related Quality of Life Questionnaire in Patients With Erosive Gastro-Oesophageal Reflux Disease," *Alimentary Pharmacology & Therapeutics* 29, no. 6 (2009): 615–625.

35. A. P. Hungin, R. Yadlapati, F. Anastasiou, et al., "Management Advice for Patients With Reflux-Like Symptoms: An Evidence-Based Consensus," *European Journal of Gastroenterology & Hepatology* 36, no. 1 (2024): 13–25.

36. P. J. Kahrilas, "Management of the Acid Pocket," *Gastroenterology and Hepatology* 10, no. 9 (2014): 587–589.

37. H. B. El-Serag, J. A. Satia, and L. Rabeneck, "Dietary Intake and the Risk of Gastro-Oesophageal Reflux Disease: A Cross Sectional Study in Volunteers," *Gut* 54, no. 1 (2005): 11–17.

38. N. Lakananurak, P. Pitisuttithum, P. Susantitaphong, T. Patcharatrakul, and S. Gonlachanvit, "The Efficacy of Dietary Interventions in Patients With Gastroesophageal Reflux Disease: A Systematic Review and Meta-Analysis of Intervention Studies," *Nutrients* 16, no. 3 (2024): 464, https://doi.org/10.3390/nu16030464.

39. I. Mone, B. Kraja, A. Bregu, et al., "Adherence to a Predominantly Mediterranean Diet Decreases the Risk of Gastroesophageal Reflux Disease: A Cross-Sectional Study in a South Eastern European Population," *Diseases of the Esophagus* 29, no. 7 (2016): 794–800.

40. R. Fass, S. F. Quan, G. T. O'Connor, A. Ervin, and C. Iber, "Predictors of Heartburn During Sleep in a Large Prospective Cohort Study," *Chest* 127, no. 5 (2005): 1658–1666.

41. B. C. Jacobson, S. C. Somers, C. S. Fuchs, C. P. Kelly, and C. A. Camargo, Jr., "Body-Mass Index and Symptoms of Gastroesophageal Reflux in Women," *New England Journal of Medicine* 354, no. 22 (2006): 2340–2348.

42. E. Ness-Jensen, A. Lindam, J. Lagergren, and K. Hveem, "Weight Loss and Reduction in Gastroesophageal Reflux. A Prospective Population-Based Cohort Study: The HUNT Study," *American Journal of Gastroenterology* 108, no. 3 (2013): 376–382.

43. P. Chang and F. Friedenberg, "Obesity and GERD," *Gastroenterology Clinics of North America* 43, no. 1 (2014): 161–173.

44. A. P. Witarto, B. S. Witarto, S. L. Pramudito, et al., "Risk Factors and 26-Years Worldwide Prevalence of Endoscopic Erosive Esophagitis From 1997 to 2022: A Meta-Analysis," *Scientific Reports* 13, no. 1 (2023): 15249.

45. H. El-Serag, "The Association Between Obesity and GERD: A Review of the Epidemiological Evidence," *Digestive Diseases and Sciences* 53, no. 9 (2008): 2307–2312.

46. H. Hampel, N. S. Abraham, and H. B. El-Serag, "Meta-Analysis: Obesity and the Risk for Gastroesophageal Reflux Disease and its Complications," *Annals of Internal Medicine* 143, no. 3 (2005): 199–211.

47. J. E. Pandolfino, H. B. El-Serag, Q. Zhang, et al., "Obesity: A Challenge to Esophagogastric Junction Integrity," *Gastroenterology* 130, no. 3 (2006): 639–649.

48. K. L. Collings, F. Pierce Pratt, S. Rodriguez-Stanley, M. Bemben, and P. B. Miner, "Esophageal Reflux in Conditioned Runners, Cyclists, and Weightlifters," *Medicine and Science in Sports and Exercise* 35, no. 5 (2003): 730–735.

49. J. Tome, A. K. Kamboj, and C. G. Loftus, "Approach to Disorders of Gut-Brain Interaction," *Mayo Clinic Proceedings* 98, no. 3 (2023): 458–467.

50. P. Bytzer, "What Makes Individuals With Gastroesophageal Reflux Disease Dissatisfied With Their Treatment?," *Clinical Gastroenterology and Hepatology* 7, no. 8 (2009): 816–822.

51. D. R. Beaton, L. Sharp, L. Lu, et al., "Diagnostic Yield From Symptomatic Gastroscopy in the UK: British Society of Gastroenterology Analysis Using Data From the National Endoscopy Database," *Gut* 73, no. 9 (2024): 1421–1430.

52. P. J. Kahrilas, F. Anastasiou, K. Barrett, et al., "Assessment and Treatment of Reflux-Like Symptoms in the Community: A Multidisciplinary Perspective," *British Journal of General Practice* 74, no. 742 (2024): 232–235.

53. Y. Fukkoshi, R. Akamatsu, and M. Shimpo, "The Relationship of Eating Until 80% Full With Types and Energy Values of Food Consumed," *Eating Behaviors* 17 (2015): 153–156.

54. P. O. Katz, K. B. Dunbar, F. H. Schnoll-Sussman, K. B. Greer, R. Yadlapati, and S. J. Spechler, "ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease," *American Journal of Gastroenterology* 117, no. 1 (2022): 27–56.

55. N. de Bortoli, G. Guidi, I. Martinucci, et al., "Voluntary and Controlled Weight Loss Can Reduce Symptoms and Proton Pump Inhibitor Use and Dosage in Patients With Gastroesophageal Reflux Disease: A Comparative Study," *Diseases of the Esophagus* 29, no. 2 (2016): 197–204.

56. H. Moll, E. Frey, P. Gerber, et al., "GLP-1 Receptor Agonists for Weight Reduction in People Living With Obesity but Without Diabetes: A Living Benefit-Harm Modelling Study," *EClinical Medicine* 73 (2024): 10266.

57. B. D. Liu, S. C. Udemba, K. Liang, et al., "Shorter-Acting Glucagon-Like Peptide-1 Receptor Agonists Are Associated With Increased Development of Gastro-Oesophageal Reflux Disease and Its Complications in Patients With Type 2 Diabetes Mellitus: A Population-Level Retrospective Matched Cohort Study," *Gut* 73, no. 2 (2024): 246–254.

58. J. O'Hara, D. D. Stocken, G. C. Watson, et al., "Use of Proton Pump Inhibitors to Treat Persistent Throat Symptoms: Multicentre, Double Blind, Randomised, Placebo Controlled Trial," *BMJ* 372 (2021): m4903.

59. D. A. Patel, M. Blanco, and M. F. Vaezi, "Laryngopharyngeal Reflux and Functional Laryngeal Disorder: Perspective and Common Practice of the General Gastroenterologist," *Gastroenterology and Hepatology* 14, no. 9 (2018): 512–520.

60. J. Swoger, J. Ponsky, D. M. Hicks, et al., "Surgical Fundoplication in Laryngopharyngeal Reflux Unresponsive to Aggressive Acid Suppression: A Controlled Study," *Clinical Gastroenterology and Hepatology* 4, no. 4 (2006): 433–441.

61. A. J. Krause, E. H. Walsh, P. A. Weissbrod, T. H. Taft, and R. Yadlapati, "An Update on Current Treatment Strategies for Laryngopharyngeal Reflux Symptoms," *Annals of the New York Academy of Sciences* 1510, no. 1 (2022): 5–17.

62. A. J. Krause, T. Taft, M. Greytak, et al., "Validation of the Laryngeal Cognitive-Affective Tool," *Clinical Gastroenterology and Hepatology* 22, no. 7 (2024): 1395–1403.

63. L. Keefer, S. K. Ballou, D. A. Drossman, G. Ringstrom, S. Elsenbruch, and B. Ljótsson, "A Rome Working Team Report on Brain-Gut Behavior Therapies for Disorders of Gut-Brain Interaction," *Gastroenterology* 162, no. 1 (2022): 300–315.

64. L. Guadagnoli, R. Yadlapati, J. Pandolfino, et al., "Behavioral Therapy for Functional Heartburn: Recommendation Statements," *Clinical Gastroenterology and Hepatology* 22, no. 8 (2024): 1709–1718.

65. Y. Luo and L. Keefer, "The Clinical Value of Brain-Gut Behavioral Therapies for Functional Esophageal Disorders and Symptoms," *Neurogastroenterology and Motility* 34, no. 6 (2022): e14373.

66. M. E. Riehl and J. W. Chen, "The Proton Pump Inhibitor Nonresponder: A Behavioral Approach to Improvement and Wellness," *Current Gastroenterology Reports* 20, no. 7 (2018): 34.

67. M. E. Riehl, J. E. Pandolfino, O. S. Palsson, and L. Keefer, "Feasibility and Acceptability of Esophageal-Directed Hypnotherapy for Functional Heartburn," *Diseases of the Esophagus* 29, no. 5 (2016): 490–496.

68. H. Burton Murray and B. Ljótsson, "Future of Brain-Gut Behavior Therapies: Mediators and Moderators," *Gastroenterology Clinics of North America* 51, no. 4 (2022): 723–739, https://doi.org/10.1016/j.gtc.2022.06.011.

69. E. Walsh, A. J. Krause, M. Greytak, et al., "Laryngeal Recalibration Therapy Improves Laryngopharyngeal Symptoms in Patients With Suspected Laryngopharyngeal Reflux Disease," *American Journal of Gastroenterology* 119 (2024): 2198–2205, https://doi.org/10.14309/ajg.0000000000002839.

70. R. Yadlapati, E. Walsh, and T. Taft, "Laryngeal Recalibration Therapy in Clinical Practice for Laryngopharyngeal Symptoms," *American Journal of Gastroenterology* (2024), https://doi.org/10.14309/ajg.0000000000003176. Online ahead of print.

71. H. Hamasaki, "Effects of Diaphragmatic Breathing on Health: A Narrative Review," *Medicine* 7, no. 10 (2020): 65, https://doi.org/10.3390/medicines7100065.

72. P. Kahrilas, F. Anastasiou, A. J. Bredenoord, et al., "Proton Pump Inhibitors: Rational Use and Use-Reduction—The Windsor Workshop," *Digestive Diseases* 42, no. 3 (2024): 211–220.

73. R. Yadlapati, C. P. Gyawali, and J. E. Pandolfino, "AGA Clinical Practice Update on the Personalized Approach to the Evaluation and Management of GERD: Expert Review," *Clinical Gastroenterology and Hepatology* 20, no. 5 (2022): 984–994.

74. T. Tran, A. M. Lowry, and H. B. El-Serag, "Meta-Analysis: The Efficacy of Over-The-Counter Gastro-Oesophageal Reflux Disease Therapies," *Alimentary Pharmacology & Therapeutics* 25, no. 2 (2007): 143–153.

75. W. O. Rohof, R. J. Bennink, A. J. Smout, et al., "An Alginate-Antacid Formulation Localizes to the Acid Pocket to Reduce Acid Reflux in Patients With Gastroesophageal Reflux Disease," *Clinical Gastroenterology and Hepatology* 11, no. 12 (2013): 1585–1591; quiz e90.

76. A. De Ruigh, S. Roman, J. Chen, et al., "Gaviscon Double Action Liquid (Antacid & Alginate) is More Effective Than Antacid in Controlling Post-Prandial Oesophageal Acid Exposure in GERD Patients: A Double-Blind Crossover Study," *Alimentary Pharmacology & Therapeutics* 40, no. 5 (2014): 531–537.

77. B. Barberio, P. Visaggi, E. Savarino, et al., "Comparison of Acid-Lowering Drugs for Endoscopy Negative Reflux Disease: Systematic Review and Network Meta-Analysis," *Neurogastroenterology and Motility* 35, no. 1 (2023): e14469.

78. C. T. Chiu, C. M. Hsu, C. C. Wang, et al., "Randomised Clinical Trial: Sodium Alginate Oral Suspension is Non-Inferior to Omeprazole in the Treatment of Patients With Non-Erosive Gastroesophageal Disease," *Alimentary Pharmacology & Therapeutics* 38, no. 9 (2013): 1054–1064.

79. P. Woodland, C. Lee, Y. Duraisamy, et al., "Assessment and Protection of Esophageal Mucosal Integrity in Patients With Heartburn Without Esophagitis," *American Journal of Gastroenterology* 108, no. 4 (2013): 535–543.

80. B. Palmieri, A. Merighi, D. Corbascio, V. Rottigni, G. Fistetto, and A. Esposito, "Fixed Combination of Hyaluronic Acid and Chondroitin-Sulphate Oral Formulation in a Randomized Double Blind, Placebo Controlled Study for the Treatment of Symptoms in Patients With Non-Erosive Gastroesophageal Reflux," *European Review for Medical and Pharmacological Sciences* 17, no. 24 (2013): 3272–3278.

81. C. Reimer, A. B. Lødrup, G. Smith, J. Wilkinson, and P. Bytzer, "Randomised Clinical Trial: Alginate (Gaviscon Advance) vs. Placebo as Add-On Therapy in Reflux Patients With Inadequate Response to a Once Daily Proton Pump Inhibitor," *Alimentary Pharmacology & Therapeutics* 43, no. 8 (2016): 899–909.

82. V. Savarino, F. Pace, and C. Scarpignato, "Randomised Clinical Trial: Mucosal Protection Combined With Acid Suppression in the Treatment of Non-Erosive Reflux Disease—Efficacy of Esoxx, a Hyaluronic Acid-Chondroitin Sulphate Based Bioadhesive Formulation," *Alimentary Pharmacology & Therapeutics* 45, no. 5 (2017): 631–642, https://doi.org/10.1111/apt.13914.