

Nonmedical Therapeutic Strategies for Nonerosive Reflux Disease

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Abstract: There has been a marked decline over the last several years in drug development for gastroesophageal reflux disease and specifically for nonerosive reflux disease (NERD), despite there being many areas of unmet need. In contrast, we have seen a proliferation, during the same period of time, in development of novel, nonmedical therapeutic strategies for NERD using cutting-edge technology. Presently, compliance and lifestyle modifications are readily available noninvasive therapeutic interventions for NERD. Other nonmedical therapies include, the Stretta procedure, transoral incisionless fundoplication, and the magnetic sphincter augmentation device (LINX). Antireflux surgery, in experienced hands, has been repeatedly shown to be efficacious in resolving NERD-related symptoms. Psychological therapeutic interventions and alternative medicine techniques, such as acupuncture, continue to show promise, especially in NERD patients who failed antireflux treatment.

Key Words: nonerosive reflux disease, anti-reflux surgery, endoscopic therapy, gastroesophageal reflux disease, compliance, lifestyle modifications

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Nonerosive reflux disease (NERD) was originally defined as the presence of typical gastroesophageal reflux disease (GERD) symptoms caused by intra-esophageal reflux (acidic or weakly acidic) in the absence of visible esophageal mucosal injury at endoscopy.¹ At the Montreal Consensus meeting less than a decade ago, NERD was defined as the presence of troublesome reflux-associated symptoms and the absence of mucosal breaks.² Studies using high-resolution magnification endoscopy have demonstrated the presence of minimal mucosal changes at the squamocolumnar junction in NERD patients with previously normal conventional upper endoscopy.³ However, these minimal mucosal changes, which require special endoscopic equipment to detect, have not been shown to distinguish clinically between erosive esophagitis (EE), NERD, and functional heartburn and thus far have not been incorporated into the definition of NERD.

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NERD accounts for up to 70% of patients with heartburn and is the most common phenotypic presentation of GERD.⁴ In general, the proportion of NERD patients responding to a standard dose of proton pump inhibitor (PPI) is approximately 20% to 30% lower than that documented for patients with EE. In a systematic review of the literature, PPI symptomatic response pooled rate was 36.7% (95% CI, 34.1%-39.3%) in NERD patients and 55.5% (95% CI, 51.5%-59.5%) in those with EE.⁵ Therapeutic gain was 27.5% in NERD patients as compared with 48.9% in EE patients. Moreover, patients with NERD demonstrate a close relationship between response to PPI therapy and degree of esophageal acid exposure: the greater the distal esophageal acid exposure, the higher the proportion of NERD patients reporting symptom resolution.⁶ This is the opposite of what has been observed in patients with EE, where increased esophageal inflammation has been associated with a lower response rate to PPI once daily. Patients with NERD also demonstrate longer lag time to sustained symptom response when compared with EE patients (2- to 3-fold). Furthermore, patients with NERD demonstrate similar symptomatic response to half and full standard dose of PPI,⁷ unlike patients with EE who demonstrate an incremental increase in healing and symptom resolution.

Dilation of intercellular spaces (DISs) has been identified in GERD, and specifically in NERD patients, by electron micrograph.⁸ It has been proposed that DISs are essential for symptom generation in these patients. Presently it is presumed that DISs enable diffusion of refluxed acid or nonacid content into the intercellular spaces, thus sensitizing nerve endings located within the esophageal mucosa.^{9,10}

The natural course of NERD and EE is still an area of intense controversy.^{11,12} Fass and Ofman¹³ proposed a new paradigm suggesting that GERD patients exhibit 3 phenotypic presentations: NERD, EE, and Barrett's esophagus. On the basis of this paradigm, most NERD and EE patients remain within their respective GERD groups throughout their lifetime.^{13,14} The long-standing assumption that NERD and EE represent 1 continuous disorder has been challenged by studies demonstrating that the 2 disorders have different epidemiological and pathophysiological characteristics as well as responses to treatment.^{11,14} Currently, available natural course studies in NERD have suggested that lack of progression is more common than progression along the GERD spectrum.¹⁵

Medical therapeutic strategies remain the mainstay of treatment for NERD patients. Of those, proton pump inhibitors (PPIs) are considered the most effective and safest therapeutic modality in this challenging group of patients. However, the last decade has seen a shift in treatment development for GERD and specifically for NERD. There has been a marked decline in drug development but at the same time a dramatic increase in testing

of novel, nonmedical therapeutic techniques. Consequently, this review will focus on the evolution of nonmedical therapeutic strategies for NERD in the last decade.

CLINICAL ENDPOINTS

Therapeutic trials for NERD commonly last 4 weeks as compared with therapeutic trials for EE, which typically last 8 weeks. Initially, therapeutic trials for NERD used clinical endpoints that were similar to those utilized for EE trials. However, the focus of therapeutic trials for NERD patients is solely on symptoms control, unlike that for patients with EE. Complete absence of heartburn at 4 weeks was a common clinical endpoint that was borrowed from EE trials.^{6,16,17} Other clinical endpoints included percentage of days without heartburn, percentage of nights without heartburn, and mean daily antacid consumption.^{7,17} Many NERD studies defined resolution of heartburn at 4 weeks as no heartburn symptoms during the last 7 days of the treatment period.¹⁸

It is highly unlikely that EE clinical endpoints are relevant to NERD patients, given the complexity of the disorder and the heterogeneity of these patients. Thus, when Katz et al¹⁹ used complete resolution of heartburn after 4 weeks of treatment with either esomeprazole 40 or 20 mg once daily in NERD patients, the response rate in study 1 was 33.1% and 33.9%, respectively, and 36.4% and 41.6%, respectively, in study 2. However, when the authors used mean percentage of heartburn-free days during 4 weeks of treatment, there was a marked increase in the response rate in study 1 to 62.8% and 62.7%, respectively, and in study 2 to 66.4% and 68.0%, respectively. Furthermore, Lind et al⁶ evaluated symptomatic response rate in 509 NERD patients who had been randomized to omeprazole 20 or 10 mg daily. When using complete absence of heartburn as the endpoint, the response rate was 46.1% and 31%, respectively. However, when they used resolution of heartburn (defined as at least 1 event during last week of treatment) as the clinical endpoint, the response rate increased to 61% and 49%, respectively (Fig. 1). Dean et al⁵ demonstrated that the pooled difference (treatment and placebo) in the proportion of NERD patients with

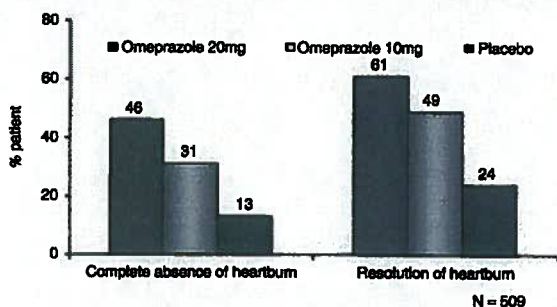


FIGURE 1. The proportion of NERD patients responding to treatment at 4 weeks using 2 different clinical endpoints. A more restrictive clinical endpoint (complete absence of heartburn) results in a much lower symptomatic response rate as compared with a less restrictive clinical endpoint (resolution of heartburn). Adapted from Lind et al.⁶ Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

heartburn resolution by time using PPI once daily was 0.22 for complete resolution and 0.32 for sufficient resolution of symptoms after 2 weeks of treatment as well as 0.26 and 0.33 after 4 weeks of treatment.

In the pivotal trial of dexlansoprazole MR, the authors used clinical endpoints that are more suitable for NERD patients.²⁰ The primary efficiency endpoint was the percentage of 24-hour heartburn-free days, defined as days with neither daytime nor nighttime heartburn. Other efficacy endpoints were similar to the primary clinical endpoint, such as percentage of nights without nighttime heartburn and percentage of days without daytime heartburn.

NONMEDICAL THERAPIES

Compliance/Adherence

Poor compliance and adherence to PPI treatment are not uncommon among GERD patients in general nor in NERD patients in particular. Several studies have demonstrated a rapid decline in compliance from the time the antireflux medication was first prescribed. In 1 large survey, only 55% of GERD patients took their PPI once daily for 4 weeks as prescribed, whereas 37% took their PPI no more than 12 days in 4 weeks.²¹ As with all drug therapies, compliance further declines with increase in dosing.²²

Moreover, poor adherence with timing of PPI consumption is rampant among GERD patients, and NERD patients are no different. Gunaratnam et al²³ demonstrated that of the 100 patients with persistent GERD symptoms while on PPI treatment, only 46% were dosing optimally. Of those who dosed suboptimally, 38.9% consumed their PPI >60 minutes before a meal, 29.6% after a meal, and 27.8% at bedtime. In a Gallup survey, 52% of GERD patients reported taking their PPI at bedtime.²¹

Ensuring compliance and adherence to PPI dosing time is our "low hanging fruit" when it comes to better management of NERD patients. Treating physicians should repeatedly emphasize to their patients the need to consume antireflux medications on a daily basis if needed. In addition to compliance, proper timing of PPI consumption is essential for maximum efficacy of the medication.²⁴ Overall, proper compliance and adequate dosing time should be part of the first management steps for all NERD patients.

LIFESTYLE MODIFICATIONS

The specific value of implementing lifestyle modifications in NERD patients has yet to be elucidated. Heavy meals, exercise, increased alcohol consumption, and other daily activities might lead to or exacerbate symptoms in patients with NERD.⁴ Consequently, it is important to recommend avoidance of specific lifestyle activities that have been identified by patients or physicians as triggering GERD-related symptoms.² In addition, weight loss, elevation of the head of the bed, and avoiding food consumption at least 3 hours before bedtime have been shown to improve symptoms in GERD patients.²⁵ As with compliance and adherence, lifestyle modifications should also be considered as part of the first management step for all patients with NERD.

ENDOSCOPIC THERAPY

Endoscopic techniques to treat GERD were developed more than a decade ago, and most have since been

discontinued because of unacceptable side effects, modest or lack of long-term efficacy, cost, time invested, and lack of reversibility.^{26,27} The mechanisms of action of these procedures included decrease of proximal migration of acid reflux, decrease of transient lower esophageal sphincter relaxation (TLESR) rate, mechanical obstruction of reflux, increase in lower esophageal sphincter (LES) basal pressure, and possibly decrease of esophageal sensitivity to reflux.

Currently there are 2 endoluminal procedures that are clinically available and another one that is under investigation. EsophyX (EndoGastric Solutions, Redmond, WA), which is primarily marketed to surgeons, is used to perform transoral incisionless fundoplication (TIF). The device creates a full-thickness serosa-to-serosa plication and constructs a valve 3 to 5 cm in length and 200 to 300 degrees in circumference.²⁸ TIF increases LES length and resting basal pressure as well as reduces or normalizes intrasophageal pH and cardia circumference. The technique also markedly improves GERD-related symptoms, quality of life, and esophageal inflammation. Most importantly, TIF reduces or completely eliminates PPI consumption by different types of GERD patients, including those with NERD.^{29,30} Long-term follow-up is limited to approximately 3 years, and studies have reported worrisome side effects including esophageal perforation and significant GI bleeding.³¹ In addition, many of the therapeutic trials included small number of participants, lacked comparison with a sham control, and provided limited descriptions of the participants. In one of the largest multicenter trials, which included 86 patients treated with PPI (most with EE but all with hiatal hernia <2 cm in length), authors reported the results of a 12-month follow-up.²⁹ The study demonstrated that after 1 year, 73% of participants reported $\geq 50\%$ improvement in health-related quality of life (HRQL), 85% discontinued daily PPI use, and 37% normalized esophageal acid exposure.

The Stretta procedure (Mederi Therapeutics Inc., Greenwich, CT) uses an endoluminal approach to deliver low-power, temperature-controlled radiofrequency energy into the gastroesophageal junction. This relatively simple procedure, primarily performed by gastroenterologists, has been observed to reduce the frequency of TLESRs and consequently reduce gastroesophageal reflux episodes and esophageal acid exposure.^{32,33} Clinical studies have demonstrated a sustained improvement in GERD-related symptoms, quality of life, and use of antireflux medications over a period of 4 years.³⁴ Dughera et al³⁵ conducted a study that evaluated 69 participants treated with the Stretta procedure and their subsequent 48-month follow-up. The authors demonstrated a significant HRQL reduction in mean heartburn score and significant improvement in GERD as compared with baseline ($P = 0.001$ and 0.003 , respectively). Importantly, 72.3% of the participants were completely off PPI therapy after 48 months. Only 1 participant developed prolonged, but transient, gastroparesis.

Of all currently available endoscopic treatments for GERD, the Stretta procedure has the longest follow-up (up to 10 y). It is also one of the few endoscopic techniques for GERD that has been tested in a sham-controlled trial.³⁶ Concerns have been raised about the potential long-term anatomic complications of the Stretta procedure such as esophageal stricture or neurolysis. However, recent studies have argued against fibrosis and neurolysis as the main complications of the Stretta procedure in GERD. Instead, structural rearrangement of the smooth muscle and redistribution

of the interstitial cells of Cajal in the smooth muscle of the LES have been proposed.³⁷ In addition, patients who have undergone the Stretta procedure seem to have normal abdominal vagal function and normal esophageal motor activity.³⁸

The SRS Endoscopic Stapling System (Medigus, Tel Aviv, Israel) is a novel technique to treat GERD patients, including those with NERD. The procedure has not yet been approved and is currently undergoing clinical trials. The SRS is used to perform anterior fundoplication using a modified endoscope that incorporates a miniature camera, an ultrasound probe, and stapler at the tip.³⁹ A recent study compared the safety and efficacy of SRS with laparoscopic antireflux surgery (LARS).⁴⁰ The authors demonstrated that the procedure times for SRS and LARS were 47 and 89 minutes, respectively ($P < 0.05$). However, the mean discharge time from the hospital was longer for SRS as compared with LARS (3 vs. 1.2 d, $P < 0.05$). There was no significant difference in the need for PPI consumption between the 2 groups at a 6-month follow-up. The mean GERD-HRQL scores significantly improved in 64% of the participants who underwent SRS. The mean score in these patients decreased from 24.8 to 8.9 ($P = 0.016$). There was 1 esophageal perforation in the SRS group. The SRS technique is primarily promoted to surgeons and requires further evaluation about its long-term efficacy.

In general, the success of any endoscopic technique for GERD depends on careful patient selection and a high level of expertise of the surgeon or endoscopist.

ANTIREFLUX SURGERY

Laparoscopic fundoplication remains the leading antireflux procedure for both adults and children with GERD. The main goal of antireflux surgery is to prevent any type of reflux as opposed to PPI treatment, which prevents only acid reflux. Antireflux surgery creates a mechanical valve at the gastroesophageal junction, increases LES basal pressure, and decreases the rate of TLESR. In the expert hand, antireflux surgery is very effective and results in a high patient satisfaction rate. Potential side effects include dysphagia, bloating, inability to vomit or belch, diarrhea, and wrap failure. Predictors for success of antireflux surgery include careful preoperative assessment of NERD patients, expertise of the surgeon, and evidence of symptoms relief while on antireflux treatment.⁴¹

Several studies compared the efficacy of Nissen fundoplication between patients with NERD and those with EE. The studies consistently demonstrated similar clinical outcome.^{42,43} Patients with NERD have shown similar improvement postoperatively in quality of life, PPI use, esophageal acid exposure time, symptom-reflux association, LES basal pressure, reoperation rate, and symptom relief.⁴³

Broeders and colleagues demonstrated that even 5 years after Nissen fundoplication, there was a similar decrease in PPI use in both NERD (82% to 21%) and EE patients (81% to 15%) ($P < 0.001$). HRQL scores improved equally in both groups (NERD from 50.3 to 65.2, $P < 0.001$, and EE from 52.0 to 60.7, $P = 0.016$). However, in all of the aforementioned studies, participants were fully evaluated to ensure that they had NERD with abnormal esophageal acid exposure. Interestingly, a study by Omura et al⁴⁴ showed that NERD participants with normal esophageal acid exposure also responded very well to antireflux surgery.

Despite the high efficacy of antireflux surgery for preventing both acid and nonacid reflux, the interest in this procedure has declined over the last decade because of concerns about short-term and long-term complications, reoperation, and recurrence of GERD-related symptoms.⁴⁵⁻⁴⁷ Furthermore, medical therapy is a good option for all patients with GERD, whereas surgical intervention requires careful patient selection and is limited by comorbidities and patient age.

MAGNETIC SPHINCTER AUGMENTATION DEVICE (LINX)

The magnetic sphincter augmentation device (LINX Reflux Management System Thorax Medical, Shoreview, MN) is used to augment the LES.⁴⁸ The device comprises a miniature ring of interlinked titanium beads with magnetic core that are placed around the gastroesophageal junction. The magnetic bond between adjacent beads augments sphincter competence. The beads temporarily separate to accommodate a swallowed bolus and allow belching or vomiting and reapproximate to augment the LES in the closed position. LINX is inserted by a simple standardized laparoscopic procedure that does not alter the anatomy of the cardia.²⁶

In a recent multicenter prospective trial, 44 participants with documented typical symptoms of GERD for at least 6 months and incomplete symptomatic response to once-daily PPI therapy as well as abnormal esophageal acid exposure while off PPI treatment, underwent laparoscopic placement of LINX around the gastroesophageal junction.⁴⁹ After 3 years, 20 participants who were available for follow-up demonstrated a significant decrease in mean % total time pH < 4 from 11.9% at baseline to 3.8% ($P < 0.001$), with 80% (18/20) achieving normalization of esophageal acid exposure ($\leq 5.3\%$). The mean total GERD-HRQL score of participants (off PPIs) at ≥ 4 years was significantly better (3.3 ± 3.7) as compared with baseline (25.7 ± 6.4) ($P < 0.001$). In another study, Ganz et al⁵⁰ published a 3-year follow-up of 100 participants who underwent LINX placement. Normalization of esophageal acid exposure, which was the primary endpoint, was achieved by 64% of the participants. The authors also demonstrated that the mean % total time pH < 4 had decreased from 10.9% to 3.3% ($P < 0.001$), and that 87% of the participants were still off PPI at the 3-year follow-up ($P < 0.001$). The median total GERD-HRQL score was 27 at baseline (off PPI) as compared with 2 at 2 years after LINX placement ($P < 0.005$). In this trial, dysphagia occurred in 68% of the participants after the LINX procedure, but only 4% of them reported this symptom at 3 years.

The LINX procedure provides an alternative to the traditional antireflux surgery in a selected patient population. Although the results of the studies show great promise,

concerns remain high about potential long-term adverse events, in particular the possibility of the ring eroding into the esophagus or migrating from its original anatomic placement (Table 1). More long-term studies are needed.

THE LES STIMULATION SYSTEM (ENDOSTIM)

Electrical stimulation of the LES using the EndoStim has not yet been approved in the United States. The technique has been shown to increase LES resting pressure in animal models.⁵¹⁻⁵³ Human studies, however, focused primarily on patients with EE who are on PPI treatment and have low resting LES pressure as well as abnormal 24-hour esophageal acid exposure.^{54,55} The authors demonstrated that short-term electrical stimulation of the LES improved LES resting pressure, esophageal acid exposure, GERD-HRQL, and PPI consumption without affecting the amplitude of esophageal peristalsis or LES relaxation. Long-term follow-up of up to 1 year after implanting the EndoStim revealed durability of the original therapeutic effect.⁵⁶ Thus far, there are no specific studies in NERD patients using this technique. It is possible that NERD patients with documented abnormal esophageal acid exposure may also benefit from the EndoStim. However, the risk of long-term repeated stimulation of the LES needs to be further evaluated. In addition, comparison with medical or other nonmedical techniques is needed.

ACUPUNCTURE

Acupuncture has been utilized in various gastrointestinal disorders and has demonstrated a significant effect on acid secretion, gastrointestinal motility, neurohormonal levels, and sensory perception thresholds for pain.^{57,58} Acupuncture has also been used effectively in patients with GERD who failed symptomatically on PPI once daily. In 1 study, the authors demonstrated that adding acupuncture to PPI once daily was more effective than doubling the PPI dose for controlling GERD-related symptoms in patients who failed standard-dose PPI.⁵⁹ However, there are no studies that solely evaluated the value of acupuncture in patients with NERD. Two recent studies from China, where NERD accounts for >90% of the GERD patients, revealed that acupuncture significantly inhibited intraesophageal acid and bile reflux, improved GERD-related symptoms, and was safe and well tolerated.^{60,61}

In a recent study, the authors assessed the value of electroacupuncture in 480 GERD participants.⁶¹ Electroacupuncture was delivered once daily for a period of 6 weeks. The 24-hour intraesophageal pH, bile reflux, endoscopic grading, and symptom score were all significantly reduced at the end of treatment. All 8 domains of the Short Form-36 Health-related Quality of Life Questionnaire increased as compared with prior treatment ($P < 0.01$).

TABLE 1. Comparison of the Different Procedures for GERD

Procedure	Anesthesia	Cost	No. Patients	Years of Experience	No. Centers	FDA-reported Adverse Events
Stretta	Conscious	\$2000-\$3500	15,000	13	125	29
ExophyX	General	\$7000	11,000	7	200	96
Medigus	General	\$3200	> 100	2	2	0
LINX	General	\$12,000	1000	5	70	24

Adapted from Franciosa et al.³⁸

PSYCHOLOGICAL INTERVENTION

Psychological comorbidity is very common in GERD patients and seems to affect all GERD phenotypes.⁶² Patients with NERD, when compared with patients with EE, demonstrate a significantly higher prevalence of psychological disorders.⁶² Patients with poor correlation of symptoms with acid reflux events display a high level of anxiety and hysteria as compared with patients who demonstrate a close correlation between symptoms and acid-reflux events.⁶³ Anxiety and depression have been shown to increase reports of GERD-related symptoms in population-based studies. Patients who respond less well to PPI treatment are more likely to experience psychological distress.⁶⁴ Stress has been demonstrated to enhance perception of esophageal acid exposure.

Treatment for GERD, especially in those who are not responsive to antireflux treatment, may require further evaluation of psychological comorbidity because it is likely to play an important role in failure to respond to PPI treatment.⁶² In addition, psychological intervention using cognitive behavioral therapy, hypnotherapy, biofeedback, and muscle relaxation techniques have all been shown to improve GERD solely or in combination with medical or surgical antireflux treatment.⁶⁵⁻⁷⁰

CONCLUSIONS

There has been a shift in the last few years from medical to nonmedical therapeutic developments for GERD and specifically for NERD. Although there has been a marked decline in drug development for GERD, different new nonmedical techniques are either under development or have been already introduced into the market. Of all nonmedical interventions, compliance and lifestyle modifications are our "low hanging fruit" in treating NERD patients. The introduction of the LINX surgical procedure may provide an additional nonmedical option for NERD patients, but at the same time it may overtake traditional antireflux surgery while its long-term safety profile remains unknown. Several endoscopic techniques are currently available, and their utilization in NERD patients will likely increase, depending on their safety profile. Acupuncture and psychological intervention are both promising therapeutic strategies that have been underutilized in NERD patients by practicing physicians.

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