

Unmet Needs in the Treatment of Gastroesophageal Reflux Disease

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Gastroesophageal reflux disease (GERD) is a highly prevalent gastrointestinal disorder. Proton pump inhibitors have profoundly revolutionized the treatment of GERD. However, several areas of unmet need persist despite marked improvements in the therapeutic management of GERD. These include the advanced grades of erosive esophagitis, nonerosive reflux disease, maintenance treatment of erosive esophagitis, refractory GERD, postprandial heartburn, atypical and extraesophageal manifestations of GERD, Barrett's esophagus, chronic proton pump inhibitor treatment, and post-bariatric surgery GERD. Consequently, any future development of novel therapeutic modalities for GERD (medical, endoscopic, or surgical), would likely focus on the aforementioned areas of unmet need.

(J Neurogastroenterol Motil 2015;21:309-319)

Key Words

Gastroesophageal Reflux; Heartburn; Proton Pump Inhibitors

Introduction

Gastroesophageal reflux disease (GERD) is a chronic and highly prevalent medical problem. Population-based studies have demonstrated that 44% and 20% of the US adult population reported GERD-related symptoms (heartburn and acid regurgitation) at least once a month and once a week, respectively.¹ Most patients with GERD fall into one of 3 categories: nonerosive reflux disease (NERD), erosive esophagitis (EE), and Barrett's esophagus (BE). The 2 main phenotypes of GERD (NERD and

EE) appear to have different pathophysiological and clinical features and, most importantly, differ in their response to antireflux treatment.² The goal of antireflux treatments is to effectively relieve GERD-related symptoms, heal and maintain remission of EE, prevent complications of GERD, and improve health-related quality of life.

Currently, proton pump inhibitors (PPIs) and histamine type 2 receptor antagonists (H2RAs, albeit with lower potency) represent the cornerstone of GERD treatment. It has been demonstrated that PPIs achieve a profound inhibitory effect on gastric acid secretion that results in high rates of esophageal mucosal

Received: June 15, 2015 Revised: June 17, 2015 Accepted: June 18, 2015

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Financial support: None.

Conflicts of interest: None.

Author contributions: Ram Dickman, Carla Maradey-Romero, Rachel Gingold-Belfer, and Ronnie Fass drafted and developed the manuscript.

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healing and effective (as well as durable) control of GERD-related symptoms.^{3,4}

Despite the marked developments in medical, endoscopic, and surgical therapy, there are still many areas of unmet need in the treatment of GERD. Advanced grades of EE (Los Angeles grades C [LA-C] and D [LA-D]) demonstrate the lowest healing rates in patients on PPI once daily. Patients with NERD often fail to respond adequately to PPI treatment. Moreover, the current clinical experience in the treatment of atypical and extraesophageal manifestations of GERD (eg, noncardiac chest pain [NCCP], chronic cough, and hoarseness) has been profoundly disappointing. Unfortunately, most PPI therapeutic trials in patients with pharyngeal, laryngeal, or pulmonary symptoms (presumed to be GERD related) have failed to demonstrate any benefit over placebo.

Other areas of unmet need in GERD treatment include nighttime and postprandial heartburn, refractory GERD, maintenance treatment of EE, on-demand or intermittent therapy for GERD, BE, chronic PPI treatment, and post-bariatric surgery GERD (Table 1).

Advanced Grades of Erosive Esophagitis —

Systematic reviews of epidemiological studies have revealed that the prevalence of reflux esophagitis in patients with GERD is between 10% and 25% in Western countries and between 5% and 17% in Asian and Pacific countries.⁵⁻⁹ The prevalence of advanced EE (LA-C and LA-D) in elderly GERD patients may reach 37%.¹⁰ However, most studies demonstrated a range be-

tween 15% and 30%.^{8,9,11-14}

Advanced grades of EE are considered an area of unmet need in GERD because of relatively low symptomatic response and healing rates as well as a higher relapse rate, even with continuation of the initial healing dose of PPI.¹³ Overall, studies have reported that approximately 4% to 15% of patients with EE fail to achieve complete healing of esophageal inflammation after 8 weeks of treatment with standard-dose PPI.¹⁵ Patients with severe EE (LA-C and LA-D) demonstrated an even higher PPI failure rate than those with less severe esophageal inflammation (LA-A and LA-B). In a study by Castell et al¹⁶ that included 1284 patients with EE who were randomized to once-daily lansoprazole 30 mg or omeprazole 20 mg, revealed that 6.7% and 8.4%, respectively, of those with LA-A or LA-B EE failed to heal after 8 weeks of treatment, compared with 11.3% and 14.7%, respectively, of those with LA-C or LA-D. Richter et al¹⁷ demonstrated that the failure rate of patients with EE receiving either omeprazole 20 mg or esomeprazole 40 mg once daily was 9.6% and 6.6% for LA-A, 28.7% and 10.6% for LA-B, 29.6% and 12.8% for LA-C, and 26.2% and 20% for LA-D, respectively. Interestingly, a recent study found that the mean healing rate in EE was only 61.6%.⁸

Importantly, the rate of symptom resolution in EE patients receiving standard dose PPI was 10-15% lower than the observed healing rate of esophageal inflammation.^{13,18} Consequently, patients with EE receiving standard dose PPIs may still suffer from heartburn or regurgitation despite a complete resolution of the esophageal inflammation.¹⁹ Moreover, even when continuing the initial healing dose as maintenance treatment for a period of 6 months, 15-23% of the patients with LA-A or LA-B, respectively, and 24-41% with LA-C or LA-D, respectively, relapsed while on treatment.²⁰ Higuchi et al⁸ showed that (after a mean 1.1 years of PPI therapy) approximately 40% of patients did not achieve remission of esophageal inflammation and that healing of esophageal inflammation was significantly lower (42%) in patients with severe EE compared with patients having LA-A (71%).

In summary, symptomatic response and healing rates of patients with severe EE have been relatively limited during PPI treatment. Thus, advanced grades of EE remain an area of unmet need for both symptomatic response and relapse of symptoms and esophageal inflammation.

Nonerosive Reflux Disease —

The recognition of NERD as a distinct presentation of

Table 1. The Unmet Needs in Treatment of Gastroesophageal Reflux Disease

1	Healing and symptom's response in advanced erosive esophagitis
2	Nonerosive reflux disease
3	Postprandial heartburn
4	Nighttime heartburn
5	Maintenance treatment in erosive esophagitis
6	On-demand/intermittent therapy
7	Refractory GERD
8	Atypical manifestations of GERD
9	Extraesophageal manifestations of GERD
10	Dependency on food for efficacy
11	Chronic PPI treatment
12	Barrett's esophagus
13	Post-bariatric surgery GERD

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

GERD is an important development in the field of GERD. While the definition of NERD has not changed significantly over the years, this disorder accounts for the majority of GERD patients seen in clinical practice. Overall, the results of recent epidemiological studies suggest that the prevalence of NERD in the GERD population is approximately 70%.²

NERD is one of the major areas of unmet need in the treatment of GERD and is related to less than optimal response to PPI therapy. In fact, NERD patients have a significantly lower symptomatic response rate (by 20-30%) to PPI therapy as compared with patients having EE; consequently, NERD contributes the highest number of GERD patients to the refractory heartburn group.^{2,15} In a systematic review of the literature, PPI symptomatic response pooled rate was 36.7% in NERD patients and 55.5% in EE patients.²¹ The therapeutic gain was 27.5% in NERD compared with 48.9% in EE. A recent post hoc analysis of 4 randomized placebo-controlled trials demonstrated that partial heartburn response occurred in 20% of patients with NERD and 14% of those with EE.²²

In addition to the low symptomatic response rate, NERD patients also demonstrate a 2-3 fold increase in the lag time to symptomatic response to PPI therapy. By using the ReQuestTM questionnaire, the median time to first report of symptom relief was 2 days and 10-13 days to sustained symptom relief for NERD patients treated with either pantoprazole or esomeprazole (both 20 mg/day).

While many therapeutic trials of NERD patients did not exclude the functional heartburn group, it appears that even NERD patients with abnormal pH test demonstrate a lower symptomatic response rate to PPI once daily as compared with EE patients.²³ Possible explanations include the important role of esophageal hypersensitivity (up to 87% in NERD patients) in NERD as compared with EE patients and the fact that the majority of NERD patients have mildly abnormal esophageal acid exposure.²³

In summary, the symptomatic response rate of NERD patients to standard dose PPI is significantly lower than that reported for EE patients. It is possible that esophageal hypersensitivity, which is not responsive to antireflux treatment, may drive this therapeutic discrepancy and thus create an important area of unmet need.

Postprandial Heartburn

Meal ingestion is the most common trigger for GERD-re-

lated symptoms.^{24,25} Postprandial heartburn drives millions of Americans to seek antireflux treatment on a daily basis. However, the currently available therapeutic modalities are not fast or effective enough to provide good control of postprandial heartburn.²⁶⁻³⁰

In patients who consume antireflux medications only in response to acute heartburn, PPIs appear to have no value due to the time required to reach maximum efficacy. Consequently, PPIs are not considered a good therapeutic option for postprandial heartburn, leaving patients to utilize compounds such as antacids, Gaviscon, sucralfate, or H2RAs. Furthermore, even in GERD patients who are taking PPIs on a regular basis, an especially large, fatty, spicy, or late-evening meal can result in breakthrough symptoms. Indeed, El-Serag et al³¹ found that high dietary fat intake was associated with an increased risk of GERD-related symptoms and EE, whereas high fiber intake correlated with a reduced risk of symptoms.

In summary, we are still devoid of effective antireflux therapeutic modalities for postprandial heartburn in patients who prefer to use them only when symptoms occur. Thus, postprandial heartburn remains an important area of unmet need.

Nighttime Heartburn

Nighttime heartburn is very common, affecting most patients with GERD. In a nationwide Gallup telephone survey of 1000 adults who were experiencing heartburn at least once a week, approximately 79% of respondents reported nocturnal heartburn. Of those, 75% reported that symptoms affected their sleep, and 40% reported problems in their ability to function the following day.³² Of those reporting nighttime heartburn, 71% were taking over-the-counter medications, but only 29% rated this approach as effective.

Another nationwide survey demonstrated that over 80% of adults taking PPIs for GERD reported nocturnal symptoms during the previous month, and 23.4% described their symptoms as severe or very severe.³³ Almost 22% of responders were on PPI twice daily, and 42% supplemented the prescribed PPI with an over-the-counter PPI, H2RA, or antacid.³³ Of those patients on PPI twice daily, almost 40% stated that they doubled the dose due to inadequate control of nighttime GERD-related symptoms.³⁴ Several studies have also shown that the response rate of PPI once daily for nighttime heartburn is significantly lower (up to 53%) than the response rate for daytime heartburn (up to 66%).^{35,36}

In summary, nighttime heartburn has the most important impact on the quality of life for GERD patients. However, night-

time heartburn appears to be less responsive to antireflux treatment than daytime heartburn. Thus, nighttime heartburn remains one of the most important areas of unmet need.

Maintenance Treatment of Erosive Esophagitis

GERD is a chronic, relapsing disorder that requires long-term maintenance treatment for a substantial number of patients. This is particularly important for patients with EE. Once healing of mucosal erosions and symptom relief have been achieved by initial therapy, long-term maintenance treatment is necessary for most patients with EE (LA grades B-D). It has been demonstrated that, after discontinuation of maintenance treatment, relapse rates approach 90% in patients with EE and 75% in patients with NERD within 6 months after initial treatment.³⁷ Moreover, even after initial healing of esophageal inflammation, symptomatic relapse occurs within the next 12 months in approximately 83.6% of patients with EE.¹³

More disconcerting is the high relapse rate of esophageal inflammation that patients with EE experience while on maintenance PPI treatment. Labenz et al³⁸ have demonstrated a very high relapse rate of EE in patients taking the same PPI dose that initially healed their esophageal inflammation. Of those with LA-A and LA-B, 10% and 29%, respectively, and those with LA-C and LA-D, 16% and 41%, respectively, relapsed while on PPI once daily during 6 months of maintenance treatment.³⁸ In this study, healing and remission rates among patients with LA-D at baseline were the lowest, regardless of the PPI dose or brand.³⁸ In a community-based study by Carlsson et al,³⁷ up to 25% of GERD patients continued to be symptomatic while on a standard dose of PPI. In patients with EE grade 3 based on Savary-Miller classification, 100% of those who were treated with H2RAs and 20% who were treated with a PPI experienced symptoms relapse within 12 months of initiating treatment.³⁹

In summary, a substantial proportion of patients with EE, especially those with advanced grading (LA-C and LA-D) will relapse symptomatically, with or without mucosal inflammation, while on maintenance PPI treatment. This area of unmet need has become a major concern for both physicians and patients when long-term maintenance treatment for EE is required.

On-demand/Intermittent Therapy

Noncontinuous (on-demand or intermittent) PPI maintenance

treatment strategies have been an area of intense interest for several decades. This is primarily due to studies showing that most patients with symptomatic GERD (60%) are contented with on-demand or intermittent PPI therapy.⁴⁰ On-demand therapy is a self-managed therapeutic strategy in which PPI intake is completely symptom driven, but patients are instructed not to take more than one PPI dose daily.⁴¹ Studies have shown that 50% of the patients who consume PPI daily become on-demand takers within one month.²⁴ Thus, noncontinuous PPI treatment is preferred over continuous PPI treatment by many patients with GERD. In addition, because the risk of complications is minimal in patients with NERD or LA-A and LA-B EE, noncontinuous PPI treatment has become a very attractive therapeutic strategy. Furthermore, it may alleviate concerns of GERD patients about the potential for adverse events when chronic, daily PPI treatment is used.

Thus far, there are no approved indications for on-demand or intermittent therapy for any of the currently available PPIs in the United States. Consequently, noncontinuous PPI treatment remains an important area of unmet need in GERD.

Refractory Gastroesophageal Reflux Disease

Refractory GERD is defined as partial response or lack of response in GERD patients taking PPI twice daily over a period of at least 3 months.⁴² Others suggest that lack of symptomatic response to PPI once daily is sufficient to consider patients as having refractory GERD.⁴³ Currently, this disorder is the most common presentation of GERD in gastroenterology practice.¹⁵ It has been estimated that between 10% and 40% of GERD patients fail to respond symptomatically, either partially or completely, to a standard-dose PPI.¹⁵

In a US survey that included 617 GERD patients taking PPIs, 71% used the PPI once a day, 22.2% twice a day, and 6.8% more than twice a day, or on an as-needed basis.⁴⁴ Approximately 42.1% of all patients supplemented their prescription PPI with other antireflux regimens, including over-the-counter antacids and H2RAs. Although 72.8% of the patients were satisfied with their PPI treatment, 85% still experienced GERD-related symptoms.⁴⁴ An American Gastroenterological Association survey of patients with GERD revealed that 38% reported incomplete response to PPI treatment.⁴⁵ Most of the non-responders supplemented their PPI therapy with other antireflux regimens, primarily over-the-counter antacids. In the 2000 Gallup

Study of Consumers' Use of Stomach Relief Products, 36% of responders reported taking nonprescription medication in addition to a prescription medication for GERD.²⁴ Of those, 56% stated that they took their prescription medication daily but still needed to supplement it with nonprescription medication for breakthrough symptoms.

Most non-responders to PPIs are NERD and functional heartburn patients because of the relatively large size of each of these groups among those who suffer from heartburn.⁴⁶ Importantly, the pooled symptomatic response rate to PPIs once daily at 4 weeks was only 37% for patients with NERD compared with 56% for patients with EE.²¹ Various mechanisms have been proposed to contribute to PPI failure: these include poor compliance or adherence to PPI treatment, residual acid reflux, weakly acidic and weakly alkaline reflux, bile reflux, esophageal hypersensitivity, comorbidities (functional bowel disorders and gastro-paresis), and psychological comorbidity among others.⁴⁶

Treatment of refractory GERD remains an area of unmet need regardless of the underlying cause. Thus far, attempts to develop novel therapies that could be helpful in refractory GERD have been disappointing. The transient lower esophageal sphincter relaxation reducers, which were specifically developed to address residual acid reflux, bile reflux, or non-acid reflux, represented a promising class of drugs that failed to demonstrate efficacy in large clinical trials of patients with refractory GERD.⁴⁷

Atypical Manifestations of Gastroesophageal Reflux Disease

NCCP is defined as recurrent chest pain that is indistinguishable from ischemic heart pain after a reasonable workup has excluded a cardiac cause.⁴⁸ NCCP is highly prevalent. Chest pain is currently the second most common presentation to hospital emergency departments; however, only 25% of people who experience chest pain actually present to a hospital.⁴⁹ The mean annual prevalence of NCCP in 6 population-based studies was approximately 25%.⁵⁰ In one population-based US survey, the prevalence of NCCP among GERD patients was 23% without a gender predilection.⁷ An Australian epidemiological study demonstrated a prevalence rate of 33%^{51,52} as well as a reduction in population prevalence with increasing age. Similar prevalence rates of 23% and 19% were reported by epidemiological studies from South America and China, respectively.^{53,54}

GERD is the most important esophageal cause of NCCP. In a community-based study, 53% of all NCCP patients experi-

enced heartburn and 58% acid regurgitation.⁵² Furthermore, Locke et al⁷ have demonstrated that NCCP was more commonly reported by patients (37%) who experienced heartburn symptoms at least weekly as compared with 30.7% of those who had infrequent heartburn (less than once a week) and 7.9% of those without any GERD symptoms. Ambulatory 24-hour esophageal pH testing studies have demonstrated that approximately 50% of NCCP patients have abnormal esophageal acid exposure.

Studies have demonstrated that the symptom response rate to short-course PPI treatment in NCCP patients with objective evidence of GERD (esophagitis and/or abnormal pH test) is between 78% and 92%.^{55,56} Conversely, response to PPI treatment in NCCP patients without objective evidence of GERD ranged between 10% and 14%.⁵⁶⁻⁵⁸ However, there are less than a handful of randomized, placebo-controlled trials that evaluated the value of PPI treatment in GERD-related NCCP.^{59,60} The results of these studies have not been consistent, and thus far the value of antireflux treatment in GERD-related NCCP remains to be elucidated.

Presently, none of the antireflux medications is specifically indicated for GERD-related NCCP; consequently, GERD-related NCCP remains an important area of unmet need.

Extraesophageal Manifestations of Gastroesophageal Reflux Disease

Surprisingly, despite decades of research in the area of extraesophageal manifestations of GERD, we are still lacking an effective therapeutic strategy, and none of the currently available antireflux medications is indicated for any of them.

The extraesophageal manifestations of GERD include, among others, asthma, chronic cough, hoarseness, dental erosions, and sleep disorders. Early population-based studies suggested that GERD patients are at an increased risk of developing ear, nose, and throat or pulmonary symptoms.⁶¹ The ProGERD study (6000 patients with EE and NERD) found that approximately 30% of the patients reported extraesophageal manifestations of GERD including 385 (13.3%), 307 (10.6%), and 131 (4.5%) patients who demonstrated chronic cough, laryngeal disorders, and asthma, respectively.⁶²

Furthermore, most randomized control trials using PPIs in patients with pharyngeal, laryngeal, or pulmonary symptoms (presumed to be GERD related) demonstrated poor response or very modest benefit at best. Moreover, there is no accepted test to establish the diagnosis of extraesophageal manifestations. Thus,

while association between extraesophageal manifestations and GERD has been commonly reported, a causal relationship remains to be substantiated.⁶³

In the adult population, GERD is the third most common cause of chronic cough after postnasal drip and asthma.⁶⁴ In a US population-based study, the frequency of chronic cough in patients with no GERD symptoms, infrequent GERD symptoms, and frequent GERD symptoms was 11%, 15%, and 22%, respectively.⁷ Irwin et al⁶⁵ showed that GERD may serve as the leading etiology in 10% of patients with chronic cough.

Patients with chronic cough that is presumed to be GERD related are currently treated by twice-daily PPI for a period of 3 months. However, this therapeutic strategy is supported only by open-label trials and not by randomized placebo-controlled studies. Baldi et al⁶⁶ found no significant difference in symptom improvement for patients with chronic cough who were treated with 30 mg lansoprazole, either once a day or twice a day, over a period of 12 weeks. Two recent, double-blind, placebo-controlled trials in adult patients with chronic cough did not demonstrate that PPIs are more effective than placebo.^{67,68} A recent meta-analysis of 5 randomized, placebo-controlled trials in adult patients with chronic cough did not find sufficient evidence in favor of PPI therapy.⁶⁹

Hoarseness has also been considered to be an important extraesophageal manifestation of GERD. In a US population-based study, the frequency of hoarseness in patients with weekly GERD symptoms was 23% compared with 11% for those without GERD symptoms.⁷ Typical GERD-related symptoms (heartburn and regurgitation) are absent in the majority of patients with chronic laryngitis, and the presence of esophageal inflammation ranges from 19% to 40% in these patients.^{70,71} Abnormal esophageal pH monitoring was found in 55-79% and 18-70% of patients with chronic hoarseness or posterior laryngitis, respectively.⁷¹⁻⁷⁴

Studies have shown that PPI therapy is not more beneficial than placebo for the treatment of hoarseness and other laryngeal manifestations in patients with documented posterior laryngitis. In a large randomized, placebo-controlled, multicenter trial of 145 patients, Vaezi et al⁷⁵ were unable to demonstrate that 40 mg esomeprazole twice daily for 16 weeks was better than placebo for symptom resolution or improvement in laryngeal signs of laryngopharyngeal reflux. A subsequent meta-analysis of the placebo-controlled studies in laryngopharyngeal reflux has reported minimal therapeutic benefit of PPIs over placebo.⁷⁶

GERD has also been shown to be present in 50-80% of asth-

matic patients.^{77,78} Reports of GERD-related symptoms in adults with asthma range from 65% to 77%.^{61,79-81} In a large case-controlled study, El-Serag et al⁶¹ reported that EE and esophageal stricture were associated with chronic bronchitis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, bronchiectasis, and pneumonia, with odds ratios ranging from 1.15 to 1.50. In a recent 5-year follow-up of the original ProGERD study, the prevalence of asthma in GERD patients had increased from 4.5% at entry to 7.8% at the end of follow-up.⁸² Kiljander et al⁸³ showed that 35% of asthma patients had abnormal 24-hour esophageal pH monitoring.

Response to PPI therapy in asthmatics remains to be fully elucidated. In a systematic review of all clinical trials using medical therapy in asthmatic patients with GERD (between the years 1966 and 1996) it was found that antireflux treatment improved asthma symptoms, reduced consumption of asthma-related medications, and improved evening peak expiratory flow in 69%, 62%, and 26% of subjects, respectively.⁸⁴ In a placebo-controlled study, it was found that esomeprazole 40 mg twice daily, given for 4 months, improved peak expiratory flow in 45.4% of subjects with asthma who presented with both GERD and nocturnal respiratory symptoms.⁸⁵ Conversely, a recent study of 412 patients with poorly controlled asthma, conducted by the American Lung Association Asthma Clinical Research Center, did not find any benefit for either esomeprazole 40 mg twice daily or placebo after 24 weeks of treatment.⁸⁶ Similarly, a Cochrane Review of antireflux therapy in patients with asthma found only minimal improvement of asthma symptoms with therapy.⁸⁷

Overall, extraesophageal manifestations of GERD clearly represent an area of unmet need in GERD. Further understanding of the mechanistic relationship between GERD and their symptoms will help to find better therapeutic modalities.

Dependency on Food for Efficacy

Proper timing of PPI administration is needed for maximum efficacy. Thus, a PPI should be taken 30 minutes before a meal (preferably before breakfast). However, more than 50% of GERD patients do not adhere to proper timing of PPI consumption when prescribed by a primary care physician.⁸⁸

Gunaratnam et al⁸⁹ showed that only 46% of refractory GERD patients were dosing their PPI optimally. Of those who dosed suboptimally, 39% took their PPI at bedtime, and 4% took it as needed. In a 2000 Gallup survey, consumption of antireflux medications prior to going to bed was reported by 52% of

subjects.²⁴ Furthermore, in a US survey involving almost 500 physicians demonstrated that 70% of primary care physicians and 20% of gastroenterologists advised patients to take their PPI at bedtime or did not believe that proper timing of drug administration was important.⁹⁰

In summary, a more flexible schedule that obviates the need for proper timing recommendations may improve compliance as well as clinical efficacy of PPIs.

Long-term or High-dose Proton Pump Inhibitor Therapy

There has recently been growing evidence of adverse effects related to chronic PPI treatment.⁹¹ These include increased risk of hip, wrist, and spine fracture; community-acquired pneumonia; *Clostridium difficile* colitis; microscopic colitis; bacterial overgrowth; vitamin/mineral/electrolyte deficiencies; and fundic gland polyps.⁹²⁻⁹⁷ While the risk for most of these complications is relatively modest, concerns have been raised about the safety of long-term PPI therapies.

Duration and dosing of PPI treatment have been shown to increase the risk for developing the aforementioned adverse events.⁹¹ Importantly, it has been estimated that nearly 30% of GERD patients are treated with a double-dose PPI.⁴⁴

A growing concern by patients and physicians alike provided the impetus for identifying alternative efficacious therapeutic options (medical, endoscopic, or surgical) for GERD patients who require long-term and/or high-dose PPI treatment (Table 2).

Table 2. Currently Available Alternative Therapeutic Options for Chronic or High-dose Proton Pump Inhibitor Treatment

Medical ^a	Non-medical
- Antacids/ Gaviscon	- Compliance/adherence to PPI - Lifestyle modifications
- Sucralfate	- Complementary/alternative medicine
- H2RAs	- Psychological intervention
- Prokinetics	Endoscopic:
- Baclofen	- Stretta procedure - EsophyX Transoral incisionless fundoplication - Medigus Ultrasonic Surgical Endostapler
	Surgical:
	- Surgical fundoplication - Magnetic sphincter augmentation device (LINX)

^aUse separately or as an add-on to proton pump inhibitor (PPI) treatment. H2RAs, histamine 2 receptor antagonists.

Barrett's Esophagus

BE is considered a complication of chronic GERD.^{98,99} The prevalence of specialized intestinal metaplasia in patients with GERD is between 6% and 12%, and the adjusted odds ratio for developing adenocarcinoma over a 20-year period is 7.7 and 43.5 for patients with recurrent and severe symptoms of GERD, respectively.⁹⁸ As a group, patients with BE have demonstrated the highest level of acid exposure in the distal esophagus compared with those having NERD or EE, suggesting the need for more aggressive antireflux treatment.¹⁰⁰

However, there is a discrepancy in BE between symptom resolution and control of intraesophageal acid exposure.¹⁰¹ Studies with ambulatory 24-hour esophageal pH monitoring revealed that 20-80 % of symptomatically controlled BE patients continued to demonstrate some level of abnormal acid exposure, suggesting that these patients may be undertreated.^{102,103} Interestingly this phenomenon has been described even when high doses of PPI (up to 4 times daily) have been used.¹⁰⁴

Thus far, none of the currently available PPIs is indicated for patients with BE. Large randomized, placebo-controlled trials are also needed to assess the value of antireflux treatment for controlling the symptoms of BE patients. This is in addition to the evaluation of chronic PPI treatment post-BE ablation.

Bariatric Surgery

In recent years, bariatric surgery has become one of the mainstay treatments for weight loss among obese patients.¹⁰⁵ Presently, the most commonly performed bariatric surgeries are laparoscopic adjustable gastric banding, Roux en-Y gastric bypass, and laparoscopic sleeve gastrectomy.¹⁰⁶ However, there have been growing concerns about side effects induced by these surgical techniques, including stenosis at the anastomosis site, stomal ulcer, fistula, band erosion, and motor dysfunction of the esophagus, stomach, and small bowel among others.¹⁰⁷⁻¹¹¹

Thus far, only a few studies have assessed the objective presence of GERD prior to bariatric surgery, most specifically in patients undergoing laparoscopic sleeve gastrectomy or adjustable gastric banding. There is a lack of uniformity in assessing the presence of GERD pre-and post-bariatric surgery, using validated GERD-questionnaires, ambulatory pH monitoring, or upper endoscopy.

GERD occurs in up to 70% of obese patients. Most im-

portantly, several studies have reported that bariatric surgery might exacerbate or induce new onset GERD-related symptoms in asymptomatic patients undergoing laparoscopic adjustable gastric banding¹¹²⁻¹¹⁴ or laparoscopic sleeve gastrectomy.¹¹⁵⁻¹¹⁷ Furthermore, Dupree et al¹¹⁵ reported that up to 9% of patients undergoing sleeve gastrectomy presented with new-onset GERD postoperatively and that approximately 84% continued to have GERD symptoms after the surgery. Moreover, the presence of GERD has been shown to increase the risk of postoperative complications in 15% of the patients.¹¹⁵ Importantly, patients with GERD post bariatric surgery appear to be more resistant to anti-reflux treatment and thus serve as an important area of unmet need.

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