Medical Treatments of GERD
The Old and New

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KEYWORDS

- Gastroesophageal reflux • Proton pump inhibitors
- Transient lower esophageal sphincter relaxation inhibitors • Prokinetics
- Esophageal mucosal repair • Visceral analgesia

KEY POINTS

- The mainstay of pharmacologic therapy for GERD is gastric acid suppression with PPIs, with no major differences among the available PPIs for healing of erosive esophagitis and achieving symptom control.
- PPIs are superior to H2RAs for healing of erosive esophagitis and achieving symptom control.
- TLESR inhibitors have been shown to reduce reflux episodes and symptoms, but at the present time only the GABA-B agonist baclofen is available for this purpose because development of other compounds was stopped due to low efficacy or side effects.
- Esophageal defense mechanisms can be augmented by improving esophageal clearance with prokinetics but this approach is limited by low efficacy and side effects; alternatively, epithelial repair can be enhanced with novel agents such as rebamipide, but data on this form of therapy are very limited.
- Targeting esophageal sensation as a means to treat GERD symptoms may be possible by esophageal mucosal nociceptor blockade or through modulation of afferent signals and their cortical interpretation using compounds such as TRPV1 nociceptor antagonists or antidepressants, or by cognitive techniques like hypnotherapy; as with other interventions, data are limited.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a very common clinical problem. Heartburn is experienced on a weekly basis by nearly 20% of the US population.[1] GERD has become the most frequent gastroenterological outpatient diagnosis as well as the most common indication for upper endoscopy in the United States.[2] Medical treatment of this condition is primarily based on gastric acid suppression by agents such as proton pump inhibitors (PPIs). These medications are often prescribed empirically to

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treat symptoms that are attributed to reflux. Given the high prevalence of GERD, PPI sales in the United States totaled $13.6 billion in 2009.[3] Although these medications are often effective, up to one-third of patients may have insufficient symptomatic relief despite their use.[4] Thus, a very important clinical challenge in the current era of rising GERD prevalence[5] and very frequent PPI use is the large number of patients in whom symptoms persist despite this form of therapy,[6] which has created a need for alternative treatment approaches. As with any disease state, the pathophysiology of the disorder provides specific therapeutic targets. In this article, existing as well as new and evolving approaches to treating GERD are discussed, focusing on pathophysiology-based therapeutic targets.

A PATHOPHYSIOLOGY-BASED APPROACH TO THE MEDICAL TREATMENT OF GERD

In a generally accepted pathophysiological model of GERD,[7,8] reflux of gastric contents into the esophagus occurs as a result of the interplay among different factors in the upper gastrointestinal tract. Potentially harmful agents to the esophageal mucosa include gastric (acid and pepsin) or duodenal (bile acids and trypsin) secretions. To prevent movement of these harmful gastroduodenal contents into the esophagus, the lower esophageal sphincter (LES), in concert with the crural diaphragm, forms a barrier at the esophagogastric junction. If this barrier is breached and the esophageal mucosa is exposed to the damaging gastroduodenal agents, mucosal protection occurs through esophageal clearance facilitated by peristalsis, and by epithelial defense and repair mechanisms. The pathophysiological sequence of events leading to GERD manifestations may include (1) frequent failure of the antireflux barrier due to transient LES relaxations, a hypotensive LES, or anatomic disruption of the esophagogastric junction (ie, hiatus hernia); (2) the occurrence of reflux episodes with specific physicochemical characteristics, such as liquid/gas composition, acidity, and proximal extension of refluxate in the esophagus[9]; (3) macroscopic or microscopic loss of esophageal mucosal integrity due to exposure to gastric contents that is frequent or severe enough to overwhelm the esophageal defense mechanisms[10]; (4) activation of esophageal mucosa nociceptors[11]; (5) triggering of afferent signaling pathways[12]; (6) cortical processing of these signals leading to the perception of heartburn or other symptoms of GERD.[13]

In terms of pharmacologic approaches to the treatment of GERD, one can intervene in any of the steps in the above sequence (**Table 1**) through (1) altering gastric contents by neutralization of acid; (2) augmentation of the antireflux barrier; (3) enhancement of mucosal defense mechanisms (improving esophageal clearance and epithelial defense/repair); (4) blocking esophageal nociceptors; (5) modulation of afferent signals and their interpretation in the brain cortex.

Neutralization of Gastric Contents

Neutralization of gastric acid has been a mainstay of medical therapy for GERD for many years and can be achieved through antacids, histamine-2 receptor antagonists (H2RAs), or PPIs.

Antacids are not antisecretory agents; they neutralize acid that has been secreted into the stomach but they do not block the acid secreting proton pumps. Antacids are primarily used for relief of mild infrequent symptoms[14]; they can also be used for occasional breakthrough symptoms in patients taking PPIs. Options for antisecretory therapy include H2RAs and PPIs. H2RAs competitively block histamine-stimulated acid secretion. The available H2RAs (famotidine, ranitidine, nizatidine, cimetidine) are equivalent in their ability to suppress gastric acid secretion and control

Table 1
Potential therapeutic interventions for GERD based on their corresponding pathophysiological mechanism

Pathophysiological Mechanism	Therapeutic Intervention
Gastric acid is harmful to the esophageal mucosa if reflux occurs	Gastric acid neutralization • Antacids • Histamine-2 receptor antagonists • Proton pump inhibitors
Failure of the antireflux barrier leads to reflux episodes	TLESR inhibitors • GABA-B agonists • mGluR5 antagonists • Other: cannabinoid receptor agonists, CCK antagonists
Esophageal defense mechanisms are overwhelmed as a result of frequent reflux, leading to loss of mucosal integrity	Prokinetics (enhance peristalsis and clearance) • Metoclopramide, domperidone, itopride, mosapride Enhance mucosal defense • Rebamipide
Activation of nociceptors in esophageal mucosa	TRPV1 receptor antagonists • AZD1386
Firing of afferent signals, interpretation of these signals in the brain cortex resulting in perception of symptoms	Antidepressants • SSRIs, others Cognitive approaches • Acupuncture • Hypnosis • Johrei

Abbreviation: SSRIs, selective serotonin reuptake inhibitors.

symptoms.[15] PPIs are more potent than H2RAs because they block the final common pathway for acid secretion by covalently binding to the proton pump, thus blocking the H^+/K^+ATPase exchange pathway.

Comparative effectiveness of H2RAs versus PPIs

Although H2RAs have been shown to be superior to placebo for healing erosive esophagitis (EE) and controlling heartburn, PPIs are more effective than H2RAs and have become the therapy of choice for healing esophagitis and providing symptomatic relief. That PPIs are superior to H2RAs has been well established for quite some time and thus the studies evaluating this issue are several years old. In a 1997 meta-analysis, the mean (±SD) overall proportion of healed EE irrespective of drug dose or treatment duration was highest with PPIs (84% ± 11%) versus H2RAs (52% ± 17%), or placebo (28% ± 16%).[16] The mean proportion of patients who became heartburn-free was also higher with PPIs (77.4% ± 10.4%) versus H2RAs (47.6% ± 15.5%), and PPIs provided faster, more complete heartburn relief (11.5%/wk) versus H2RAs (6.4%/wk).

More than a decade ago, a few studies suggested that H2RAs may be useful for night-time acid suppression in patients who experienced nocturnal reflux symptoms despite taking a twice-daily PPI.[17] However, higher quality studies with prolonged follow-up later on showed tachyphylaxis for this effect of H2RAs.[18] Therefore, although they can be used intermittently on an as-needed basis for breakthrough nocturnal symptoms, a standing nighttime dose of H2RAs cannot be recommended for these patients.

Comparative effectiveness of different PPIs

Seven PPIs are currently in use in the United States; 3 are available over the counter (omeprazole, lansoprazole, and omeprazole-sodium bicarbonate) and the other 4 can only be obtained by prescription (rabeprazole, pantoprazole, esomeprazole, and dexlansoprazole). A 2006 meta-analysis compared the efficacy of esomeprazole versus 3 other PPIs (omeprazole, lansoprazole, and pantoprazole) in patients with EE.[19] The meta-analysis, which included 15,316 patients in 10 studies, found that at 8 weeks, there was a 5% relative increase (relative risk [RR], 1.05; 95% confidence interval [CI] 1.02–1.08) in the probability of healing of EE with esomeprazole, yielding an absolute risk reduction of 4% and number needed to treat of 25. The calculated number needed to treat by Los Angeles grade of EE (LA grades A–D) were 50, 33, 14, and 8, respectively. Esomeprazole conferred an 8% relative increase (RR, 1.08; 95% CI 1.05–1.11) in the probability of GERD symptom relief at 4 weeks. Although esomeprazole appeared to confer a statistically significant improvement, there was only modest clinical benefit in 8-week healing of esophagitis and symptom relief in all-comers with EE. The clinical benefit appeared negligible in less severe erosive disease, but may be of importance in more severe disease. However, only one-third of GERD patients are found to have esophagitis and when present it is predominantly mild (LA grades A and B).

Comparative trial data for the more recently available PPIs (omeprazole-sodium bicarbonate and dexlansoprazole) are very limited; there are no major clinical advantages with these medications. Omeprazole-sodium bicarbonate, an immediate-release PPI, was found to be superior to pantoprazole for control of nocturnal gastric pH when each was administered at bedtime,[20] but this was a measurement of intragastric (not esophageal) pH, and whether this effect leads to better symptom control has not been studied. Dexlansoprazole, a dual delayed release PPI that became available in 2009, was found to be superior to lansoprazole for healing of EE in one trial, and noninferior in another; these studies showed no difference in control of heartburn for dexlansoprazole compared with lansoprazole.[21]

Although one can conclude that symptom relief is overall equivalent for all PPIs, switching to a different PPI for patients with incomplete symptom relief is a very common clinical practice, based on the possibility of intrasubject variability in response to different PPIs. Increasing from once-daily to twice-daily dosing to improve symptom relief is also commonly done in the clinical arena. However, there are only limited data to support these practices. A randomized controlled trial in patients with persistent GERD symptoms despite a single-daily dose of PPI showed that increasing lansoprazole to twice daily or switching therapy to esomeprazole once daily both resulted in symptomatic improvement in roughly 20% of patients, without a clear advantage for either strategy.[22] Similarly, another randomized trial found that increasing lansoprazole to twice daily was as effective as changing it to omeprazole once daily in patients with incomplete response to once-daily lansoprazole.[23] There are no available data evaluating the effect of switching PPIs more than once.

Comparative effectiveness of PPIs versus anti-reflux surgery

Laparoscopic anti-reflux surgery (LARS) is a well-established treatment for GERD, with high-quality trials supporting its efficacy in patients with esophagitis as well as those with abnormal distal esophageal acid exposure on ambulatory reflux monitoring.[24] A recent, multicenter randomized clinical trial assessed symptomatic remission after a 5-year follow-up in 180 patients treated with laparoscopic fundoplication versus 192 treated with esomeprazole.[25] All patients had EE or abnormal pH at baseline, and they had all responded to esomeprazole in a 3-month run-in period.

Estimated remission rates at 5 years were 92% (95% CI 89%–96%) in the esomeprazole group and 85% (95% CI 81%–90%) in the LARS group (log-rank $P = .048$). The difference between groups was no longer statistically significant following best-case scenario modeling of the effects of study dropout. The prevalence and severity of heartburn at 5 years were similar for the esomeprazole and LARS groups (16% and 8%, $P<.14$); regurgitation was more frequent with esomeprazole (13% and 2%, $P<.001$), but other symptoms were more common after fundoplication: 5% and 11% for dysphagia ($P<.001$), 28% and 40% for bloating ($P<.001$), and 40% and 57% for flatulence ($P<.001$). Thus, this high-quality trial with long-term follow-up showed that with contemporary antireflux therapy for GERD, either by pharmacologic acid suppression with esomeprazole or by laparoscopic fundoplication, most patients achieve and remain in remission at 5 years.

Potassium-competitive acid blockers

In contrast to PPIs, which bind to proton pumps in an irreversible fashion, potassium-competitive acid blockers (PCABs) inhibit H^+/K^+ATPase in a competitive and reversible manner. Additional differences from PPIs include a higher concentration in the parietal cell compared with plasma, and a peak effect after the first dose rather than after repeated dosing.[26] Despite these potential pharmacokinetic and pharmacodynamic advantages, none of these agents have made it to the clinical arena because of side effects or a lack of superiority when compared with PPIs. For instance, the PCAB AZD8065 was found to have similar efficacy for healing EE and controlling heartburn when compared with omeprazole.[27] Whether PCABs with greater effectiveness than PPIs along with an acceptable side effect profile will become available in the future remains to be seen.

Augmentation of the Antireflux Barrier Function

All of the pharmacologic agents that work by neutralizing gastric acid do not prevent gastroesophageal reflux from occurring; they simply alter the gastric contents, rendering them less harmful to the esophageal mucosa. Although acid suppression is an effective therapy for symptom control in many patients, up to one-third will continue to experience uncomfortable symptoms despite acid suppression with PPIs. In some of these patients, the persistent symptoms are due to ongoing reflux of either acid or nonacid (ie, with a pH above 4.0, also termed weakly acidic) material. An early study in heartburn patients that underwent impedance-pH monitoring before and after 7 days of omeprazole found that PPI therapy did not achieve a significant reduction in the total number of reflux episodes (acid and nonacid reflux combined), causing instead a change in the ratio of acid to nonacid reflux.[28] After PPI therapy the percentage of acid reflux decreased from 45% to 3%, while nonacid reflux increased from 55% to 97%. Heartburn was more commonly linked to acid reflux but was also induced by nonacid reflux, and regurgitation was unchanged by acid suppression because it was frequently caused by nonacid reflux in the treated state. The observation that nonacid reflux can cause symptoms that are indistinguishable from those that are caused by acid has been corroborated by subsequent studies.[9,29] Furthermore, a systematic review that quantified acid and nonacid reflux in studies of GERD patients taking a PPI found that weakly acidic reflux underlies most reflux episodes in these patients and is the main cause of persistent symptoms despite PPI therapy.[30]

One approach for the management of acid or nonacid reflux in these patients is to focus on augmenting the function of the antireflux barrier and this can be accomplished through fundoplication,[31] or by pharmacologic inhibition of transient lower

esophageal sphincter relaxations (TLESRs). TLESRs are not induced by swallowing and instead occur through a vago-vagal reflex that is triggered by gastric distension.[32] Several neurotransmitters and receptors have been found to be involved in the modulation of TLESRs, including nitric oxide, opioids, cholecystokinin (CCK), muscarinic receptors, and cannabinoid receptors; among these, γ-aminobutyric acid (GABA) and glutamate may be the dominant neurotransmitters in this signaling pathway.[33,34]

GABA-B agonists

The GABA-B agonist baclofen has been available for many years for the treatment of spasticity. More recently, this agent was found to reduce TLESRs and reflux episodes in humans.[35] Baclofen has also been shown to decrease the number of postprandial acid and nonacid reflux events,[36] nocturnal reflux activity,[37] and duodenogastric reflux as detected by monitoring for bile reflux.[38] Given the limited treatment options for GERD symptoms refractory to PPIs, a trial of baclofen at a dosage of 5 to 20 mg TID can be considered in patients with objective documentation of continued symptomatic reflux despite optimal PPI therapy, but there are no long-term data evaluating the efficacy of baclofen in GERD. Furthermore, its use is limited by frequent side effects, including nausea, somnolence, dizziness, and fatigue. Furthermore, baclofen is not US Food and Drug Administration–approved for the treatment of GERD.

Newer GABA-B agonists have been developed with the aim of reducing TLESRs with fewer side effects. Unfortunately, development has been stopped because of insufficient efficacy or side effects. The GABA-B agonist lesogaberan was found to decrease TLESRs and reflux episodes in healthy subjects,[39] but a randomized, double-blind, control trial evaluating its use as adjunct therapy to PPIs in patients with refractory symptoms found only modest, albeit statistically significant, clinical benefit[40] and further development was therefore halted. Arbaclofen placarbil, a prodrug of the pharmacologically active R-isomer of baclofen, was shown to reduce reflux episodes in GERD patients.[41] However, further development was stopped after a subsequent randomized, double-blind, placebo-controlled trial showed that arbaclofen was not superior to placebo in reducing heartburn events over 4 weeks.[42] Thus, the only available GABA-B agonist at the present time continues to be baclofen.

Metabotropic glutamate receptor-5 antagonists

Peripherally located metabotropic glutamate receptors have been associated with control of TLESRs by modulation of the mechanosensitivity of vagal afferents. The negative allosteric modulator of metabotropic glutamate receptor-5 (mGluR5) ADX10059 was found to reduce TLESRs and esophageal acid exposure in a proof-of-concept study.[43] However, development of this medication was discontinued later on because of hepatotoxicity. More recently, AZD2066, another mGluR5 antagonist, was found to decrease TLESRs and reflux episodes in healthy subjects without causing serious adverse events,[44] but there are no other trials available.

Other TLESR inhibitors

The cannabinoid receptor agonists, dronabinol[45] and rimonabant,[46] have been shown to reduce postprandial TLESRs; however, these compounds were deemed unsuitable for further trials because of side effects, mainly nausea and vomiting. Another potential therapeutic target in this arena is CCK. Although the CCK antagonist loxiglumide was found to reduce TLESRs, the effect on postprandial reflux was only modest and further development was not pursued.[47]

Enhancement of Mucosal Defense and Repair Mechanisms

Pharmacologic enhancement of the esophageal defense mechanisms can theoretically be achieved by two approaches. One is to improve esophageal clearance of refluxate through augmentation of peristalsis. Another alternative is to enhance epithelial repair mechanisms.

Prokinetics

Prokinetic agents can theoretically enhance esophageal clearance of refluxed gastric contents by improving peristalsis. The only prokinetic currently available in the United States is metoclopramide, which has been shown to augment LES pressure, increase gastric emptying, and enhance esophageal peristalsis.[48] However, in a randomized double-blind study of patients with EE, metoclopramide failed to improve esophageal acid exposure and esophageal clearance when compared with placebo.[49] In another study, adding metoclopramide to the H2RA ranitidine did not result in any additional benefit for healing EE or controlling reflux symptoms.[50] There are no data to support the use of metoclopramide as an adjunct to PPI therapy. In addition, metoclopramide has important central nervous system side effects including drowsiness, agitation, irritability, depression, and dystonic reactions, and it can cause tardive dyskinesia (the latter in less than 1% of patients).[51] For all of these reasons, metoclopramide is not recommended as a treatment for GERD.[52] Other prokinetics, such as domperidone, itopride, and mosapride, may have modest benefits for the treatment of GERD but studies are limited and none of these agents are available in the United States.[15]

Mucosal repair

Dilation of the intercellular space diameter (ISD) of the esophageal epithelium, measured by transmission electron microscopy, was found to be an early morphologic marker of tissue damage in a GERD animal model.[53] This finding was later confirmed in esophageal biopsies from GERD patients with as well as without EE,[54] and the technique has emerged as a sensitive way to assess esophageal mucosal integrity. A subsequent study found that symptomatic GERD patients have increased ISD; furthermore, treatment with a PPI resulted in normalization of ISD and resolution of heartburn.[55] A more recent study demonstrated that ISD is increased in GERD patients with heartburn that fails to respond to PPI therapy compared with healthy controls.[10] Thus, promoting restoration of esophageal mucosal integrity through other pharmacologic approaches is an attractive idea.

Rebamipide, a cytoprotective antiulcer agent that enhances the production of endogenous prostaglandins, has been recently evaluated for the treatment of GERD. In a study of patients with esophagitis LA classification grade A or B that achieved symptomatic relief after an 8-week course of lansoprazole, maintenance therapy with lansoprazole plus rebamipide resulted in a significantly lower rate of relapse compared with lansoprazole alone.[56] In a more recent study of patients with normal endoscopy who had not achieved symptom relief with a PPI, the addition of rebamipide failed to result in significant improvement when compared with placebo.[57] However, GERD was not confirmed by reflux monitoring so it is possible that some of the patients had a functional GI disorder rather than GERD. Further studies will be needed to clarify the role of rebamipide in GERD.

The serotonin 5-HT_4 receptor agonist tegaserod has been shown to have a significant stimulatory impact on several salivary protective factors as well as esophageal epidermal growth factor secretion and may therefore have esophagoprotective properties.[58] In an open-label study of patients that were randomized to tegaserod alone, esomeprazole alone, or tegaserod plus omeprazole, heartburn relief was significantly

more frequent with combined therapy compared with either monotherapy.[59] However, tegaserod has been removed from the market because of serious adverse cardiovascular effects.

Modulating Sensation

The final steps in the sequence of events leading to symptoms caused by reflux involves activation of esophageal mucosal nociceptors, firing of afferent signals, and interpretation of these signals in the brain cortex, all of which offer potential therapeutic targets for control of esophageal symptoms.

Nociceptor blockade

Among the several nociceptors that have been identified in the esophagus, the transient receptor potential vanilloid receptor 1 (TRPV1) is regarded as the most important one.[12] TRPV1, a polymodal nonselective calcium-permeable cation channel, is activated by exposure to capsaicin and related natural irritants (referred to as vanilloids), such as heat and acids,[11] and may also play a role in the response to mechanical stimulation such as distension.[60] A recent study demonstrated increased TRPV1 levels in esophageal biopsies from patients with heartburn and erosive as well as nonerosive reflux disease.[61] Therefore, blocking nociceptors could potentially relieve esophageal symptoms.

The TRPV antagonist AZD1386 reduced esophageal pain thresholds in healthy volunteers, but the effect was specific for heat-induced pain and the thresholds for perception of acid infusion or balloon distension were not affected.[62] In a more recent placebo-controlled, double-blind, crossover study that compared AZD1386 to placebo in patients with nonerosive reflux disease and partial PPI response, AZD1386 had no analgesic effect on experimental esophageal pain.[63] Despite these negative results, nociceptor blockade remains an attractive therapeutic target.

Visceral analgesia and cortical modulation

In some patients who do not improve with standard therapies for GERD, there may be a component of visceral hypersensitivity and thus regulating afferent signaling and cortical interpretation of these signals may provide relief. Antidepressant medications may modulate esophageal sensation peripherally at the sensory afferent level, as well as in the central nervous system.[24] In a recent double-blind, randomized, controlled trial the selective serotonin reuptake inhibitor citalopram was compared with placebo in patients with hypersensitive esophagus who complained of typical symptoms (heartburn, regurgitation, chest pain). After 6 months of treatment, ongoing symptoms were significantly less common with citalopram compared with placebo (38% vs 66%).[64] Other treatments that focus on cortical modulation have shown positive effects in small studies. In a controlled trial of guided relaxation compared with a placebo intervention in GERD patients, symptom ratings were significantly lower in the relaxation training group.[65] In patients with heartburn refractory to once-daily PPI who were randomized to acupuncture versus doubling the dose of PPI, acupuncture was found to be superior for symptom control.[66] Other interventions that have been found to be beneficial for functional chest pain may be useful in GERD, including hypnotherapy[67] and Johrei (a therapy based on transmission of healing energy that has been used for chronic pain),[68] but these have not been evaluated specifically in GERD.

SUMMARY

The mainstay of pharmacologic therapy for GERD is gastric acid suppression with PPIs, with generally no major differences among the available PPIs for healing of

EE and achieving symptom control, but definite superiority for these treatment endpoints when comparing them with the H2RAs. Despite their proven effectiveness, up to one-third of patients may have insufficient symptomatic relief despite PPI therapy, prompting a search for alternative treatments. The antireflux barrier function can be enhanced with TLESR inhibitors, but at the present time only the GABA-B agonist baclofen is available for this purpose as development of other compounds was stopped because of low efficacy or side effects. Although esophageal defense can be theoretically enhanced by improving esophageal clearance with prokinetics, the efficacy of these agents for this purpose has been limited and side effects are important with metoclopramide, the only currently available prokinetic in the United States. Another avenue for improving esophageal defense is to support the esophageal mucosa with compounds such as rebamipide, which increases endogenous prostaglandin production and has shown a positive impact on maintenance of GERD relief in limited trials. Finally, the sensory pathways responsible for GERD symptoms can be targeted by esophageal mucosal nociceptor blockade or modulation of afferent signals and their interpretation in the brain cortex with a variety of compounds or cognitive techniques. Blocking the TRPV1 nociceptor has not resulted in significant improvement of pain thresholds in early studies. Visceral analgesia with the selective serotonin reuptake inhibitor citalopram has been shown to be effective for symptom control in patients with hypersensitive esophagus in a randomized trial. Cortical modulation with techniques such as relaxation training or acupuncture may also offer benefits to GERD patients, but trials are limited. As can be gleaned from this summary, the data supporting these new and evolving approaches for treating GERD are limited and most of these agents are not ready for routine clinical use. However, further clinical trials and additional insights into the pathophysiology of GERD that can be translated into therapeutic targets are awaited.

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