Chapter 6
Novel Upcoming Therapies

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Introduction

Currently, the main medical therapeutic modalities for gastroesophageal reflux disease (GERD) are proton pump inhibitors (PPIs) and histamine type 2 receptor antagonists (H_2RAs). The effect of both classes of drugs is mediated through gastric acid suppression, albeit with different potency. Other underlying mechanisms for GERD treatment include neutralizing gastric acidity (antacids), creating a foamy raft in the stomach that prevents or replaces gastric acid reflux (alginate-based formulations), and improving esophageal clearance and gastric emptying (prokinetics).

The main goals of GERD treatment are to relieve symptoms, heal, and maintain remission of erosive esophagitis (EE), prevent complications, and improve health-related quality of life (HRQL) [1]. Presently, PPIs provide unsurpassed clinical efficacy in GERD patients, primarily due to their profound inhibitory effect on acid secretion. However, even in patients receiving PPI therapy, the resolution of esophageal mucosal inflammation is much more predictable than resolution of symptoms [2].

The different GERD phenotypes demonstrate varied degrees of response to antireflux treatment. Nonerosive reflux disease (NERD) patients, for example, have a significantly lower response rate to PPI therapy as compared with other GERD groups and consequently constitute the majority of patients with refractory heartburn. Failure of PPI therapy is the most common presentation of GERD in gastroenterology practice [3, 4].

Presently, there are several unmet needs in GERD treatment. Approximately 10–15 % of patients with EE fail to achieve complete healing after 8 weeks of treatment [5]. Moreover, even when the initial healing dose of the PPI is continued, 15–23 % of patients with Los Angeles grades A and B and 24–41 % of those with grades C

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Table 6.1 Novel treatment modalities for GERD

Medical	Endoscopic	Surgical
H_2RAs Lavoltidine	*EsophyX* Transoral incisionless fundoplication (*TIF*)	The LES stimulation system (*EndoStim*)
PPIs Tenatoprazole	Medigus ultrasonic surgical endostapler (*MUSE*)	
PPI combinations Vecam Secretol (Omeprazole + lansoprazole) PPI + alginate NMI 826 (nitric-oxide-enhanced PPI)		
P-CABs TAK-438		
Prokinetics 5-HT4 agonist (Reveprexide)		
Pain modulators TRVP1 (AZD1386)		
Bile acid sequestrant IW-3718		

LES lower esophageal sphincter, *PPI* proton pump inhibitor, *H_2RAs* histamine type 2 receptor antagonists

and D relapse within 6 months of initiating maintenance treatment. In addition, up to 40 % of NERD patients remain symptomatic while on standard dose (once daily) of PPI therapy [6]. Treatment of extraesophageal manifestations of GERD has been clinically disappointing [7]. Most of the randomized controlled trials in patients with pharyngeal, laryngeal, or pulmonary symptoms, which are suspected to be GERD related, demonstrate lack of relief or modest benefit with PPI treatment versus placebo. Other unmet needs in GERD include rapid and more effective control of postprandial heartburn, improved control of volume reflux and acid regurgitation, relief of nighttime heartburn symptoms, acid control in Barretts's esophagus (BE) patients, and a more flexible schedule of PPI administration [1].

The goal of the present review is to provide an overview of the new and future drug developments for GERD treatment (Table 6.1).

Histamine Type 2 Receptor Antagonists

H2RAs reduce gastric acid secretion by competitive inhibition of the interaction between histamine and H_2 receptors that are located on the parietal cells. In addition, H_2RAs reduce pepsin and gastric acid volume [8]. Currently, there are four Food and Drug Administration (FDA)-approved H_2RAs in the USA: cimetidine, famatodine, nizatidine, and ranitidine.

The different H_2RAs are considered equivalent in suppressing gastric acid secretion when administered in equipotent doses. The pharmacokinetic and pharmaco-

dynamic differences among the H_2RAs seem to be clinically nonsignificant [9]. Although H_2RAs are effective in controlling basal acid secretion, they have limited efficacy in suppressing postprandial acid secretion. Presently, H_2RAs are used to control symptoms and heal mild to moderate EE (Los Angeles grades A and B) [10]. In addition, several studies have demonstrated that approximately 30% of NERD patients report symptom relief after receiving an H2RA twice daily for 4 weeks [11, 12]. H_2RAs are particularly helpful in relieving postprandial heartburn for up to 12 h [13]. They are also effective in preventing postprandial heartburn if given 30 min before a meal [14]. In addition, H_2RA at bedtime significantly reduced the duration of nocturnal acid breakthrough (NAB) [15].

Nizatidine

Nizatidine is one of the currently available H_2RAs. A recent study evaluated the effect of nizatidine on the rate of transient lower esophageal sphincter relaxations (TLESRs) and the level of esophageal acid exposure. Ten healthy subjects were randomized to receive nizatidine (150 mg) twice a day versus placebo 60 min before a meal for 7 days. Subsequently, patients underwent esophageal manometry and pH testing. Nizatidine significantly increased lower esophageal sphincter (LES) basal pressure as compared with placebo. In addition, nizatidine significantly reduced esophageal acid exposure by decreasing the rate of TLESRs and consequently acid exposure as compared with placebo [16]. The aforementioned effects, in addition to accelerating gastric emptying, are likely due to direct or indirect inhibitory effect of nizatidine on acetylcholinesterase.

Lafutidine

This is a novel second-generation H_2RA. The drug has been primarily used as an antisecretory agent in Japan. In a randomized, double-blind, placebo-controlled study that included 584 subjects with an endoscopic diagnosis of Los Angeles grades A and B EE, patients received lafutidine (20 mg once daily), famotidine (40 mg once daily), or placebo for 8 weeks. The authors demonstrated that lafutidine had an endoscopic healing rate of 71% as compared with 61.4 and 9.7%, in the famotidine and placebo groups, respectively [17]. In another study, 23 patients diagnosed with NERD (two or more heartburn episodes per week, a questionnaire for the diagnosis of reflux esophagitis score of 6 or above, and a negative upper endoscopy) underwent a 24-h pH test at baseline and again after 4 weeks of treatment with lafutidine (10 mg twice daily). The authors demonstrated a significant decrease in the percentage of time that intraesophageal pH was <4 (3.07–1.17%). In addition, the percentage of time that intragastric pH was >3 also increased significantly (26.6–56.5%) [18].

Another multicenter study compared lafutidine with rabeprazole in treating uninvestigated dyspepsia. Subjects were randomized to lafutidine (10 mg) or rabeprazole (20 mg), both once daily for 4 weeks. Both lafutidine and rabeprazole provided a similar rate of symptom relief in patients with heartburn-predominant uninvestigated dyspepsia. The study supports the value of lafutidine as an effective empiric therapy in this subgroup of patients [19].

Lavoltidine (AH234844)

Lavoltidine, also known as loxtidine, is a potent noncompetitive H_2RA. Because of an increased incidence of carcinoid tumors observed in rats and mice after loxtidine treatment, the drug was suspended in 1988. The carcinogenic effect was probably related to the prolonged achlorhydria that was induced by loxtidine. However, it is unlikely that the drug has similar carcinogenic effect on the human gastric mucosa [20]. Since lavoltidine has shown rapid onset of action, high potency, and prolonged duration of effect after a single dose, GlaxoSmithKline conducted two clinical trials with the drug less than a decade ago. One study was a phase 2 pharmacokinetic/pharmacodynamic study which started in 2006. The study compared four different AH234844 (lavoltidine) doses (dose range not available) with esomeprazole (40 mg/day) and ranitidine (300 mg/day) in healthy male subjects [21]. Another phase 1 pharmacodynamic study, which was started in 2007, compared 24-h intragastric pH on days 1, 2, and 7 while subjects were on lavoltidine (40 mg) once daily [22]. Presently, there is no available information about the status of these studies (http://www.gsk-clinicalstudyregister.com/compounds/lavoltidine#ps).

One of the main limitations of H_2RAs is tachyphylaxis that develops quickly, usually within 2 weeks of repeated administration. This pharmacological phenomenon results in a decline in acid suppression that limits the regular use of H2RAs in clinical practice [23, 24]. Thus, it is still unknown if the new H_2RAs have a similar limitation. Furthermore, it will be important to see if the new H_2RAs are more effective in treating GERD patients as compared with the first generation of H_2RAs.

Proton Pump Inhibitors

The introduction of the PPIs into the US market in the early 1990s revolutionized the treatment of acid peptic disorders. This class of drugs is currently considered the best therapeutic option for GERD [25]. The high potency of PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole) is the result of their ability to inhibit the proton pump (H^+, K^+-ATPase), which is the final common pathway of gastric acid secretion. They suppress nocturnal, daytime, and

food-stimulated acid secretion [26]. Currently, PPIs are the most successful antisecretory agents for healing inflammation of the esophageal mucosa and relieving GERD-related symptoms because of their profound and sustained acid inhibition [5, 8]. PPIs have made an important therapeutic impact on advanced EE, GERD complications, and atypical manifestations of GERD. Even in BE, PPIs have made a significant impact on symptoms control, mucosal healing, and esophageal acid exposure.

A recent Cochrane review examined 134 therapeutic trials that included 36,978 subjects with EE and concluded that PPIs demonstrated a better healing effect and faster symptom relief than H_2RAs [27]. The study did not find any major difference in efficacy among the currently available PPIs. However, the effect of PPIs on symptoms differs between patients with NERD and those with EE. The symptomatic therapeutic gain of PPIs over placebo in NERD patients is much lower than that observed in patients with EE [28]. In a systematic review, the therapeutic gain for standard-dose PPI in relieving heartburn symptoms compared with placebo ranged from 30 to 35% for sufficient heartburn control and from 25 to 30% for complete heartburn control. Pooled response rates to PPIs once daily were significantly higher after 4 weeks of treatment for patients with EE compared with NERD patients (56 vs. 37%).

Since the introduction of PPIs into the market, refractory GERD has become the main presentation of GERD in clinical practice. Specifically, approximately 10–15% of patients with EE fail to achieve complete healing after 8 weeks of treatment. This subset of patients usually demonstrates moderate to severe disease (Los Angeles grades C and D) and comprises approximately 25–30% of all EE patients [5]. Moreover, even when continuing the initial healing dose as maintenance treatment for a period of 6 months, 15–23% of patients with Los Angeles grades A or B and 24–41% of those with grades C or D relapse while on treatment. In addition, up to 40% of NERD patients remain symptomatic while on standard dose (once-daily) PPI therapy [6]. Treatment of extraesophageal manifestations of GERD with a PPI has been relatively disappointing, and many trials showed that the drug does no better than placebo in improving or relieving symptoms [7]. Important shortcomings of PPIs include lack of effective control of postprandial and nighttime heartburn as well as limited effect on esophageal acid exposure in BE patients. In addition, PPIs demonstrate a dependence on food consumption for maximal efficacy.

At present, switching to another PPI or doubling the PPI dose has become the most common therapeutic strategy for GERD patients who symptomatically fail to achieve symptom control on PPI with once-daily dosing [3, 8]. According to a recent Cochrane review, doubling the PPI dose is associated with greater healing of EE, with the number needed to treat of 25. However, there is no clear dose–response relationship for heartburn resolution in either EE or NERD [33]. Although doubling the PPI dose has become the standard of care, there is no evidence to support further escalation of the PPI dose beyond PPI twice daily for either symptom control or healing of EE. When doubling the PPI dose, one dose should be given 30–60 min

before breakfast and the other 30–60 min before dinner. The support for splitting the dose originates primarily from physiological studies demonstrating improved control of intragastric pH when one dose is taken in the morning and the other in the evening as compared with both doses being taken before breakfast [29].

Several approaches have been used to improve the acid suppressive effect of PPIs. They include development of enantiomers that undergo slower hepatic metabolism, incorporation of technology that prolongs drug absorption, and combining PPI's with compounds that maximize PPI absorption and thus bioavailability.

Extended-Release PPIs

Tenatoprazole

Tenatoprazole is a novel compound that, unlike other PPIs, is not a benzimidazole molecule. It is characterized by an imidazopyridine backbone with substantially prolonged plasma half-life. Tenatoprazole (40 mg once daily) demonstrated better nighttime acid control than esomeprazole (40 mg once daily) in healthy subjects [30]. Another study found that this drug markedly inhibits intragastric acidity unrelated to dosing time or food intake [31]. S-tenatoprazole-Na, an enantiomer of tenatoprazole, was significantly better in providing gastric acid suppression when compared with esomeprazole (40 mg once daily). Furthermore, it was also demonstrated that higher doses of the drug produced greater acid suppression in a dose–response fashion [32].

AGN 201904-Z (Alevium)

AGN 201904-Z (Alevium) is a prodrug of omeprazole. It is acid stable and therefore requires no enteric coating. This drug has a long plasma half-life due to slow absorption throughout the small intestine. After absorption, the drug is rapidly hydrolyzed in the systemic circulation to omeprazole [33]. A comparison of Alevium (600 mg once daily), with esomeprazole (40 mg once daily) in 24 healthy subjects resulted in significantly greater and more prolonged acid suppression during both daytime and nighttime. Alevium once daily showed a 1.9-fold increase in serum half-life as compared with esomeprazole. After 5 days of treatment, Alevium demonstrated a significantly higher mean 24-h intragastric pH, nocturnal median pH, and percentage of time intragastric pH was greater than 4 as compared with esomeprazole ($P = 0.0001$) [34] (Table 6.2).

Table 6.2 Compounds under development that have been discontinued

Class	Drug	Reason for discontinuation
H_2RAs	Loxtidine	Neuroendocrine tumors in rats
PPIs	AGN201904-Z (Alevium ®)	Poor efficacy
PPI combinations	OX17	Poor efficacy?
P-CABs	Linaprazan (AZD 8065) Soraprazan Revaprazan	Modest or no clinical benefits over PPIs
TLESR reducers	$GABA_B$: Arbaclofen placarbil, Lesogaberan (AZD3335)	Poor efficacy Side effects: diarrhea, nausea, and increased transaminases
	mGluR5 (ADX10059, AZD2066)	Side effects: increased transaminases and hepatic failure
	CB agonist (rimonabant)	Side effects: depression and suicidal tendencies
	CCK/gastrin receptors antagonist (spiroglumide, itriglumide and loxiglumide)	Poor efficacy
Prokinetics	5-HT4 agonist (Tegaserod)	Poor efficacy

TLESR transient lower esophageal sphincter relaxation *PPI* proton pump inhibitor, *H_2RAs* histamine type 2 receptor antagonists, *CCK* cholecystokinin, *$GABA_B$* gamma-aminobutiric acid B, *CB* cannabinoid

PPI Combinations

PPI-VB101 (Vecam)

PPI-VB101 (Vecam) is the coadministration of a PPI with a succinic acid, a food additive that activates proton pumps in the parietal cells. The succinic acid has a pentagastrin-like activity that potentiates activation of proton pumps [35]. The rationale behind this combined therapy is to increase the efficacy of the PPI by maximizing activation of proton pumps. In addition, it may allow administration of PPI without regard to food. In an open-label study, 36 healthy subjects were randomized to receive once-daily Vecam (20 or 40 mg) at bedtime or omeprazole (20 mg) before breakfast. The effect of the different therapeutic arms on intragastric acidity was compared over a 24-h period. Vecam (40 mg) was significantly better in keeping nighttime intragastric pH > 4 as compared with Vecam (20 mg) and omeprazole ($P < 0.0001$). Similarly Vecam (20 mg) showed significantly better control of intragastric pH as compared with omeprazole (20 mg; $P = 0.0069$) [36].

OX17

OX17 is an oral tablet containing a combination of omeprazole and famotidine (doses are unclear) [37]. This combination has shown a 60% increase in total time intragastric pH > 4 as compared with omeprazole alone. Further developments of

this drug have been discontinued [38]. A combination of tenatoprazole and H_2RA has been recently patented (US 20060241136 A1) [39]. However, we are still awaiting studies demonstrating the clinical value of this novel compound as compared with PPI alone.

NMI-826

NMI-826 is a nitric-oxide (NO)-enhanced PPI. The drug has been shown to be more effective than a PPI alone in healing gastric ulcers [40].

Secretol

Secretol is a novel pharmacological compound that combines omeprazole with lansoprazole. Currently, secretol is undergoing a phase II trial that compares its healing rates and symptom control with esomeprazole in subjects with severe EE (www.clinicaltrials.gov NCT01129713). The combined compounds are likely to be niched in certain areas of unmet needs in GERD rather than competing with the currently available PPIs.

PPI-Prokinetics

Rabeprazole Plus Itopride

This compound contains a fixed-dose combination of rabeprazole 20 mg and itopride 150 mg [41, 42]. The efficacy and safety of this drug has been evaluated in patients with functional dyspepsia and NERD [43]. The authors demonstrated that 93% of the patients reported a relief of their symptoms after a 4-week course of therapy. Presently, this formulation is not available in the USA.

Pantoprazole Plus Domperidone

The safety and efficacy of this combination drug composed of pantoprazole 40 mg and domperidone 20 mg (10 mg immediate release form and rest 10 mg in delayed release form tablets) has been evaluated in GERD patients [44]. The authors demonstrated a significant improvement of GERD-related symptoms at week 4 as compared to baseline ($P<0.001$). Currently, this combined drug is not available in the USA.

Potassium-Competitive Acid Blockers (P-CABs)

P-CABs represent a heterogeneous group of drugs that share the same final mechanism of action. This class of drugs inhibits gastric H^+/K^+-ATPase in a K^+competitive but reversible mechanism. Consequently, P-CABs do not require prior proton pump activation to achieve their antisecretory effect. P-CABs exhibit an early onset inhibition of acid secretion due to rapid rise in peak plasma concentration [45]. Given the pharmacokinetic and pharmacodynamic profile of P-CABs, they are likely to be beneficial as an on-demand therapy for symptomatic GERD.

Attempts to develop P-CABs in the past two decades have failed to produce even one compound that reached the market. Comparative trials were unable to demonstrate clinical superiority of P-CABs over currently available PPIs. This is primarily due to common utilization of traditional study designs rather than trials specifically focusing on the unique characteristics of P-CABs. In addition, several P-CABs have been associated with severe adverse effects such as liver toxicity. Thus, despite their promising pharmacokinetics and pharmacodynamics profile, their future in the GERD market remains to be elucidated.

Linaprazan (AZD 8065)

Linaprazan (AZD 8065) demonstrated similar efficacy as esomeprazole in healing and controlling symptoms of GERD patients with EE [46]. However, the drug did not demonstrate any clinical benefits over esomeprazole in symptom control of patients with NERD [47].

Soraprazan

Soraprazan showed an immediate inhibition of acid secretion in in vitro models. In animal models, the drug was found to be superior to esomeprazole in onset of action as well as extent and duration of intragastric $pH > 4$ [48]. Presently, there are no clinical data available for soraprazan.

Revaprazan

Revaprazan was demonstrated to be equivalent to PPIs in acid suppression. In a recent study, the authors compared the bioavailability and tolerability of revaprezan alone to revaprezan plus iotopride. Revaprezan demonstrated bioequivalence to the combination with iotopride without any clinically significant drug-to-drug interaction [49]. Recently, a phase II clinical trial aimed to investigate the safety, tolerability, and

efficacy of revaprazan (YH1885L) in NERD patients has been completed. However, no clinical data are available yet (www.clinicaltrials.gov NCT01750437).

TAK 438

TAK 438 (vonoprazan) demonstrated greater potency and longer lasting inhibitory effect on gastric acid secretion when compared with lansoprazole in animal models [50, 51]. Recently, two randomized, double-blind, placebo-controlled phase I trials were conducted in healthy male volunteers in Japan ($n=60$) and the UK ($n=48$) [52]. TAK 438 given in increasing oral doses (10–40 mg once daily) for 7 days was assessed for safety, tolerability, pharmacokinetics, and pharmacodynamics. The authors demonstrated that on day 7 of treatment with 40 mg once daily of TAK 438, the mean 24-h intragastric pH > 4 was 100 % in the cohort from Japan and 93.2 % in the UK cohort (*P* values not available). Also, TAK 438 (all doses) increased serum concentrations of gastrin, pepsinogen I and II in both studies (*P* values not available). The drug induced some dose-dependent minor adverse events that included, increased serum triglycerides and eosinophil's count, decreased white blood cell-count, nasopharyngitis, headache, abdominal pain, oral herpes, and neck pain [52].

Transient Lower Esophageal Sphincter Relaxation (TLESR) Reducers

TLESR is the main mechanism of gastroesophageal reflux, both acidic and nonacidic, accounting for all reflux episodes in healthy subjects and the majority (55–80 %) of reflux episodes in GERD patients [53]. A wide range of receptors is involved in triggering TLESR including gamma-aminobutiric acid B ($GABA_B$), metabotropic glutamate receptor 5 (mGlucR5), cannabinoid (CB), cholecystokinin (CCK), 5-hydroxytryptamine-4, muscarinic, and opioid [54].

CB Receptor Agonists

Delta-9-tetrahydrocannabinol, a CB1/CB2 receptor agonist, inhibits the rate of TLESRs [55]. A study that evaluated the effect of delta-9-tetrahydrocannabinol on TLESRs in dogs and healthy subjects showed that this compound significantly reduced the number of meal-induced TLESRs. However, the drug also significantly reduced the LES basal pressure. Furthermore, adverse effects such as nausea, vomiting, hypotension, and tachycardia led to premature termination of the study. [56].

Rimonabant is a CB1 receptor antagonist. In a placebo-controlled trial that was conducted in healthy subjects, the drug demonstrated increased LES basal pressure

and decreased rate of TLESRs and postprandial reflux. The drug was withdrawn from further investigation due to psychological side effects such as depression and suicidal tendency [57].

CCK/Gastrin Receptors Antagonist

Gastrin and CCK_2 receptors are identical. Given the physiological importance of gastrin in the stimulation of gastric acid secretion, the development of a selective CCK_2 receptor antagonist offers a potential therapeutic choice for acid-related disorders [48, 58]. Only a few CCK receptor antagonists have been tested in humans, among them spiroglumide, itriglumide, and loxiglumide. Loxiglumide has been shown to inhibit the rate of meal-induced TLESR [58–60]. It is unclear, however, if the effect of loxiglumide is limited to the physiological post-meal increase in TLESRs and reflux episodes, and thus the drug would have no impact on pathological reflux. Itriglumide inhibits gastrin-stimulated acid secretion but might delay mucosal healing; tolerance to the drug may also develop [61].

Other TLESR reducers have been primarily studied as add-on treatments for patients who failed once-daily PPI. However, the development of several novel agents targeting this mechanism has met many obstacles, and thus far none of them has made it to the market [62]. These included the $GABA_B$ agonists arbaclofen placarbil [63, 64], lesogaberan (AZD 3355) [65, 66], mGlucR5 antagonists ADX 10059 [26, 67], and AZD2066 [68].

Prokinetics

Prokinetic agents have been proposed to improve GERD-related symptoms by different potential mechanisms that include improvement in esophageal peristalsis, acceleration of esophageal acid clearance, increase in LES basal pressure, and improved gastric emptying. The clinical benefit of prokinetics as sole treatment for GERD has been modest at best. Moreover, their use has been hampered by many adverse effects.

Mosapride

Mosapride citrate has both 5-HT4 receptor agonist and 5-HT3 receptor antagonist effects. This drug significantly reduced acid reflux and improved GERD-related symptoms primarily as an add-on therapy [69, 70].

Itopride

Itopride is a dopamine (D2) receptor antagonist, which also inhibits acetylcholinesterase. This drug has been shown to improve GERD-related symptoms and reduce esophageal acid exposure in patients with mild EE [71]. Itopride inhibits TLESRs without significantly affecting esophageal peristalsis.

Azithromycin

Azithromycin is a macrolide with motilin agonist properties. The drug also promotes acetylcholine release and stimulates serotonin receptors (5HT3). In a recent study, azithromycin reduced the number of acid reflux events and the size of hiatal hernia as measured by high-resolution manometry. The mean size of the hiatal hernias was larger when reflux episodes were acidic as compared with weakly acidic or nonacidic reflux events. In addition, the acid pocket was more often located below the diaphragm (distal position) [72]. In another study, the effect of azithromycin was evaluated in subjects after lung transplantation (LTx). Subjects receiving the drug demonstrated a significantly lower number of total ($P=0.012$) and acid reflux events ($P=0.0037$) in a 24-h period as well as bile acids levels in bronchoalveolar lavage fluid ($P=0.0106$) [73].

Prucolopride

Prucolopride, a first-in-class dihydrobenzofuran-carboxamide, is a potent selective 5-HT4 receptor agonist with enterokinetic properties. The drug is currently used for chronic constipation. Due to its pharmacodynamic profile, the drug may have a role in GERD patients [74].

Reveprexide

A recent randomized, double-blind, placebo-controlled, parallel-group phase IIb study aimed to evaluate the effect of reveprexide, a 5-HT4 receptor agonist, in 477 patients with GERD who partially responded to PPI treatment [75]. Patients were randomized into four different groups, reveprexide 0.1, 0.5, or 2.0 mg three times a day in addition to their PPI, or placebo plus PPI for 8 weeks. The study demonstrated no difference in percentage of regurgitation-free days among the three reveprexide arms as compared with placebo (0.1 mg, $P=0.128$; 0.5 mg, $P=0.062$; 2.0 mg, $P=0.650$). However, the percentage of heartburn-free day was significantly higher in the reveprexide 0.5-mg group as compared with placebo ($P<0.05$). Occurrence of adverse events was dose dependent, with a rate of approximately 60%

in the reveprexide 2.0-mg group. The most common adverse events include, diarrhea, nausea, headache, abdominal pain, upper respiratory tract infection, back pain, and worsening of pulmonary hypertension [75].

Pumosetrag

Pumosetrag (DDP733) is a partial 5HT3 receptor agonist with gastrointestinal (GI) prokinetic activities. DDP733 increased LES basal pressure in experimental animal models. In addition, DDP733 significantly reduced the rate of reflux events and increased the mean amplitude of distal esophageal contractions without changing the LES basal pressure in healthy human subjects [53, 76].

Pain Modulators

In GERD patients with evidence of esophageal hypersensitivity, such as those with NERD or PPI failure due to nonacidic reflux, pain modulators are likely to play a pivotal therapeutic role [1, 6, 77]. Pain modulators, or visceral analgesics, have been shown to significantly improve symptoms in patients with noncardiac chest pain (NCCP), functional heartburn, and refractory GERD [78]. Non-organ-specific pain modulators such as tricyclic antidepressants (TCAs), trazodone, selective serotonin reuptake inhibitors (SSRIs), and serotonin/norepinephrine reuptake inhibitors (SNRIs) are commonly used in clinical practice to treat functional esophageal disorders [79, 80]. It is believed that these agents confer their visceral analgesic effect by acting at the CNS level and/or peripherally at the sensory afferent level.

AZD1386

AZD1386 is a transient receptor potential vanilloid-1 (TRPV1) antagonist. In a recent randomized, placebo-controlled study that was conducted in 22 healthy male subjects, the authors evaluated the effect of two different doses of AZD1386 (30 and 95 mg). The authors used a multimodal stimulating probe in the esophagus (distension, heat, acid, and electrical stimulation) for drug assessment. AZD1386 (30 and 95 mg) increased esophageal pain thresholds to heat 23 and 28 %, respectively ($P < 0.01$). The drug did not have an effect on perception thresholds for chemical, mechanical, or electrical stimuli [77]. Furthermore, another recent study aimed to investigate the effect of AZD1386 on experimental esophageal pain in NERD patients with partial PPI response reported no analgesic effect on esophageal pain in this patient population [81]. Elevated liver enzymes during drug treatment has been a major concern [82]. In addition, the drug-induced hyperthermia, which could represent a challenge in clinical practice [83].

Rozerem

Rozerem is a melatonin receptor agonist (MT1 and MT2), approved in the USA for the treatment of insomnia [84]. The drug has been studied in GERD patients with nighttime reflux and sleep disturbances. In a study conducted by Jha et al., patients were randomized to receive either rozerem 8 mg or placebo at bedtime for 7 days (www.clinicaltrials.gov NCT01128582) [85]. The authors demonstrated that patients who received rozerem showed a statistically significant decrease in symptom scores, as compared with those who received placebo for daytime and nighttime heartburn (42 vs. 29%, 42 vs. −78%, respectively), 24-h heartburn (42 vs. 3%), and 24-h acid regurgitation (38 vs. −19%; all $P<0.05$). This study was the first to demonstrate that rozerem significantly improved GERD-related symptoms [86].

Pregabalin

Pregabalin is a centrally acting modulator of voltage-sensitive calcium channels. Chua et al. conducted a double-blind, placebo-controlled randomized study in 15 healthy volunteers that assessed the effects of pregabalin on the development of secondary esophageal hypersensitivity [87]. The administration of pregabalin was as follow: 75 mg twice/day for 3 days, then 150 mg twice/day for one day, and finally 150 mg the same day of the study. The authors demonstrated that pregabalin reduced the development of acid-induced hypersensitivity in the proximal esophagus at 30 and 90 min after acid stimulation as compared with placebo. This drug could potentially be used in GERD patients who failed to respond to an adequate anti-reflux therapy.

Mucosal Protectants

Rebamipide is an amino acid derivative of 2-(1*H*)-quinolinone with an anti-inflamatory function and thus may be effective as an esophageal mucosa protectant. A placebo-controlled study in 149 NERD subjects who failed PPI treatment assessed the efficacy of this compound. Unfortunately, the authors were unable to demonstrate a significant effect of rebamipide on subjects' symptoms [88]. In another study, investigators evaluated the effect of combining a PPI with rebamipide on healing esophageal mucosal ulcers that occurred due to endoscopic submucosal dissection (ESD). During the first 2 days after ESD, all subjects received an intravenous dose of omeprazole (20 mg) then switched to either rabeprazole (10 mg) once daily alone or to oral rabeprazole plus rebamipide (100 mg) given three times daily for the following 26 days. It was demonstrated that the number of subjects whose ulcer reached the scar stage 28 days after the ESD was significantly greater in the combination group (68%) as compared with the PPI group (35%; $P=0.011$) [89].

Growth factors, such as epidermal growth factor (EGF) and macrophage colony-stimulating factors (M-CSF), have a key role in mucosal healing. While early studies in animal models were promising, the value of these growth factors in GERD remains to be studied [90].

Bile Acid Sequestrant

IW-3718

IW-3718 (Ironwood, Cambridge, MA) is a novel, gastric retentive formulation of a bile acid sequestrant developed using the proprietary Acuform® drug delivery technology [91]. Recently, a randomized, double-blind, placebo-controlled, multisite, phase IIa study enrolled 93 patients with GERD who partially failed to respond to PPI therapy (www.clinicaltrials.gov NCT02030925). Patients were randomized to receive either 1000 mg of IW-3718 or placebo twice daily for 4 weeks while continued to take their PPI during the study. The exploratory study evaluated a number of GERD-related symptoms rather than specifying a primary end point, and as such was not powered to establish the statistical significance of a particular end point. The percentage of heartburn-free days for IW-3718-treated patients increased by 30.3% in the overall trial population and 34.6% in the bile reflux-positive subgroup (vs. 24.7 and 23.6%, respectively, for the placebo-treated groups). Additionally, 45.7% of the IW-3718-treated patients and 56.3% of the bile reflux-positive subgroup were considered responders (degree of relief of overall GERD symptoms) as compared with 27.7 and 29.4%, respectively, in the placebo-treated groups [91].

Endoscopic Therapy

EsophyX

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 3–5 cm in length and 200–300° in circumference [92]. TIF increases LES length and resting basal pressure as well as reduces or normalizes intraesophageal 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 [93, 94]. Long-term follow-up is limited to approximately 3 years, and studies have reported worrisome side effects including esophageal perforation and significant GI bleeding [95]. 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-GERD patients treated with a PPI (most with EE but all with hiatal hernia <2 cm in length), the authors reported the results of a 12-month follow-up [93]. The study demonstrated that after 1 year, 73% of the participants reported 50% improvement in HRQL, 85% discontinued daily PPI use, and 37% normalized esophageal acid exposure.

Most recently, The Randomized EsophyX vs Sham, Placebo-Controlled Transoral Fundoplication (RESPECT) trial, reported about 696 GERD patients who were randomized to either TIF procedure or sham surgery [96]. Two weeks postoperatively, TIF patients were switched to received placebo and sham surgery continued on once- or twice-daily omeprazole 40 mg for 6 months. The authors demonstrated by intention-to-treat analysis, that TIF eliminated troublesome regurgitation in 67% of the patients as compared with 45% of those who were treated with sham surgery and a PPI ($P=0.023$). The mean number of reflux episodes decreased from 135 before TIF to 94 after TIF procedure ($P<0.001$). Mean percent total time pH<4 improved from 9.3 before TIF to 6.4 after the TIF procedure ($P<0.001$). In the sham surgery group, neither the mean number of reflux episodes or the mean percent total time pH<4 were significantly different during a 48-h pH testing off PPIs for 7 days (all $P=$NS). Severe complications were rare.

Medigus Ultrasonic Surgical Endostapler (MUSE)

The transoral endoscopic device (MUSE™, formerly called SRS, Medigus, Omer, Israel) is a novel technique to treat GERD patients, including those with NERD. The MUSE system received FDA clearance in 2014. The MUSE system is used to perform anterior fundoplication using a modified endoscope that incorporates a miniature camera, an ultrasound probe, and stapler at the tip [97]. A recent study compared the safety and efficacy of MUSE system (formerly SRS) with laparoscopic antireflux surgery (LARS) [98]. The authors demonstrated that the procedure times for MUSE and LARS were 47 and 89 min, respectively ($P<0.05$). However, the mean discharge time from the hospital was longer for MUSE as compared with LARS (3 vs. 1.2 days, $P<0.05$). There was no significant difference in the need for PPI consumption between the two groups at a 6-month follow-up. The mean GERD-HRQL scores significantly improved in 64% of the participants who underwent MUSE as compared with baseline ($P=0.016$). There was one esophageal perforation in the MUSE group [98].

Recently, Zacherl et al. conducted a multi-center, prospective trial in 66 patients who were diagnosed with GERD (≥2 years documented GERD symptoms, PPI treatment greater than 6 months and abnormal ambulatory esophageal pH monitoring off PPI therapy) and who underwent MUSE procedure with a 6-month follow-up [99]. There was at least 50% reduction in GERD-HRQL total score between baseline (off PPI) and 6-month follow-up scores (9% CI 60–83%) in 72.7% (48/66)

of the patient. The median GERD-HRQL total score significantly improved in 9% (6/66) of patients at 6-month follow-up as compared to baseline scores off PPI treatment ($P<0.001$). The mean % total time with esophageal pH < 4.0 decreased from 10.9 at baseline (off PPI) to 7.3 at 6-month follow-up ($P<0.001$). No significant changes were observed in the esophageal manometry performed at baseline and at 6-month follow-up (all P = NS). There were only two adverse events and neither required further intervention (elevated C-reactive protein and a non-procedure related psychiatric emergency) [99]. The MUSE system is primarily promoted to surgeons and requires further evaluation about its long-term efficacy.

Surgical Therapy

The LES Stimulation System (EndoStim)

Electrical stimulation of the LES using the EndoStim has not yet been approved in the USA. The technique has been shown to increase LES resting pressure in animal models [100–102]. 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-h esophageal acid exposure [103, 104]. 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 [105]. 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.

References

1. Hershcovici T, Fass R. Gastro-oesophageal reflux disease: beyond proton pump inhibitor therapy. Drugs. 2011;71(18):2381–9.
2. Fass R. Alternative therapeutic approaches to chronic proton pump inhibitor treatment. Clin Gastroenterol Hepatol. 2012;10(4):338–45, quiz e39–40.
3. Fass R, Sifrim D. Management of heartburn not responding to proton pump inhibitors. Gut. 2009;58(2):295–309.
4. Fass R. Proton pump inhibitor failure—what are the therapeutic options? Am J Gastroenterol. 2009;104 Suppl 2:S33–8.
5. Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology. 1997;112(6):1798–810.

6. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease–where next? Aliment Pharmacol Ther. 2005;22(2):79–94.
7. Moore JM, Vaezi MF. Extraesophageal manifestations of gastroesophageal reflux disease: real or imagined? Curr Opin Gastroenterol. 2010;26(4):389–94.
8. Fass R, Hixson LJ, Ciccolo ML, Gordon P, Hunter G, Rappaport W. Contemporary medical therapy for gastroesophageal reflux disease. Am Fam Physician. 1997;55(1):205–12, 17–8.
9. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology. 2000; 118(2 Suppl 1):S9–31.
10. Wang WH, Huang JQ, Zheng GF, Xia HH, Wong WM, Lam SK, et al. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis. World J Gastroenterol. 2005;11(26):4067–77.
11. Venables TL, Newland RD, Patel AC, Hole J, Wilcock C, Turbitt ML. Omeprazole 10 milligrams once daily, omeprazole 20 milligrams once daily, or ranitidine 150 milligrams twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease in general practice. Scand J Gastroenterol. 1997;32(10):965–73.
12. Fujiwara Y, Higuchi K, Nebiki H, Chono S, Uno H, Kitada K, et al. Famotidine vs. omeprazole: a prospective randomized multicentre trial to determine efficacy in non-erosive gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2005;21 Suppl 2:10–8.
13. Pappa KA, Gooch WM, Buaron K, Payne JE, Giefer EE, Sirgo MA, et al. Low-dose ranitidine for the relief of heartburn. Aliment Pharmacol Ther. 1999;13(4):459–65.
14. Pappa KA, Williams BO, Payne JE, Buaron KS, Mussari KL, Ciociola AA. A double-blind, placebo-controlled study of the efficacy and safety of non-prescription ranitidine 75 mg in the prevention of meal-induced heartburn. Aliment Pharmacol Ther. 1999;13(4):467–73.
15. Peghini PL, Katz PO, Castell DO. Ranitidine controls nocturnal gastric acid breakthrough on omeprazole: a controlled study in normal subjects. Gastroenterology. 1998;115(6):1335–9.
16. Iwakiri K, Kawami N, Sano H, Tanaka Y, Umezawa M, Futagami S, et al. The effects of nizatidine on transient lower esophageal sphincter relaxations (TLESRs) and acid reflux in healthy subjects. J Smooth Muscle Res. 2011;47(6):157–66.
17. Ohara S, Haruma K, Kinoshita Y, Kusano M. A double-blind, controlled study comparing lafutidine with placebo and famotidine in Japanese patients with mild reflux esophagitis. J Gastroenterol. 2010;45(12):1219–27.
18. Inamori M, Iida H, Hosono K, Endo H, Sakamoto Y, Takahashi H, et al. The histamine H2 receptor antagonist lafutidine in Japanese patients with non-erosive reflux disease. Hepatogastroenterology. 2010;57(104):1430–4.
19. Dewan B, Philipose N. Lafutidine 10 mg versus Rabeprazole 20 mg in the treatment of patients with heartburn-dominant uninvestigated dyspepsia: a randomized, multicentric trial. Gastroenterol Res Pract. 2011;2011:640685.
20. Gatehouse D, Wedd DJ, Paes D, Delow G, Burlinson B, Pascoe S, et al. Investigations into the genotoxic potential of loxtidine, a long-acting H2-receptor antagonist. Mutagenesis. 1988;3(1):57–68.
21. NCT00405119. A study to investigate the effectiveness of AH234844 (lavoltidine) compared with nexium and ranitidine. https://clinicaltrials.gov/ctz/show/NCT00405119.
22. NCT00551473. Open-label comparison of 24 h gastric pH on days 1, 2, 7 with once-daily administration of lavoltidine 40 mg. https://clinicaltrials.gov/ctz/show/NCT00551473.
23. Fackler WK, Ours TM, Vaezi MF, Richter JE. Long-term effect of H2RA therapy on nocturnal gastric acid breakthrough. Gastroenterology. 2002;122(3):625–32.
24. Scarpignato C. New drugs to suppress acid secretion: current and future developments. Drug Discov Today Ther Strateg. 2007;4(3):155–63.
25. Horn J. The proton-pump inhibitors: similarities and differences. Clin Ther. 2000;22(3):266–80, discussion 5.
26. Howden CW. Appropriate acid suppression in the treatment of acid-related conditions. Pharmacol Ther. 1994;63(1):123–34.

27. Khan M, Santana J, Donnellan C, Preston C, Moayyedi P. Medical treatments in the short term management of reflux oesophagitis. Cochrane Database Syst Rev. 2007;18(2):CD003244.
28. Dean BB, Gano AD Jr, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. Clin Gastroenterol Hepatol. 2004;2(8):656–64.
29. Hatlebakk JG, Katz PO, Kuo B, Castell DO. Nocturnal gastric acidity and acid breakthrough on different regimens of omeprazole 40 mg daily. Aliment Pharmacol Ther. 1998;12(12):1235–40.
30. Galmiche JP, Bruley Des Varannes S, Ducrotte P, Sacher-Huvelin S, Vavasseur F, Taccoen A, et al. Tenatoprazole, a novel proton pump inhibitor with a prolonged plasma half-life: effects on intragastric pH and comparison with esomeprazole in healthy volunteers. Aliment Pharmacol Ther. 2004;19(6):655–62.
31. Thomson AB, Cohen P, Ficheux H, Fiorentini P, Domagala F, Homerin M, et al. Comparison of the effects of fasting morning, fasting evening and fed bedtime administration of tenatoprazole on intragastric pH in healthy volunteers: a randomized three-way crossover study. Aliment Pharmacol Ther. 2006;23(8):1179–87.
32. Hunt RH, Armstrong D, Yaghoobi M, James C. The pharmacodynamics and pharmacokinetics of S-tenatoprazole-Na 30 mg, 60 mg and 90 mg vs. esomeprazole 40 mg in healthy male subjects. Aliment Pharmacol Ther. 2010;31(6):648–57.
33. Sachs G, Shin JM, Hunt R. Novel approaches to inhibition of gastric acid secretion. Curr Gastroenterol Rep. 2010;12(6):437–47.
34. Hunt RH, Armstrong D, Yaghoobi M, James C, Chen Y, Leonard J, et al. Predictable prolonged suppression of gastric acidity with a novel proton pump inhibitor, AGN 201904-Z. Aliment Pharmacol Ther. 2008;28(2):187–99.
35. Chowers Y, Atarot T, Kostadinov A, Nudelman M, Bar-Peled O, Brenman L, Pankratov O, Naveh M. PPI activity is optimized by VB101, a parietal cell activator. Gastroenterology. 2008;134(4 Suppl 1):A–172.
36. Chowers Y, Atarot T, Pratha VS, Fass R. The effect of once daily omeprazole and succinic acid (VECAM) vs once daily omeprazole on 24-h intragastric pH. Neurogastroenterol Motil. 2012;24(5):426–31, e208–9.
37. Orexo announces results confirming the clinical profile of OX17 in reflux disease (GERD). http://www.orexo.com/en/Investor-Relations/Press-releases/?guid=341021. Accessed 9 Feb 2015.
38. Novartis AG has sent a notice of termination of the license agreement on OX17 for GERD. http://www.orexo.com/en/Portfolio/OX17/. Accessed 9 Feb 2015.
39. Dutta U, Armstrong D. Novel pharmaceutical approaches to reflux disease. Gastroenterol Clin North Am. 2013;42(1):93–117.
40. Sorba G, Galli U, Cena C, Fruttero R, Gasco A, Morini G, et al. A new furoxan NO-donor rabeprazole derivative and related compounds. Chembiochem. 2003;4(9):899–903.
41. Sahoo BK, Das A, Agarwal S, Bhaumik U, Bose A, Ghosh D, et al. Pharmacokinetics and bioequivalence study of a fixed dose combination of rabeprazole and itopride in healthy Indian volunteers. Arzneimittelforschung. 2009;59(9):451–4.
42. Mohamed HM. A study of selective spectrophotometric methods for simultaneous determination of Itopride hydrochloride and Rabeprazole sodium binary mixture: resolving sever overlapping spectra. Spectrochim Acta A Mol Biomol Spectrosc. 2014;136PC:1308–15.
43. Ghosh A, Halder S, Mandal S, Mandal A, Basu M, Dabholkar P. Rabeto plus: a valuable drug for managing functional dyspepsia. J Indian Med Assoc. 2008;106(11):752–4.
44. Singhal S DP, Bhatt A, Pokharna R, Sharma D, Kumar G, Kar P. Evaluation of safety and efficacy of pantoprazole and domperidone combination in patients with gastroesophageal reflux disease. Internet J Gastroenterol. 2005;4(2).
45. Anderson KO, Dalton CB, Bradley LA, Richter JE. Stress induces alteration of esophageal pressures in healthy volunteers and non-cardiac chest pain patients. Dig Dis Sci. 1989;34(1):83–91.

46. Kahrilas PJ, Dent J, Lauritsen K, Malfertheiner P, Denison H, Franzen S, et al. A randomized, comparative study of three doses of AZD0865 and esomeprazole for healing of reflux esophagitis. Clin Gastroenterol Hepatol. 2007;5(12):1385–91.
47. Dent J, Kahrilas PJ, Hatlebakk J, Vakil N, Denison H, Franzen S, et al. A randomized, comparative trial of a potassium-competitive acid blocker (AZD0865) and esomeprazole for the treatment of patients with nonerosive reflux disease. Am J Gastroenterol. 2008;103(1):20–6.
48. Simon WA, Herrmann M, Klein T, Shin JM, Huber R, Senn-Bilfinger J, et al. Soraprazan: setting new standards in inhibition of gastric acid secretion. J Pharmacol Exp Ther. 2007;321(3):866–74.
49. Choi HY, Noh YH, Jin SJ, Kim YH, Kim MJ, Sung H, et al. Bioavailability and tolerability of combination treatment with revaprazan 200 mg + itopride 150 mg: a randomized crossover study in healthy male Korean volunteers. Clin Ther. 2012;34(9):1999–2010.
50. Hori Y, Matsukawa J, Takeuchi T, Nishida H, Kajino M, Inatomi N. A study comparing the antisecretory effect of TAK-438, a novel potassium-competitive acid blocker, with lansoprazole in animals. J Pharmacol Exp Ther. 2011;337(3):797–804.
51. Arikawa Y, Nishida H, Kurasawa O, Hasuoka A, Hirase K, Inatomi N, et al. Discovery of a novel pyrrole derivative 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamin e fumarate (TAK-438) as a potassium-competitive acid blocker (P-CAB). J Med Chem. 2012;55(9):4446–56.
52. Jenkins H, Sakurai Y, Nishimura A, Okamoto H, Hibberd M, Jenkins R, et al. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther. 2015;41(7):636–48.
53. Hershcovici T, Mashimo H, Fass R. The lower esophageal sphincter. Neurogastroenterol Motil. 2011;23(9):819–30.
54. Rohof WO, Aronica E, Beaumont H, Troost D, Boeckxstaens GE. Localization of mGluR5, GABAB, GABAA, and cannabinoid receptors on the vago-vagal reflex pathway responsible for transient lower esophageal sphincter relaxation in humans: an immunohistochemical study. Neurogastroenterol Motil. 2012;24(4):383–e173.
55. Lehmann A, Blackshaw LA, Branden L, Carlsson A, Jensen J, Nygren E, et al. Cannabinoid receptor agonism inhibits transient lower esophageal sphincter relaxations and reflux in dogs. Gastroenterology. 2002;123(4):1129–34.
56. Beaumont H, Jensen J, Carlsson A, Ruth M, Lehmann A, Boeckxstaens G. Effect of delta9-tetrahydrocannabinol, a cannabinoid receptor agonist, on the triggering of transient lower oesophageal sphincter relaxations in dogs and humans. Br J Pharmacol. 2009;156(1):153–62.
57. Scarpellini E, Blondeau K, Boecxstaens V, Vos R, Gasbarrini A, Farre R, et al. Effect of rimonabant on oesophageal motor function in man. Aliment Pharmacol Ther. 2011;33(6):730–7.
58. Lehmann F, Hildebrand P, Beglinger C. New molecular targets for treatment of peptic ulcer disease. Drugs. 2003;63(17):1785–97.
59. Clave P, Gonzalez A, Moreno A, Lopez R, Farre A, Cusso X, et al. Endogenous cholecystokinin enhances postprandial gastroesophageal reflux in humans through extrasphincteric receptors. Gastroenterology. 1998;115(3):597–604.
60. Zerbib F, Bruley DVS, Scarpignato C, Leray V, D'Amato M, Roze C, et al. Endogenous cholecystokinin in postprandial lower esophageal sphincter function and fundic tone in humans. Am J Physiol. 1998; 275(6 Pt 1):G1266–73.
61. Beglinger CDL, Schroller S, D'Amato M, Persiani S Oral itriglumide, a specific CCK2/gastrin receptor antagonist, inhibits gastrin stimulated gastric acid secretion in humans. Gut. 2004;54 Suppl VII:A36.
62. Hershcovici T, Fass R. Transient lower oesophageal sphincter relaxation reducers–have we hit a brick wall? Aliment Pharmacol Ther. 2011;33(11):1256–7, author reply 7–8.
63. Lal R, Sukbunthern g J, Tai EH, Upadhyay S, Yao F, Warren MS, et al. Arbaclofen placarbil, a novel R-baclofen prodrug: improved absorption, distribution, metabolism, and elimination properties compared with R-baclofen. J Pharmacol Exp Ther. 2009;330(3):911–21.

64. Vakil NB, Huff FJ, Bian A, Jones DS, Stamler D. Arbaclofen placarbil in GERD: a randomized, double-blind, placebo-controlled study. Am J Gastroenterol. 2011;106(8):1427–38.
65. Boeckxstaens GE BH, Hatlebakk J, Silberg D, Adler J, Denison H. Efficacy and tolerability of the novel reflux inhibitor, AZD3355, as add-on treatment in GERD patients with symptoms despite proton pump inhibitor therapy. Gastroenterology. 2009;136 Suppl 1:A436.
66. Boeckxstaens GE, Beaumont H, Mertens V, Denison H, Ruth M, Adler J, et al. Effects of lesogaberan on reflux and lower esophageal sphincter function in patients with gastroesophageal reflux disease. Gastroenterology. 2010;139(2):409–17.
67. Zerbib F, Bruley des Varannes S, Roman S, Tutuian R, Galmiche JP, Mion F, et al. Randomised clinical trial: effects of monotherapy with ADX10059, a mGluR5 inhibitor, on symptoms and reflux events in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2011;33(8):911–21.
68. Rohof WO, Lei A, Hirsch DP, Ny L, Astrand M, Hansen MB, et al. The effects of a novel metabotropic glutamate receptor 5 antagonist (AZD2066) on transient lower oesophageal sphincter relaxations and reflux episodes in healthy volunteers. Aliment Pharmacol Ther. 2012;35(10):1231–42.
69. Ruth M, Hamelin B, Rohss K, Lundell L. The effect of mosapride, a novel prokinetic, on acid reflux variables in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 1998;12(1):35–40.
70. Futagami S, Iwakiri K, Shindo T, Kawagoe T, Horie A, Shimpuku M, et al. The prokinetic effect of mosapride citrate combined with omeprazole therapy improves clinical symptoms and gastric emptying in PPI-resistant NERD patients with delayed gastric emptying. J Gastroenterol. 2010;45(4):413–21.
71. Kim YS, Kim TH, Choi CS, Shon YW, Kim SW, Seo GS, et al. Effect of itopride, a new prokinetic, in patients with mild GERD: a pilot study. World J Gastroenterol. 2005;11(27):4210–4.
72. Rohof WO, Bennink RJ, de Ruigh AA, Hirsch DP, Zwinderman AH, Boeckxstaens GE. Effect of azithromycin on acid reflux, hiatus hernia and proximal acid pocket in the postprandial period. Gut. 2012;61(12):1670–7.
73. Mertens V, Blondeau K, Pauwels A, Farre R, Vanaudenaerde B, Vos R, et al. Azithromycin reduces gastroesophageal reflux and aspiration in lung transplant recipients. Dig Dis Sci. 2009;54(5):972–9.
74. Frampton JE. Prucalopride. Drugs. 2009;69(17):2463–76.
75. Shaheen NJ, Adler J, Dedrie S, Johnson D, Malfertheiner P, Miner P, et al. Randomised clinical trial: the 5-HT4 agonist revexepride in patients with gastro-oesophageal reflux disease who have persistent symptoms despite PPI therapy. Aliment Pharmacol Ther. 2015;41(7):649–61.
76. Choung RS, Ferguson DD, Murray JA, Kammer PP, Dierkhising RA, Zinsmeister AR, et al. A novel partial 5HT3 agonist DDP733 after a standard refluxogenic meal reduces reflux events: a randomized, double-blind, placebo-controlled pharmacodynamic study. Aliment Pharmacol Ther. 2008;27(5):404–11.
77. Krarup AL, Ny L, Astrand M, Bajor A, Hvid-Jensen F, Hansen MB, et al. Randomised clinical trial: the efficacy of a transient receptor potential vanilloid 1 antagonist AZD1386 in human oesophageal pain. Aliment Pharmacol Ther. 2011;33(10):1113–22.
78. Fass R. Functional heartburn: what it is and how to treat it. Gastrointest Endosc Clin N Am. 2009;19(1):23–33, v.
79. Hershcovici T, Achem SR, Jha LK, Fass R. Systematic review: the treatment of noncardiac chest pain. Aliment Pharmacol Ther. 2012;35(1):5–14.
80. Dickman R, Maradey-Romero C, Fass R. The role of pain modulators in esophageal disorders—no pain no gain. Neurogastroenterol Motil. 2014;26(5):603–10.
81. Krarup AL, Ny L, Gunnarsson J, Hvid-Jensen F, Zetterstrand S, Simren M, et al. Randomized clinical trial: inhibition of the TRPV1 system in patients with nonerosive gastroesophageal reflux disease and a partial response to PPI treatment is not associated with analgesia to esophageal experimental pain. Scand J Gastroenterol. 2013;48(3):274–84.
82. Kort ME, Kym PR. TRPV1 antagonists: clinical setbacks and prospects for future development. Prog Med Chem. 2012;51:57–70.

83. Gunthorpe MJ, Chizh BA. Clinical development of TRPV1 antagonists: targeting a pivotal point in the pain pathway. Drug Discov Today. 2009;14(1–2):56–67.
84. Liu J, Wang LN. Ramelteon in the treatment of chronic insomnia: systematic review and meta-analysis. Int J Clin Pract. 2012;66(9):867–73.
85. Jha LK GR, Grewal YS, et al. Rozerem improves reports of symptoms in GERD patients with chronic insomnia. Gastroenterology. 2012;142 Suppl 1:S592 (abstract).
86. Fujiwara Y, Arakawa T, Fass R. Gastroesophageal reflux disease and sleep. Gastroenterol Clin North Am. 2013;42(1):57–70.
87. Chua YC, Ng KS, Sharma A, Jafari J, Surguy S, Yazaki E, et al. Randomised clinical trial: pregabalin attenuates the development of acid-induced oesophageal hypersensitivity in healthy volunteers—a placebo-controlled study. Aliment Pharmacol Ther. 2012;35(3):319–26.
88. Adachi K, Furuta K, Miwa H, Oshima T, Miki M, Komazawa Y, et al. A study on the efficacy of rebamipide for patients with proton pump inhibitor-refractory non-erosive reflux disease. Dig Dis Sci. 2012;57(6):1609–17.
89. Araki H, Kato T, Onogi F, Ibuka T, Sugiyama A, Nakanishi T, et al. Combination of proton pump inhibitor and rebamipide, a free radical scavenger, promotes artificial ulcer healing after endoscopic submucosal dissection with dissection size > 40 mm. J Clin Biochem Nutr. 2012;51(3):185–8.
90. Kawahara Y, Nakase Y, Isomoto Y, Matsuda N, Amagase K, Kato S, et al. Role of macrophage colony-stimulating factor (M-CSF)-dependent macrophages in gastric ulcer healing in mice. J Physiol Pharmacol. 2011;62(4):441–8.
91. Ironwood Reports Positive Top-Line Data from Exploratory Phase IIa Trial Of IW-3718 in Refractory Gastroesophageal Reflux Disease. http://news.ironwoodpharma.com/Press-Releases/Ironwood-Reports-Positive-Top-Line-Data-from-Exploratory-Phase-IIa-Trial-Of-IW-3718-in-Refractory-Ga-114.aspx. Accessed 16 March 2015.
92. Cadiere GB, Rajan A, Rqibate M, Germay O, Dapri G, Himpens J, et al. Endoluminal fundoplication (ELF)—evolution of EsophyX, a new surgical device for transoral surgery. Minim Invasive Ther Allied Technol. 2006;15(6):348–55.
93. Cadiere GB, Buset M, Muls V, Rajan A, Rosch T, Eckardt AJ, et al. Antireflux transoral incisionless fundoplication using EsophyX: 12-month results of a prospective multicenter study. World J Surg. 2008;32(8):1676–88.
94. Bell RC, Freeman KD. Clinical and pH-metric outcomes of transoral esophagogastric fundoplication for the treatment of gastroesophageal reflux disease. Surg Endosc. 2011;25(6):1975–84.
95. Hoppo T, Immanuel A, Schuchert M, Dubrava Z, Smith A, Nottle P, et al. Transoral incisionless fundoplication 2.0 procedure using EsophyX for gastroesophageal reflux disease. J Gastrointest Surg. 2010;14(12):1895–901.
96. Hunter JG, Kahrilas PJ, Bell RC, Wilson EB, Trad KS, Dolan JP, et al. Efficacy of transoral fundoplication vs omeprazole for treatment of regurgitation in a randomized controlled trial. Gastroenterology. 2015;148(2):324–33, e5.
97. Topuz U, Umutoglu T, Bakan M, Ozturk E. Anesthetic management of the SRS endoscopic stapling system for gastro-esophageal reflux disease. World J Gastroenterol. 2013;19(2):319–20.
98. Danalioglu A, Cipe G, Toydemir T, Kocaman O, Ince AT, Muslumanoglu M, et al. Endoscopic stapling in comparison to laparoscopic fundoplication for the treatment of gastroesophageal reflux disease. Dig Endosc. 2014;26(1):37–42.
99. Zacherl J, Roy-Shapira A, Bonavina L, Bapaye A, Kiesslich R, Schoppmann SF, et al. Endoscopic anterior fundoplication with the medigus ultrasonic surgical endostapler (MUSE) for gastroesophageal reflux disease: 6-month results from a multi-center prospective trial. Surg Endosc. 2015;29(1):220–9.

100. Ellis F, Berne TV, Settevig K. The prevention of experimentally induced reflux by electrical stimulation of the distal esophagus. Am J Surg. 1968;115(4):482–7.
101. Clarke JO, Jagannath SB, Kalloo AN, Long VR, Beitler DM, Kantsevoy SV. An endoscopically implantable device stimulates the lower esophageal sphincter on demand by remote control: a study using a canine model. Endoscopy. 2007;39(1):72–6.
102. Sanmiguel CP, Hagiike M, Mintchev MP, Cruz RD, Phillips EH, Cunneen SA, et al. Effect of electrical stimulation of the LES on LES pressure in a canine model. Am J Physiol Gastrointest Liver Physiol. 2008;295(2):G389–94.
103. Rodriguez L, Rodriguez P, Neto MG, Ayala JC, Saba J, Berel D, et al. Short-term electrical stimulation of the lower esophageal sphincter increases sphincter pressure in patients with gastroesophageal reflux disease. Neurogastroenterol Motil. 2012;24(5):446–50, e213.
104. Rodriguez L, Rodriguez P, Gomez B, Ayala JC, Saba J, Perez-Castilla A, et al. Electrical stimulation therapy of the lower esophageal sphincter is successful in treating GERD: final results of open-label prospective trial. Surg Endosc. 2013;27(4):1083–92.
105. Rodriguez L, Rodriguez P, Gomez B, Ayala JC, Oksenberg D, Perez-Castilla A, et al. Long-term results of electrical stimulation of the lower esophageal sphincter for the treatment of gastroesophageal reflux disease. Endoscopy. 2013;45(8):595–604.