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INVITED REVIEWS

Gastroparesis: Medical and Therapeutic Advances

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Abstract Gastroparesis is a chronic, bothersome, and often disabling neuromuscular disorder of the upper gastrointestinal tract. The most frequently reported symptoms of gastroparesis include nausea, vomiting, epigastric pain, early satiety, and unintentional weight loss. Etiologies of gastroparesis include diabetes, connective tissue disorders, prior infection, mesenteric ischemia, and post-surgical complications. The largest category of gastroparesis patients is comprised of those in whom no definitive cause can be identified (idiopathic gastroparesis). The individual and societal burden of gastroparesis is substantial. It considerably reduces patients' quality of life accompanied by a significant negative impact to the healthcare system. The current treatments of gastroparesis are less than ideal. Dietary modification may improve symptoms in patients with mild disease. Metoclopramide is the only medication currently approved for the treatment of gastroparesis; however, it is associated with adverse effects in a sizable proportion of patients. Other medications are frequently employed to treat symptoms of nausea and vomiting, although technically all are used off-label since they are not FDA approved for the treatment of gastroparesis. These data highlight the need to identify novel, more effective treatment options for this disabling disease. This review will provide a brief synopsis on the epidemiology, etiology, and impact of gastroparesis, discussing new therapeutic advances.

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Introduction

Gastroparesis is one of the two most common gastric neuromuscular disorders, the other being functional dyspepsia. Gastroparesis is defined and properly diagnosed using a combination of subjective symptoms and objective measures [1]. First, patients should report symptoms thought to represent a delay in gastric emptying, which include epigastric pain, nausea, vomiting, early satiety, and weight loss [1, 2]. Second, a mechanical obstruction should be ruled out; this is typically performed using upper endoscopy, although a careful upper gastrointestinal series with small bowel follow-through can be sufficient. Third, a delay in gastric emptying should be documented. Although a variety of methods can be used to objectively measure gastric emptying, the 4-h solid-phase scintigraphic emptying scan is considered the most valid [1–4].

The epidemiology of gastroparesis is not well described since patients are often classified using less specific ICD-10 codes for nausea and vomiting. One carefully performed study reported that the observed prevalence of gastroparesis in Olmsted County, Minnesota, was 37.8 in women and 9.6 in men per 100,000 persons [5]. Using prevalence rates for the most commonly known cause of gastroparesis (diabetes), and data from other epidemiologic studies, it is estimated that approximately 10 million US adults suffer from symptoms of gastroparesis. What is better known, however, is the substantial negative impact that gastroparesis imposes on patients and the healthcare system. Using the well-validated short-form 36 questionnaire (SF-36) to assess quality of life, a recently published study

reported that mean SF-36 scores for mental health and social functioning in patients with gastroparesis were analogous to scores for patients with serious chronic medical disorders and depression [6]. Another study found that SF-36 subscale scores were lower in gastroparesis patients compared to the US mean general population norm for every subscale except mental health [7]. The economic impact of gastroparesis is also substantial. A questionnaire study of 228 gastroparesis patients found that gastroparesis symptoms reduced annual income in 28.5% and resulted in disability in 11% [6]. Using the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS) to evaluate charges in gastroparesis-related hospitalizations over a 10-year period Wang and colleagues reported that in 2004, gastroparesis as either the primary or secondary diagnosis accounted for $3500 million in hospital charges and 911,963 hospital days [8]. These facts highlight the need to identify superior treatment options for patients with gastroparesis in order to improve quality of life and reduce its economic burden.

Pathophysiology

Although gastroparesis is generally thought of as a homogenous disorder characterized by delayed gastric emptying, pathophysiologically, gastroparesis is a heterogeneous disorder characterized by abnormalities in fundic tone, antroduodenal dyscoordination, a weak antral pump, gastric dysrhythmias, and abnormal duodenal feedback [1, 2]. Idiopathic gastroparesis is considered to be present in the largest group of patients in whom an underlying cause cannot be identified. Gastroparesis can also develop for a variety of other reasons; some of the most common causes include long-standing diabetes, connective tissue disorders, prior surgery, mesenteric ischemia, and a variety of inflammatory or neurologic disorders [1, 2, 9, 10]. Up to 50% of type I (insulin-dependent) diabetics and 30% of type 2 (noninsulin-dependent) diabetics have symptoms consistent with gastroparesis [11–14].

Novel Diagnostics

Gastroparesis has traditionally been diagnosed using a solid-phase gastric emptying scan; the 4-h scan is considered the most valid objective measure [3, 4]. Two new methods to evaluate gastric emptying have recently become commercially available. The first involves the use of a novel breath test involving the algae *spirulina* labeled with a stable isotope measured with gas isotope ratio mass spectrometry. Advantages to this method include the ability to perform the test directly in the office without the need for specialized equipment. Also, the absence of radiation improves the safety of the test, especially in patients who may be subjected to repeat measurements. *Spirulina platensis* can be readily labeled with ^{13}C during the growing process. $^{13}CO_2$ is released from the radiolabeled *S. platensis* during digestion, and this can be easily measured in breath samples. A recent study compared gastric emptying using ^{13}C-labeled *S. platensis* to standard scintigraphy in 15 healthy volunteers and 15 patients with dyspepsia [15]. The authors reported that when 9 breath samples were collected over 4 h, gastric emptying measured using radiolabeled *S. platensis* was just as accurate as scintigraphy. Large, prospective studies in patients with gastroparesis will be required to validate these findings.

The second novel diagnostic test is the wireless motility capsule, which measures intestinal transit, pressure, temperature, and pH. The absence of radiation, plus the ability to measure whole gut transit time, increases the attractiveness of this test for many providers. In a prospective, simultaneous study comparing the wireless motility capsule to standard scintigraphy in 61 patients with gastroparesis, the correlation for the motility capsule and scintigraphy was reasonable at 0.73 at 4 h [16]. The additional information provided (pressure and whole gut transit time) may provide useful information in those patients with other disorders of gastrointestinal neuromuscular dysfunction, including scleroderma or colonic inertia. Further prospective trials are needed in larger populations to confirm these results.

Novel Medications

Dopamine Antagonists: Intranasal Metoclopramide

Metoclopramide is a dopamine D2-receptor antagonist that currently remains the only FDA approved medication for control of gastroparesis symptoms. Metoclopramide relieves symptoms through inhibition of emesis as well as prokinetic effects on gut motility (Table 1) [17]. Severe symptoms of nausea and vomiting could limit a patient's ability to tolerate oral medications, thereby increasing the practicality of intranasal administration, since intestinal absorption is not needed, despite the presence of vomiting or delayed gastric emptying. A multicenter, open-label study reported metoclopramide nasal spray (10 mg, 20 mg) to be well tolerated and as effective as the oral tablet (10 mg) in diabetic patients ($n = 89$) with gastroparesis symptoms [18]. Common adverse events in subjects included dysgeusia, headache, and fatigue [19]. A multicenter, randomized, double-blind study ($n = 285$) showed improvement in total symptom scores of gastroparesis in female patients with diabetes but not in male patients [19].

Table 1 Novel drug effects

Drug class	Antiemetic effects	Prokinetic effects
Drug name		
Dopamine D2-receptor antagonists		
Intranasal metoclopramide	+	+
Domperidone	+	+
Ghrelin agonist		
Relamorelin		+
Motilin agonist		
Camicinal		+
5-HT_3 receptor antagonist		
Granisetron patch	+	
5-HT_4 receptor agonist		
Revexepride		+
Velusetrag		+
DA-6650		+
RQ-00000010		+
VKP10811		+
NK-1 receptor agonist		
Aprepitant	+	
Tradipitant (VLY-686)	+	

Diabetic females treated with intranasal metoclopramide (10-mg dose $n = 65$, 14-mg dose $n = 70$) had a significant improvement in their gastroparesis symptoms including nausea and upper abdominal pain [19]. Two multicenter trials are currently awaiting results: One is a randomized, double-blind, placebo-controlled study of intranasal metoclopramide in women with symptomatic diabetic gastroparesis (ClinicalTrials.gov, NCT02025725), and the other is a randomized, placebo-controlled study of intranasal metoclopramide in men with symptomatic diabetic gastroparesis (ClinicalTrials.gov, NCT02025751).

Ghrelin Receptor Antagonists

TZP-101 and TZP-102 ghrelin, an endogenous peptide produced primarily in the gastric mucosa [20], has prokinetic effects mediated by vagal signaling [21] and stimulates phase III of the gastric migrating motor complex [22] (Table 2). Regulation of ghrelin appears to be impaired in patients with diabetic gastroparesis [23]. Early studies of ghrelin receptor agonists lacked efficacy. TZP-101 did not show clear effects on gastric emptying in gastroparesis patients with gastroparesis [24, 25], whereas studies of TZP-102 were stopped due to lack of efficacy in patients with diabetic gastroparesis [24, 25].

Relamorelin

More recently, relamorelin (RM-131), a synthetic ghrelin agonist with greater potency and plasma stability than native ghrelin [26] and both TZP-101 and TZP-102 [26, 27], has shown promise for the treatment of gastroparesis symptoms. Phase I studies on healthy human subjects ($n = 16$) showed that relamorelin (30 mcg s.c.) increased gastric motor activity [28]. A randomized, double-blind, placebo-controlled crossover study of type II diabetic women ($n = 10$) with delayed gastric emptying found that those treated with relamorelin (100 mcg s.c.) had an average decrease in gastric emptying halftime (solids) of 66% compared to placebo [29]. A study of type I diabetic patients with delayed gastric emptying ($n = 10$) who received relamorelin (100 mcg s.c.) showed a 54.7% improvement in gastric emptying halftime of solids compared to placebo [30]. A double-blind trial ($n = 204$) of diabetic gastroparesis subjects treated with relamorelin (10 mcg s.c.) twice daily ($n = 68$) for 28 days showed a mean decrease in gastric emptying of about 23 min and improved vomiting frequency when compared to placebo [31]. Patients who had vomiting as a baseline symptom ($n = 30$) were shown to have additional improvement in other symptoms including nausea, abdominal pain, bloating, and early satiety compared to placebo [31]. A 12-week randomized double-blind study of diabetic patients with gastroparesis ($n = 393$) showed a decrease in four-symptom composite scores across all relamorelin treatment groups (10, 30, and 100 mcg) compared to placebo [32]. Minimal adverse reactions were reported with the most common being dizziness, headache, and hyperglycemia [29, 31, 32]. Current ongoing studies include a randomized, double-blind, placebo-controlled study of RM-131 on

Table 2 Mechanisms of action of novel drugs

Drug target/drug name	Mechanism of action
Dopamine D2-receptor antagonists Intranasal metoclopramide, domperidone	Blocks dopamine receptors in the chemoreceptor zone and enhances response to acetylcholine in GI tract leading to enhanced motility and accelerated gastric emptying
Ghrelin receptor agonists Relamorelin	Activates ghrelin receptors leading to prokinetic effects on gastrointestinal motility mediated by vagal signaling and stimulation of the phase III component of the gastric migrating motor complex
5-HT_3 receptor antagonists Granisetron patch	Blocks serotonin leading to inhibition of vagal afferent nerves in the chemoreceptor trigger zone
NK-1 antagonists Aprepitant, tradipitant/VLY-686	Blocks activation of the Neurokinin-1 receptor inhibiting substance P's involvement in emetic reflex
5-HT_4 receptor agonists Revexepride, Velusetrag, RQ-00000010	Activation of 5-HT_4 receptors releases acetylcholine at the myenteric plexus, leading to increased muscular contractions and accelerated transit
Motilin receptor agonist Camicinal	Activation releases motilin which facilitates cholinergic activity in the antrum and initiates phase III contractions of the migrating motor complex

patients with vomiting symptoms and moderate to severe diabetic gastroparesis (ClinicalTrials.gov, NCT02357420).

5-HT Receptor Antagonists

5-HT_3 Receptor Antagonists: Granisetron Patch

Serotonin type 3 (5-HT_3) receptor antagonists have been used off-label to control nausea and vomiting in gastroparesis patients for years. 5-HT_3 receptor antagonists improve symptoms through inhibition of vagal afferent nerves that project to areas in the brain involved in nausea and vomiting [33]. Granisetron is a 5-HT_3 receptor antagonist that is FDA approved for the prevention of chemotherapy-associated nausea and vomiting. Granisetron is now available in a transdermal delivery system, which delivers a sustained, controlled dose over the course of 24 h [34]. A multinational, randomized, double-blind study ($n = 691$) showed that transdermal granisetron was as effective as an oral dose for the control of nausea and vomiting in patients who had received chemotherapy [35]. One concern with the use of 5-HT_3 antagonists is the potential for cardiac electrical dysrhythmias, as electrocardiographic changes and arrhythmias have been observed with use of first generation 5-HT_3 antagonists [36]. Transdermal granisetron appears to have a decreased risk of electrical dysrhythmias as a recent phase III study ($n = 240$) since QT_c prolongation was present in only 1.1% of patients receiving transdermal granisetron, whereas QT_c prolongation was present in 2.7% of patients receiving oral granisetron [37]. Transdermal delivery is an attractive route in patients with gastroparesis as cutaneous absorption is not dependent on oral intake or gastric emptying. An open-label pilot study of 36 patients with refractory gastroparesis symptoms reported a decrease in symptoms scores of 50% of subjects following 2 weeks of transdermal granisetron [38]. An open-label prescription registry study ($n = 51$) noted that transdermal granisetron (3.1 mg) was effective in reducing symptom severity scores, especially nausea and vomiting, in 76% of gastroparesis patients with refractory symptoms [39].

5-HT_4 Receptor Agonists: Revexepride

5-HT_4 receptors are located throughout the gastrointestinal tract. Their activation releases acetylcholine at the myenteric plexus, leading to increased muscular contractions and accelerated transit [40, 41]. Previous synthetic 5-HT_4 receptor agonists have unfortunately been associated with adverse cardiovascular events. Cisapride and tegaserod are both nonselective 5-HT_4 receptor agonists removed from the market due to reported cardiac side effects [42]. Cisapride was associated with QT prolongation, syncope, and ventricular arrhythmias through the activation of hERG potassium channels [42]. Tegaserod was possibly associated with ischemic cardiovascular events, believed to be due to off-target activation of the 5-HT_1 receptor, although a subsequent analysis determined that the reported cardiac events were likely not related to tegaserod use [42, 43].

Revexepride is a newly developed, highly specific, and potent 5-HT_4 receptor agonist. A double-blind, randomized, placebo-controlled trial of patients with symptoms

suggestive of gastroparesis ($n = 80$) treated with revexepride (0.02, 0.1, or 0.5 mg oral TID) failed to show differences in gastric emptying or symptom scores in treatment versus placebo control groups after 4 weeks of use [44]. One important limitation of this study was that the mean gastric emptying halftime was reported to be normal in the majority of patients at the beginning of the trial, which may have contributed to the lack of measurable difference between groups. It is unclear whether further studies will be carried out as there are no current clinical trials listed for revexepride.

Dopamine Antagonist: Domperidone

Domperidone is a peripherally acting dopamine D2-receptor antagonist that has been used internationally in the treatment of gastrointestinal symptoms for over 30 years. It is available for use in the USA only through an FDA investigational new drug application in gastroparesis patients who have failed standard therapy. Domperidone is a prokinetic and antiemetic medication that has exhibited efficacy similar to metoclopramide in multiple trials for control of gastroparesis symptoms in diabetic patients [45–48].

Neurokinin (NK) Receptor Antagonists: Aprepitant

Aprepitant is a NK-1 antagonist that is currently FDA approved for chemotherapy-induced nausea and vomiting. NK-1 receptors mediate the effects of substance P, which is a peptide involved in the induction of vomiting [49, 50]. Studies have shown that antagonists of NK-1 receptors improve both acute and delayed emetic responses to chemotherapy [51, 52]. A case report of a patient with idiopathic gastroparesis and refractory nausea and vomiting showed improvement in symptoms for an extended period of $\sim$16 weeks after 2 months of therapy with aprepitant (40 mg daily) [53]. A multicenter, randomized, double-blind study using aprepitant at 125 mg per day for the relief of nausea in patients with nausea and vomiting of presumed gastric origin is currently awaiting results (ClinicalTrials.gov NCT01149369).

Novel Interventional Treatments

Most interventional treatments for gastroparesis patients are directed at the pylorus. Unfortunately, not all patients have pyloric dysfunction and thus may not respond with pyloric-directed therapies. Recent studies have suggested that the subgroup of patients most likely to improve may include those with impaired gastric emptying in the setting of a normal endoscopy (no mechanical obstruction) but with a normal electrogastrography (EGG) with a rate of 3 Hz, suggesting that dysfunction may lie at the pylorus with antral contractions being grossly normal [54]. The following section will exclude botulinum toxin, which has not been shown to be better than placebo in multiple randomized placebo-controlled trials, and is not recommended by the most current American College of Gastroenterology (ACG) clinical guidelines [1].

Transpyloric Stent Placement

Transpyloric stenting (TPS) (Fig. 1) was initially described in a small case series in 2013, with placement of double-layered fully covered self-expandable metallic stents in 3 relatively young patients. These were deployed endoscopically without fluoroscopy, with the proximal end in the gastric antrum. All three cases had improvement or resolution of refractory symptoms with follow-up as long as 174 days [55].

A more recent retrospective case series in 2015 included 30 patients (mean age 42; 20 women) with refractory symptoms of nausea and vomiting. These patients underwent TPS placement (48 procedures with 9 patients undergoing at least 1 repeat stent placement) with stent anchorage using either standard through-the-scope clips ($n = 2$), over-the-scope clips ($n = 18$), or endoscopic suturing ($n = 24$, mean number of 2 sutures per procedure). No fixation device was used in 3 procedures. Clinical success, defined as an improvement in refractory symptoms, was greater in patients with predominant nausea

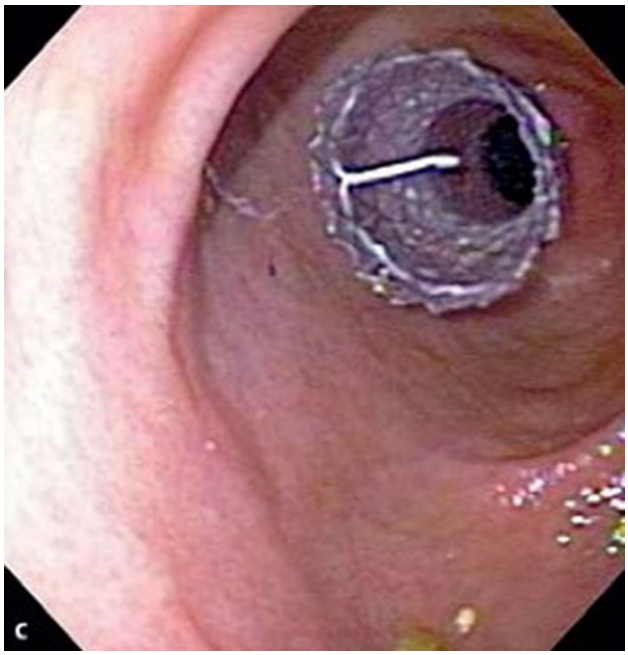

Fig. 1 Transpyloric stent. Picture courtesy of John Clarke M.D.

and vomiting, and was noted in 75% of all patients. Response was described as considerable, allowing rapid symptom control and discharge of inpatients with intractable nausea and vomiting, although the degree of improvement was not evaluated with validated questionnaires. Stent migration, during a mean follow-up of 146 days, occurred in 59% of overall procedures: 100% in the no fixation group; 50% in the through-the-scope group; 71% in the over-the-scope group; 48% in the endoscopic suturing group. The authors conclude that TPS is not a permanent solution due to stent migration, but may be considered a salvage treatment for intractable symptoms or help to select patients who may respond to more permanent pylorus-directed therapies such as pyloromyotomy [56].

Laparoscopic Pyloroplasty

The use of pyloroplasty for the treatment of gastroparesis originates from older data describing the surgical treatment of infants with functional gastric outlet obstruction due to hypertrophic pyloric stenosis. The most common surgical procedure is the Heineke–Mikulicz pyloroplasty which is typically done laparoscopically (LP). Evidence to support LP includes an initial retrospective study with 28 patients who underwent LP for refractory gastroparesis (patients with prior gastric surgery or undergoing concurrent anti reflux surgery were excluded) [57]. The authors reported a reduction in prokinetic use by 75%, normalization of gastric emptying studies in 71% of patients, and significant improvements in scores for nausea, vomiting, bloating, and abdominal pain, which persisted at 3 months [57].

A more recent large, single-center, retrospective review included 177 patients who underwent LP, although the majority of patients ($n = 160$) had another concurrent surgical intervention (including fundoplication for reflux disease, Heller myotomy for achalasia or paraesophageal hernia repair) at the time of LP. Gastroparesis was defined loosely by either an abnormal gastric emptying study, endoscopic visualization of retained food or clinical symptoms suggestive of vagal nerve injury during any previous foregut surgery. Slightly less than half of all patients (49%) were on narcotics preoperatively. The morbidity rate was noted at 6.8% with four reoperations and two confirmed leaks, four wound infections, and seven readmissions within 30 days for abdominal pain, nausea, and/or vomiting. The study reported an 86% improvement in gastric emptying scintigraphy and a significant improvement in symptom severity scores at 1 and 6 months post-op. Approximately 10% of patients underwent subsequent surgical intervention with either gastric stimulator implantation, feeding tube placement, or subtotal gastrectomy. The authors concluded that LP is a safe and effective first-line surgical therapy for refractory gastroparesis [58]. Despite these conclusions, none of the published studies so far have included a sham-controlled arm; they are retrospective in nature, and most do not include validated outcome measures.

Endoscopic Implantable Gastric Electric Stimulator (GES)

The gastric electrical neurostimulator (Enterra Therapy System, Medtronic, Inc) consists of two electrical leads attached to the anterior stomach wall near the greater curvature connected to a subcutaneously placed pulse generator. The gastric stimulator, exempted from formal FDA approval for humanitarian reasons, improves symptoms, particularly nausea and vomiting in patients with diabetic gastroparesis. Symptom improvement is less in patients with idiopathic, post-surgical gastroparesis, and patients on chronic opioids [1]. Complications related to device placement include lead migration, bowel obstruction, perforation, and wound complications. A recent study included 138 patients with a mean follow-up of 520 ± 350 days demonstrated a 75% improvement in average symptom scores with at least 43% of patients showing moderate improvement [59]. Furthermore, although LP combined with gastric stimulator placement has theoretical appeal, controlled randomized studies are lacking [60].

Newer techniques include endoscopic placement of temporary gastric electric stimulators to evaluate for a response before more permanent implantation. A double-masked, randomized, placebo-controlled, crossover trial evaluated the effects of 72 h of temporary gastric stimulation and reported a numerical decrease in daily vomiting scores during stimulation, although the results were not significant [61]. A novel wireless GES device that can be implanted endoscopically (placed using an overtube and attached with endoclips) has been developed in a swine model but this device needs to be carefully studied in humans [62].

Gastrectomy

Gastrectomy has customarily been considered an option for patients with refractory post-surgical gastroparesis. More recently, however, laparoscopic subtotal gastrectomy has been proposed as a first-line surgical treatment for gastroparesis refractory to all other interventions (see Fig. 2) or for palliation. Furthermore, this option can be considered in the treatment algorithm for patients who have no improvement after GES placement, based on a 2013 study that compared outcomes of 103 patients treated either with GES ($n = 72$) or laparoscopic subtotal ($n = 27$), total ($n = 1$), or completion gastrectomy ($n = 3$). 63% of

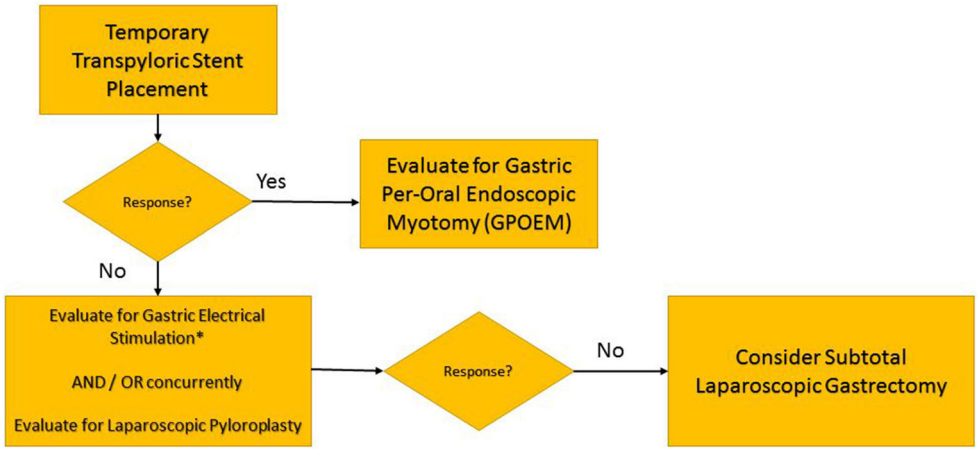

Fig. 2 An endoscopic and surgical treatment algorithm for persistent or intractable symptoms despite medical therapy. *Gastric electrical stimulation has been shown to be most effective in patients with diabetic gastroparesis who are not on opioids; Assess response to 72 h endoscopic gastric stimulator placement beforehand if available

patients in the GES group reported improvement in overall symptoms compared to 87% in the patients with a primary gastrectomy. Based on median Gastroparesis Cardinal Symptom Index (GCSI) scores [total of 9 individual symptom scores, range 0–45; (GES = 18, LSG = 16, $p = 0.12$)], symptom improvement was similar between both groups. Furthermore, all patients who failed to respond to GES had 100% symptom improvement with a subsequent gastrectomy [63]. A similar study of 35 patients who underwent laparoscopic total, or near-total, gastrectomy for refractory symptoms, reported that six patients suffered a leak requiring surgical repair; however, nausea and chronic abdominal pain improved in 69 and 70% of patients, respectively, at median follow-up of 6 months [64].

Sleeve gastrectomy has also been described in a few case series as effective in improving gastroparesis symptoms. The initial case series indicated an improvement in symptoms in 4 diabetic gastroparesis patients with resolution of symptoms at 6 months [60, 65]. A small series of nine morbidly obese patients with diabetic GP who received laparoscopic longitudinal sleeve gastrectomy indicated resolution of symptoms and improved gastric emptying [60, 66].

Gastric Per-oral Endoscopic Myotomy or GPOEM (Alternatively Called Per-oral Endoscopic Pyloromyotomy or POP)

Gastric per-oral endoscopic myotomy (GPOEM) for refractory gastroparesis is an extension of POEM, a well-studied treatment option for achalasia. The procedure involves an established sequence of mucosal entry, submucosal tunneling, and then myotomy, followed by mucosal closure. The first reported case involved a 27-year-old woman with refractory diabetic gastroparesis with 12 weeks of improvement after transpyloric stent although gastric emptying remained delayed [67]. A retrospective review of 16 patients with predominant nausea and vomiting who underwent GPOEM reported that 81% of patients had significant improvements in the mean GCSI through 12-month follow-up [68]. A European series reported 12 patients with refractory symptoms with a significant improvement in GCSI scores in 85% of cases after 3 months [69]. A multicenter study ($n = 30$, 16 of whom had failed previous therapies including botulinum toxin injection, TPS and PEG/J placement) reported an observed clinical response, defined as a reduction in the patients' self-reported symptoms, in 86% of patients during a mean follow-up of 5.5 months [70]. This procedure shows promising clinical outcomes as a new therapy, although larger sham-controlled studies and further studies to identify which patients may have the greatest benefit are warranted.

Future Therapies

Motilin Receptor Agonist: Camicinal

Motilin is an endogenous peptide that facilitates cholinergic activity in the antrum and initiates phase III contractions of the migrating motor complex [71–73]. Previous motilin receptor agonists have unfortunately been ineffective in treating gastroparesis and tachyphylaxis was a common side effect [74]. Conversely, clinical studies of the novel motilin receptor agonist ABT-229 demonstrated an increase in gastric emptying rate in healthy volunteers [75] but failed to improve symptoms in diabetic patients with gastroparesis [76, 77]. Mitemicinal (GM-611), a motilin receptor agonist derivative of the macrolide erythromycin, failed to increase gastric emptying above placebo in diabetic patients with gastroparesis [78].

Camicinal (GSK9262040) is a small, selective motilin receptor agonist that has a reduced incidence of tachyphylaxis [79]. A randomized, double-blind, placebo-

controlled study ($n = 10$) showed single oral 125-mg dose of camicinal decreased gastric emptying halftime by approximately 39 min in type 1 diabetics with gastroparesis when compared to placebo [80]. A randomized, double-blind, parallel-group, placebo-controlled study of type I & II diabetic patients with delayed gastric emptying ($n = 79$) treated with 125 mg oral camicinal had significantly decreased gastric emptying times without a difference in the magnitude of response after 28 days [81].

Highly Selective 5-HT_4 Agonists

As described above, 5-HT_4 agonists stimulate gastrointestinal motility through release of acetylcholine at the myenteric plexus [40, 41]. Velusetrag (TD-5108) is a highly selective 5-HT_4 agonist [42] that has shown promise for controlling symptoms in patients with gastroparesis. Unlike the nonselective drug cisapride, velusetrag appears to have no effect of the hERG potassium channel [82]. A double-blind, placebo-controlled, parallel-group, randomized trial of healthy subjects ($n = 60$) demonstrated acceleration of gastric emptying halftime by an average of 25 min after multiple doses (9 days) of velusetrag (seen across treatment arms of 15-, 30-, and 50-mg doses) when compared to placebo [83].

RQ-00000010 is another highly selective 5-HT_4 receptor agonist currently under investigation. A double-blind study of healthy subjects who received RQ-00000010 (oral 3-mcg doses or greater) had significantly shortened gastric emptying halftime compared to placebo [84]. Repeated doses of RQ-00000010 were well tolerated without a decrease in effect after 8 days [84]. Other 5-HT_4 receptor agonists that initially exhibited potential but are not currently in trials include DA-6650 and YPK10811.

NK-1 Antagonist VLY-686 (Tradipitant)

VLY-686 (tradipitant) is a new NK-1 receptor antagonist that is currently in the clinical stage of development. A multicenter, randomized, double-blind, placebo-controlled proof-of-concept study to assess the efficacy of VLY-686 in relieving symptoms of gastroparesis is currently ongoing (ClinicalTrials.gov/NCT02970968).

Conclusion

Gastroparesis is a chronic and often disabling neuromuscular disorder of the upper gastrointestinal tract that negatively impacts patients' quality of life. Current management options for gastroparesis are unfortunately limited. Gastroparesis patients and clinicians can be hopeful as there are novel medications including ghrelin and motilin receptor agonists being studied that appear to improve symptoms. In the past, therapy of patients with refractory symptoms was limited to open gastrectomy. Yet, surgical advances including pyloric interventions, gastric stimulators, and laparoscopic subtotal gastrectomy have provided additional options for gastroparesis patients with difficult-to-treat symptoms. Future therapies are eagerly anticipated since a significant need exists in this patient population.

Compliance with ethical standards

Conflict of interest Dr. Lacy is the PI for a gastroparesis research study funded by Vanda; no other conflicts are reported.

References

1. Camilleri M, Parkman HP, Shafi MA, et al. Clinical guideline: management of gastroparesis. *Am J Gastroenterol*. 2013;108:18–37.
2. Parkman HP, Hasler WL, Fisher RS, for the American Gastroenterological Association, et al. American Gastroenterological Association medical position statement: diagnosis and treatment of gastroparesis. *Gastroenterology*. 2004;127:1589–1591.
3. Tougas G, Eaker EY, Abell TL, et al. Assessment of gastric emptying using a low fat meal: establishment of international control values. *Am J Gastroenterol*. 2000;95:1456–1462.
4. Abell TL, Camilleri M, Donohue K, et al. Consensus recommendations for gastric empting Scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. *Am J Gastroenterol*. 2008;103:753–763.
5. Jung HK, Choung RS, Locke GR, et al. The incidence, prevalence and outcomes of patients with gastroparesis in Olmsted County, Minnesota from 1996 to 2006. *Gastroenterology*. 2009;136:1225–1233.
6. Lacy BE, Crowell MD, Mathis C, Bauer D, Heinberg LJ. Gastroparesis: quality of life and health care utilization. *J Clin Gastroenterol*. 2016. doi:10.1097/MCG.0000000000000728.
7. Revicki DA, Rentz AM, Dubois D, et al. Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms. *Quality Life Res*. 2004;13:833–844.
8. Wang YR, Fisher RS, Parkman HP. Gastroparesis-related hospitalizations in the United States: trends, characteristics, and outcomes, 1995–2004. *Am J Gastroenterol*. 2008;103:313–322.
9. Soykan I, Sivri B, Sarosiek I, et al. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. *Dig Dis Sci*. 1998;43:2398–2404.
10. Pande H, Lacy BE, Crowell MD. Inflammatory causes of gastroparesis: report of 5 cases. *Dig Dis Sci*. 2002;47:2664–2668.
11. Horowitz M, Harding PE, Maddox AF, et al. Gastric and oesophageal emptying in patients with type 2 (non-insulin dependent) diabetes mellitus. *Diabetologia*. 1989;32:151–159.
12. Enck P, Rathmann W, Spiekermann M, et al. Prevalence of gastrointestinal symptoms in diabetic patients and non-diabetic subjects. *Z Gastroenterol*. 1994;32:637–641.
13. Maleki D, Locke GR 3rd, Camilleri M, et al. Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. *Arch Intern Med*. 2000;160:2808–2816.

14. Bytzer P, Talley NJ, Leemon M, et al. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. *Arch Intern Med*. 2001;161:1989–1996.
15. Bharucha AE, Camilleri M, Veil E, et al. Comprehensive assessment of gastric emptying with a stable isotope breath test. *Neurogastroenterol Motil*. 2013; 25. doi:10.1111/nmo.12054.
16. Kuo B, McCallum RW, Koch KL, et al. Comparison of gastric emptying of a nondigestible capsule to a radio-labeled meal in healthy and gastroparetic subjects. *Aliment Pharmacol Ther*. 2008;27:186–196.
17. Perkel MS, Moore C, Hersh T, Davidson E. Metoclopramide therapy in patient with delayed gastric emptying. *Dig Dis Sci*. 1979;24:9.
18. Parkman HP, Carlson MR, Gonyer D. Metoclopramide nasal spray is effective in symptoms of gastroparesis in diabetics compared to conventional oral tablet. *Neurogastroenterol Motil*. 2014;26:521–528.
19. Parkman HP, Carlson MR, Gonyer D. Metoclopramide nasal spray reduces symptoms of gastroparesis in women, but not men, with diabetes: results of a phase 2B randomized study. *Clin Gastroenterol Hepatol*. 2015;13:1256–1263.
20. Wierup N, Bjorkqvist M, Westrom B, Pierzynowski S, Sundler F, Sjolund K. Ghrelin and motilin are cosecreted from a prominent endocrine population in the small intestine. *J Clin Endocrinol Metab*. 2007;92:3573–3581.
21. Page AJ, Slattery JA, Milte C, et al. Ghrelin selectively reduces mechanosensitivity of upper gastrointestinal vagal afferent. *Am J Physiol Gastrointest Liver Physiol*. 2007;292:1376–1384.
22. Tack J, Depoortere I, Bisschops R, et al. Influence of ghrelin on interdigestive gastrointestinal motility in humans. *Gut*. 2006;55:327–333.
23. Harch IA, Koebnick C, Tasi AM, Hahn EG, Konturek PC. Ghrelin and obestatin levels in type 2 diabetic patients with and without delayed gastric emptying. *Dig Dis Sci*. 2009;54:2161–2166.
24. Camilleri M, Acosta A. A ghrelin agonist fails to show benefit in patients with diabetic gastroparesis: let's not throw the baby out with the bath water. *Neurogastrienteol Motil*. 2013;25:859–863.
25. Shin A, Wo JM. Therapeutic applications of ghrelin agonists in the treatment of gastroparesis. *Curr Gastroenterol Rep*. 2015;17:8.
26. Van der Ploeg L, Laken H, Sharma S, et al. Preclinical gastrointestinal prokinetic efficacy and endocrine effects of the ghrelin mimetic RM-131. *Life Sci*. 2014;109:20–29.
27. Camilleri M, Acosta A. Relamorelin: a novel gastricolokinetic synthetic ghrelin agonist. *Neurogastroenterol Motil*. 2015;27:324–332.
28. Nelson AD, Camilleri M, Acosta A, et al. Effects of gherelin receptor agonist, Relamorelin, on gastric motor functions and satiation in healthy volunteers. *Neurogastroenterol Motil*. 2016;28:1705–1713.
29. Shin A, Camilleri M, Busciglio I, et al. Randomized controlled phase IB study of ghrelin agonist, RM-131 in type 2 diabetic women with delayed gastric emptying: pharmacokinetics and pharmacodynamics. *Diabetes Care*. 2013;36:41–48.
30. Shin A, Camilleri M, Busciglio I, et al. The ghrelin agonist RM-131 accelerates gastric emptying of solids and reduces symptoms in patients with type 1 diabetes mellitus. *Clin Gastroenterol Hepatol*. 2013;11:1453–1459.
31. Lembo A, Camilleri M, McCallum R, et al. Relamorelin reduces vomiting frequency and severity and accelerates gastric emptying in adults with diabetic gastroparesis. *Gastroenterology*. 2016;151:87–96.
32. Camilleri M, McCallum R, Tack J, Spence S, Gottesdiener K, Fiedorek F. Relamorelin in patients with diabetic gastroparesis: Efficacy and safety results from a phase 2B randomized, double-blind, placebo-controlled, 12 week study. *DDW*. 2017; Abstract 638
33. Hasler WL. Serotonin and the GI tract. *Curr Gastroenterol Rep*. 2009;11:383–391.
34. Ottoboni T, Gelder MS, O'Boyle E. Biochronomer technology and the development of APF530, a sustained release formulation of granisetron. *J Exp Pharm*. 2014;6:15–21.
35. Boccia RV, Gordan LN, Clark G, Howell JD, Grunberg SM. Sancuso study group. Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy. *Support Care Cancer*. 2011;19:1609–1617.
36. Kuryshev YA, Brown AM, Wang L, Benedict CR, Rampe D. Interactions of the 5-Hydroxytryptamine 3 antagonist class of antiemetic drugs with human cardiac ion channels. *J Phamacol Exp Ther*. 2000;295:614–620.
37. Manson JW, Selness DS, Moon TE, O'Mahony B, Donachie P, Howell J. Pharmacokinetics and repolarization effects of intravenous and transdermal granisetron. *Clin Cancer Res*. 2012;18:2913–2921.
38. Simmons K, Parkman HP. Granisetron transdermal system improves refractory nausea and vomiting in gastroparesis. *Dig Dis Sci*. 2014;59:1231–1234.
39. Midani D, Parkman HP. Granisetron transdermal system for treatment of symptoms of gastroparesis: a prescription registry study. *J Neurogastroenterol Motil*. 2016;22:650–655.
40. Briejer MR, Akkermans LM, Schuurkes JA. Gastrointestinal prokinetic benzamides: the pharmacology underlying stimulation of motility. *Pharmacol Rev*. 1995;47:631–651.
41. De Maeyer JH, Lefebvre RA, Schuurkes JA. 5-HT4 receptor agonists: similar but not the same. *Neurogastroenterol Motil*. 2008;20:99–112.
42. Tack J, Camilleri M, Chang L. Systematic review: cardiovascular safety profile of 5-HT4 agonists developed for gastrointestinal disorders. *Aliment Pharmacol Ther*. 2012;35:745–767.
43. Anderson JL, May HT, Blair TL, Muhlestein JB, Horne BD, Carlquist JF. Lack of association of tegaserod with adverse cardiovascular outcomes in a matched case-control study. *J Cardiovasc Pharmacol Ther*. 2009;14:170–175.
44. Tack J, Rotondo A, Meulemans A, Thielemans L, Cools M. Randomized clinical trial: a controlled pilot trial of the 5-HT4 receptor agonist Revexepride in patients with symptoms suggestive of gastroparesis. *Neurogastroenterol Motil*. 2016;28:487–497.
45. Patterson D, Abell T, Rothstein R, Koch K, Barnett J. A double-blind multicenter comparison of Domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. *Am J Gastroenterol*. 1999;94:1230–1234.
46. Dumitrascu DL, Weinbeck M. Domperidone versus metoclopramide in the treatment of diabetic gastroparesis. *Am J Gastroenterol*. 2000;95:316–317.
47. Reddymasu SC, Soykan I, McCallum RW. Doperidone: review of pharmacology and clinical applications in gastroenterology. *Am J Gastrienterol*. 2007;102:2016–2045.
48. Sugumar A, Singh A, Pasricha PK. A systematic review of the efficacy of Domperidone for the treatment of diabetic gastroparesis. *Clin Gastroenterol Hepatol*. 2008;6:726–733.
49. Diemunsch P, Grelot L. Potential of substance P antagonists as antiemetics. *Drugs*. 2000;60:533–546.
50. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *J Clin Oncol*. 2003;21:4112–4119.
51. Hesketh PJ, Schnadig ID, Schwartzberg LS, et al. Efficacy of the neurokinin-1 receptor antagonist rolapitant in preventing nausea

and vomiting in patients receiving carboplatin-based chemotherapy. *Cancer*. 2016;122:2418–2425.
52. Yahata H, Kobayashi H, Sonoda K, et al. Efficacy of aprepitant for the prevention of chemotherapy-induced nausea and vomiting with a moderately emetogenic chemotherapy regimen. *Int J Clin Oncol*. 2016;21:491–497.
53. Fahler J, Wall GC, Leman BI. Gastroparesis-associated refractory nausea treated with aprepitant. *Ann Pharmacother*. 2012;46:e38.
54. Wellington J, Scott B, Kundu S, Stuart P, Koch KL. Effect of endoscopic pyloric therapies for patients with nausea and vomiting and functional obstructive gastroparesis. *Auton Neurosci*. 2017;202:56–61.
55. Clarke JO, Sharaiha RZ, Kord VA, Lee LA, Kalloo AN, Khashab MA. Through-the-scope transpyloric stent placement improves symptoms and gastric emptying in patients with gastroparesis. *Endoscopy*. 2013;45(suppl):2.
56. Khashab MA, Besharati S, Ngamruengphong S, et al. Refractory gastroparesis can be successfully managed with endoscopic transpyloric stent placement and fixation. *Gastrointest Endosc*. 2015;82:1106–1109.
57. Hibbard ML, Dunst CM, Swanstrom LL. Laparoscopic and endoscopic pyloroplasty for gastroparesis results in sustained symptom improvement. *J Gastrointest Surg*. 2011;15:1513–1519.
58. Al Shada, Dunst CM, Pescarus R, et al. Laparoscopic pyloroplasty is a safe and effective first-line surgical therapy for refractory gastroparesis. *Surg Endosc*. 2016;30:1326–1332.
59. Heckert J, Sankineni A, Hughes WB, Harbison S, Parkman H. Gastric electric stimulation for refractory gastroparesis: a prospective analysis. *Dig Dis Sci*. 2016;61:169–175.
60. Sarosiek L, Davis B, Eichler E, McCallum RW. Surgical approaches to treatment of gastroparesis: gastric electrical stimulation, pyloroplasty, total gastrectomy and enteral feeding tubes. *Gastroenterol Clin N Am*. 2015;44:151–167.
61. Abel TL, Johnson WD, Kedar A, et al. A double-masked, randomized, placebo-controlled trial of temporary endoscopic mucosal gastric electrical stimulation for gastroparesis. *Gastrointest Endosc*. 2011;74:496–503.
62. Deb S, Tang SJ, Abell TL, et al. Development of innovative techniques for the endoscopic implantation and securing of a novel, wireless, miniature gastrostimulator. *Gastrointest Endosc*. 2012;76:179–184.
63. Zehetner J, Ravari F, Ayazi S, et al. Minimally invasive surgical approach for the treatment of gastroparesis. *Surg Endosc*. 2013;27:61–66.
64. Bhayani NH, Sharata AM, Dunst CM, Kurian AA, Reavis KM, Swanstrom LL. End of the road for a dysfunctional end organ: laparoscopic gastrectomy for refractory gastroparesis. *J Gastrointest Surg*. 2015;19:411–417.
65. Bagloo M, Besseler M, Ude A. Sleeve gastrectomy for the treatment of diabetic gastroparesis. In *Proceedings 12th World Congress of Endoscopic Surgery*, April 14–17, 2010 Landover, p. 521.
66. Meyer A, Pallati P, Shaligram A, et al. Partial longitudinal gastrectomy: a novel curative approach for gastroparesis. In *Proceedings of the 2012 Annual Meeting of the Society of American Gastrointestinal Endoscopic Surgeons*, San Diego, p. 249.
67. Khashab MA, Stein E, Clarke JO, et al. Gastric peroral endoscopic myotomy for refractory gastroparesis: first human endoscopic pyloromyotomy. *Gastrointest Endosc*. 2013;78:764–768.
68. Dacha S, Mekaroonkamol P, Li L, et al. Outcomes and quality-of-life assessment after gastric per-oral endoscopic pyloromyotomy. *Gastrointest Endosc*. 2017. doi:10.1016/j.gie.2017.01.031.
69. Gonazlez JM, Lestelle V, Benezech A, et al. Gastric per-oral endoscopic myotomy with antropyloromyotomy in the treatment of refractory gastroparesis. *Gastrointest Endosc*. 2017;85:132–139.
70. Khashab MA, Ngamruengphong S, Carr-Locke D, et al. Gastric per-oral endoscopic myotomy for refractory gastroparesis: results from the first multicenter study on endoscopic pyloromyotomy. *Gastrointest Endosc*. 2017;85:123–128.
71. Sarna SK. Cyclic motor activity; migrating motor complex. *Gastroenterology*. 1985;89:894–913.
72. Broad J, Mukherjee S, Samadi M, Martin J, Dukes G, Sanger G. Regional- and agonist-dependent facilitation of human neurogastrointestinal functions by motilin receptor agonists. *Br J Pharmacol*. 2012;167:763–774.
73. Sanger GJ, Furness JB. Ghrelin and motilin receptors as drug targets for gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol.*. 2016;13:38–48.
74. Thielemans L, Depoortere I, Perret J, et al. Desensitization of the human motilin receptor by motilides. *J Pharmacol Exp Ther*. 2005;313:1397–1405.
75. Verhagen MA, Samsom M, Maes B, Geypens BJ, Ghoos YF, Smout AJ. Effects of a new motilide, ABT-229, on gastric emptying and postprandial antroduodenal motility in healthy volunteers. *Aliment Pharmacol Ther*. 1997;11:1077–1086.
76. Talley NJ, Verlinden M, Snape W, et al. Failure of a motilin receptor agonist (ABT-229) to relieve the symptoms of functional dyspepsia in patients with and without delayed gastric emptying. *Aliment Pharmacol Ther*. 2000;14:1653–1661.
77. Talley NJ, Verlinden M, Geenen DJ, et al. Effects of a motilin receptor agonist (ABT-229) on upper gastrointestinal symptoms in type 1 diabetes mellitius. *Gut*. 2001;49:395–401.
78. McCallum RW, Cynshi O. Clinical trial: effect of mitemcinal (a motilin agonist) on gastric emptying in patients with gastroparesis. *Aliment Pharmacol Ther*. 2007;26:1121–1130.
79. Li JJ, Chao HG, Wang H, et al. Discovery of a potent and novel motilin agonist. *J Med Chem*. 2004;47:1704–1708.
80. Hellstrom PM, Tack J, Johnson LV, et al. The pharmacodynamics, safety and pharmacokinetics of single doses of the motilin agonist, camicinal in type 1 diabetes mellitus with slow gastric emptying. *Br J Pharmacol*. 2016;173:1768–1777.
81. Barton ME, Otiker T, Johnson LV, et al. A randomized, double-blind, placebo-controlled phase II study (MOT114479) to evaluate the safety and efficacy and dose response of 28 days of orally administered camicinal in diabetics with gastroparesis. *Gastroenterology*. 2014;146:S-20.
82. Beattie DT, Higgins DL, Ero MP, et al. An in vitro investigation of the cardiovascular effects of the 5-HT4 receptor selective agonists, Velusetrag and TD-8954. *Vascul Pharmacol*. 2013;58:150–156.
83. Manini ML, Camilleri M, Goldberg M, et al. Effects of Velusetrag (TD-5108) on gastrointestinal transit and bowel function in health and pharmacokinetics in heath and constipation. *Neurogastroenterol Motil*. 2010;22:42-e8.
84. Yamamoto T, Tajimi M, Takahashi N, Nii T, Zai H. First-in-human study of the novel 5-HT4 agonist, RQ-00000010, demonstrated acceleration of gastric emptying following single and multiple oral administration to healthy human subjects. *Gastroenterology*. 2013;144:S-736.