Treatment of Gastroparesis: An Update

Vivek Gumaste Joel Baum

Department of Medicine, Mount Sinai Services at Elmhurst, Elmhurst General Hospital, Elmhurst, N.Y., and Mount Sinai School of Medicine of the City University of New York, New York, N.Y., USA

Key Words

Gastroparesis • Diabetes

Abstract

Gastroparesis is a chronic disorder of gastric motility that is characterized by delayed emptying of either solids or liquids from the stomach in the absence of any mechanical obstruction. Nausea, vomiting, early satiety and bloating are some of the manifestations of gastroparesis. Idiopathic, diabetes mellitus and postsurgical states account for the majority of cases. Gastroparesis is a difficult condition to treat. Prokinetic drugs like metoclopramide and erythromycin form the mainstay of therapy but are less than ideal. Some patients may benefit from endoscopic botulinum toxin injection. Gastric electrical stimulation, though promising, is not ready for prime time yet.

Copyright © 2008 S. Karger AG, Basel

ing scintigraphy, is present in 25–55% of patients with type 1 diabetes and in 30% of those with type 2 diabetes [2–5]. Considering the widespread prevalence of diabetes, this would constitute a significant proportion of the population.

Etiology

The etiology of gastroparesis is diverse with the idiopathic variety constituting the largest group in one study [6]. Diabetes accounted for 29% of patients in that same report with postsurgical causes making up 13%. These 3 causes (idiopathic, diabetes and postsurgical) account for a majority of all cases. Other causes of gastroparesis include neurological conditions like Parkinsonism, collagen vascular diseases, Chagas disease, hypothyroidism, hyperparathyroidism and hypoparathyroidism.

Gastroparesis is a chronic disorder of gastric motility that is characterized by delayed emptying of either solids or liquids from the stomach in the absence of any mechanical obstruction. Gastroparesis assumes clinical importance because it can contribute to upper gastrointestinal symptoms like nausea, vomiting and early satiety.

The precise incidence of gastroparesis is not known, but it is estimated to affect about 4% of the population [1]. Gastroparesis, as documented by delayed gastric empty-

Clinical Manifestations and Diagnosis

Present studies indicate that the majority of those with delayed gastric emptying are women and the mean age of onset is 34 years [6].

Gastroparesis manifests itself through a combination of symptoms. Most symptoms are nonspecific and overlap with common gastrointestinal disorders like peptic ulcer disease and nonulcer dyspepsia. Nausea/vomiting,

Table 1. Proposed classification of gastroparesis severity

<i>Grade 1: Mild gastroparesis</i>
Symptoms relatively easily controlled
Able to maintain weight and nutrition on a regular diet or minor dietary modifications
<i>Grade 2: Compensated gastroparesis</i>
Moderate symptoms with partial control with pharmacological agents
Able to maintain nutrition with dietary and lifestyle adjustments
Rare hospital admissions
<i>Grade 3: Gastroparesis with gastric failure</i>
Refractory symptoms despite medical therapy
Inability to maintain nutrition via oral route
Frequent emergency room visits or hospitalizations

Reproduced from Abel et al. [9].

postprandial fullness/early satiety and bloating are the commonest manifestations. Nausea is the most consistent symptom found in over 90% of patients [6, 7]. Bloating and early satiety are present to a lesser degree, being found in 75% and 60%, respectively, in one study [6].

Abdominal pain may be present in 46–89% of patients but is unlikely to be the predominant symptom [6, 7].

As the symptoms are nonspecific with a significant degree of overlap with other gastric disorders, the initial work-up should include an upper endoscopy, even if gastroparesis is strongly suspected. This is necessary to rule out any mechanical obstruction and other common disorders like peptic ulcer diseases and nonulcer dyspepsia.

When an upper endoscopy does not reveal any organic obstruction and the endoscopic findings do not adequately explain the patient's symptoms, a definitive test to diagnose gastroparesis such as gastric scintigraphy must be done.

Assessment of Severity

Assessment of severity is important for appropriate management. One method is the Gastroparesis Cardinal Symptom Index (GCSI), which is a sum, total of 3 subscales (ranging from 1–3) for the 3 main symptom complexes: postprandial fullness/early satiety, nausea/vomiting and bloating [8].

Another simple gradation of severity is outlined in table 1 [9]. Grade 1 usually includes patients with mild

Table 2. Medications associated with impaired gastric emptying

Narcotic pain medications
Tricyclic antidepressants
Calcium channel-blocking medications
Clonidine
Dopamine agonists
Lithium
Nicotine
Progesterone containing medications
Muscarinic cholinergic receptor antagonists

intermittent symptoms that are controlled with diet modification and avoidance of exacerbating agents. Grade 2 patients have moderately severe symptoms but no weight loss and require prokinetic drugs plus antiemetic agents for control. In Grade 3, patients are refractory to medication, unable to maintain oral nutrition and require frequent emergency room visits. These patients require intravenous fluids, medications, enteral or parenteral nutrition and endoscopic or surgical therapy.

Treatment

A wide array of therapeutic interventions is available to treat gastroparesis. Diet modification, pharmacological agents, endoscopic techniques, surgery and psychological counseling are some of the modalities employed.

General and Dietary Measures

While there are no controlled trials testing the efficacy of diet modification in the therapy of gastroparesis, some dietary recommendations may prove helpful in patients with milder forms of the disease. Multiple small meals a day as opposed to 2 or 3 large meals facilitate gastric emptying. Generous intake of fluids during a meal may aid gastric emptying, as liquids empty more rapidly than solids. An overall reduction in the solid food content is also advised. A diet low in fats decreases the inhibitory effect of lipids on gastric emptying. Patients should be told to avoid a high fiber diet to prevent phytobezoar formation.

Proper mastication and postprandial walking are additional factors that may facilitate the gastric emptying process.

Table 3. Prokinetic agents

Agent	Mechanism	Dosage
Metaclopramide	dopamine D ₂ receptor antagonist	5–20 mg q.i.d.
Domperidone	dopamine D ₂ receptor antagonist	10–30 mg q.i.d.
Erythromycin	motilin receptor agonist	50–250 mg q.i.d.
Bethanechol	muscarinic receptor agonist	25 mg q.i.d.
Pyridostigmine	acetylcholinesterase inhibitor	30–60 mg t.i.d.
Tegaserod	5-HT ₄ receptor agonist	withdrawn in US
Cisapride	5-HT ₄ receptor agonist	withdrawn in US
Loxiglumide	CCK receptor antagonist	under study

Medicines that decrease gastric motility should be discontinued if possible (table 2). Identification and correction of the underlying cause of gastroparesis may be helpful in some cases. In diabetics, aggressive control of blood sugar is advocated as it is thought to facilitate the action of other therapeutic measures.

Prokinetic Agents

There are 3 broad classes of prokinetic agents used in the treatment of gastroparesis: dopamine receptor antagonists, motilin receptor agonists and 5-HT₄ receptor agonists (table 3).

Dopamine Receptor Antagonists

Metaclopramide. Metaclopramide is a 5-HT₄ agonist, a dopamine D₂ receptor antagonist and a direct stimulant of smooth muscle, all of which contributes to its prokinetic effect [1]. In addition to accelerating gastric motility, metaclopramide has an independent antiemetic effect. Metaclopramide can be administered intravenously, subcutaneously or through the oral route. A liquid preparation is also available.

Although there are several studies [10–18] that have attempted to document the efficacy of metoclopramide in gastroparesis, most of them suffer from significant design flaws or insufficient numbers. Some of the more acceptable trials are listed in table 4. The overall conclusion that can be drawn from these trials is that a minority of patients may experience symptom benefit from metoclopramide therapy. However, there appears to be poor correlation between the improvement in gastric emptying and reduction of symptoms.

When compared to erythromycin, metoclopramide proved to be inferior in terms of symptom relief in one

Table 4. Efficacy of metoclopramide in gastroparesis

Study	n	Design	Symptom reduction	GE improvement
Perkel et al. [13]	28	RDBP	yes	not stated ¹
Snape et al. [12]	10	RDBP	yes	yes
McCallum et al. [11]	40	DBP	yes	yes
Ricci et al. [14]	13	RDBP	yes	yes
<i>Metoclopramide vs. cisapride</i>				
De Caestecker et al. [15]	19	DBP	No	no
<i>Metoclopramide (M) vs. erythromycin (E)</i>				
Erbas et al. [16]	13	OL	yes (E>M)	yes
<i>Metoclopramide (M) vs. domperidone (D)</i>				
Patterson et al. [18]	45	RDB	yes	not studied
Dumitrascu et al. [17]	10	DB	yes (D>M)	yes (D>M)

GE = Gastric emptying; RDBP = randomized double-blind placebo controlled; DBP = double-blind placebo controlled; OL = open label; RDB = randomized double blind; DB = double blind.

¹ Used barium studies to measure gastric emptying.

study [16]. Other studies [17, 18] have shown that metoclopramide may be equally effective or marginally inferior to domperidone in efficacy.

Patients may develop tolerance over time and uncomfortable side effects may limit its use in up to 30% of patients. Irreversible tardive dyskinesia is a serious side effect that occurs in 1–10% of patients treated for more than 3 months [19]. Therefore, it is not advisable to maintain patients on metaclopramide for a prolonged period. When initiating therapy, the side effects should be discussed and documented in the patient record.

Domperidone. Domperidone is a peripheral dopamine D₂ receptor antagonist with prokinetic properties and a potent antiemetic effect. As it does not cross the blood-brain barrier, its central nervous system side effects are minimal.

In clinical trials, the efficacy of domperidone matches that of metaclopramide and cisapride [18]. However, its effect on solid-phase gastric emptying is lost by 6 weeks [20]. The drug is not approved in the United States by the FDA but can be made available through special application for patients with refractory gastroparesis.

Motilin Receptor Agonists

Erythromycin. Erythromycin exerts its prokinetic effect by stimulating the motilin receptors on smooth muscles and neurons in the gastroduodenal area [21]. How-

ever, unlike metaclopramide, erythromycin has no independent antiemetic effect.

Most published trials [22–26] reporting on the efficacy of erythromycin in gastroparesis have been open labeled, had inadequate numbers or lacked strict definitions [22]. A few representative studies are outlined in table 5. The conclusion gleaned from these reports is that though erythromycin improves gastric emptying, it benefits only a minority of patients with regard to symptom amelioration.

Erythromycin can be administered intravenously in hospitalized patients or provided in liquid form or oral tablets to outpatients. Its most potent effect is seen when injected intravenously [27]. The oral route (125–250 mg, 3–4 times daily) is less efficacious. Tolerance is known to occur with chronic use. An increased incidence of sudden cardiac death in patients using erythromycin has been reported [28].

Other Motilin Receptor Agonists. Mitemcinal, a new motilin agonist, which can be administered orally, has shown promise in initial trials [29]. Ghrelin, an endogenous neurohumoral mediator, is currently under study [30].

5-HT₄ Receptor Agonists

Tegaserod and Cisapride are 5-HT₄ receptor agonists, which have been used to treat gastroparesis in the past. Both agents were withdrawn from use in the United States owing to serious cardiovascular complications [1].

Symptomatic Therapy

Antiemetic drugs have been used successfully in clinical practice to treat the symptoms of gastroparesis although hard evidence for this rationale in the form of scientific studies is minimal. The most commonly used antiemetic drugs are the phenothiazines (for example prochlorperazine and thiethylperazine) and they can be used in conjunction with prokinetic agents [9].

Low-dose tricyclic antidepressants may provide relief of symptoms in patients with gastroparesis [31].

Pain may be a prominent symptom in some patients. Nonsteroidal agents, selective serotonin reuptake inhibitors and opiates have been used with varying degrees of success [9].

Endoscopic Treatment

In some patients with gastroparesis, pylorospasm may contribute to a delay in gastric emptying. Endoscopic therapy involves the injection of botulinum toxin (100–200 units in a circumferential pattern; 4 injections around

Table 5. Efficacy of erythromycin in gastroparesis

Study	n	Design	Route	Symptom reduction	GE improvement
Richards et al. [25]	10	OL	PO, IV	yes	yes
Ramirez et al. [24]	16	OL	PO, IV	yes	yes
Fiorucci et al. [23]	12	OL	IV	not stated	yes
Samsom et al. [26]	12	DBC	PO	unclear	not done

GE = Gastric emptying; OL = open label; PO = per os; IV = intravenous; DBC = double-blind controlled.

Table 6. Overview of studies with botulinum toxin injection in gastroparesis

Study	n	Dose	Follow-up	Symptom reduction	GE improvement
<i>Open</i>					
Ezzedine et al. [33]	6	100 IU	6 weeks	55%	52%
Miller et al. [34]	10	100 IU	4 weeks	38%	48%
Arts et al. [36]	20	100 IU	1 month	29%	35%
Lacy et al. [35]	8	200 IU	12 weeks	55%	33%
Bromer et al. [32]	63	200 IU	2 months	43%	NS
<i>Randomized placebo-controlled trials</i>					
Arts et al. [38]	23	100 IU	1 month	none	none
Friedenberg et al. [39]	16	200 IU	1 month	none	improved

GE = Gastric emptying; NS = not significant.

Table 7. Trials with gastric electrical stimulation

Study	Design	n	Duration months	Symptom improvement
GEMS [42]	open	33	12	yes
WAVES [43]	DBS	33	2	yes
	open	33	12	yes
Forster et al. [40]	open	25	12	improved at 3 months sustained at 12 months
Forster et al. [44]	open	55	12	improved at 6 months not sustained at 12 months
Lin et al. [45]	open	55	36	improved at 1 year sustained for 3 year
Anand et al. [46]	open	214	48	sustained for 4 year

DBS = Double-blind sham.

Table 8. Consensus recommendations for the treatment of gastroparesis

Psychological measures	Glycemic control	Nutritional care	Prokinetic medications	Antiemetic therapy	Pain control
Empathy and education Patient support groups Behavioral or relaxation therapy Hypnosis	Twice daily long-acting insulin plus periprandial short-acting insulin Insulin pump Pancreas transplant	Small, frequent meals, low in fat and fiber Primarily liquid diet Liquid nutrient supplements Enteral feedings Central or peripheral parenteral nutrition short term	Metoclopramide or erythromycin PRN Metoclopramide or erythromycin scheduled dosing Domperidone or tegaserod Pyloric botulinum toxin	Phenothiazine or dopamine receptor antagonist PRN Muscarinic receptor antagonist or 5-HT ₃ antagonist Tricyclic agents Tetrahydrocannabinol, lorazepam or alternative therapies Gastric electrical stimulation	Acetaminophen or nonsteroidal agents Tramadol or propoxyphene Tricyclic agents Newer antidepressants TCAs, SNRIs Fentanyl patch or methadone Referral for pain specialist Nerve block

A stepped care approach in a top-down vertical manner is recommended which is dependent on the severity of gastroparesis. Treatment from different categories (columns) is often used in combination. TCA = Tricyclic antidepressant agent; SNRI = selective norepinephrine reuptake inhibitor. Reproduced from Abel et al. [9].

the pylorus) into the pyloric area, which is thought to decrease pylorospasm and accelerate gastric emptying.

Several open-labeled studies [32–37] indicated a good symptomatic response (table 6) with symptom scores falling by 29–55%. Gastric emptying rates also registered a marked improvement (33–52%) and correlated well with symptom reduction. The effect of botulinum toxin lasted up to 5 months in one study [32].

However, the results from 2 randomized, placebo-controlled trials [38, 39] have not been encouraging. Arts et al. [38] failed to demonstrate any beneficial effect on either gastric emptying or symptoms over placebo. In the study by Friedenberget al. [39], gastric emptying rates improved, but provided no symptom benefit. More studies are required before reaching a final verdict on botulinum toxin injection therapy.

Dilation of the pylorus may produce the same benefit as botulinum injection [1].

Gastric Electrical Stimulation

Using exogenous electrical current to stimulate the stomach in patients with gastroparesis is a logical and attractive concept. Initial methods involved external leads, which were too large for implantation and unwieldy [40]. Recently, the FDA has given limited approval on humanitarian grounds for a gastric electrical stimulator with a pulse generator that can be implanted into the abdominal wall (Enterra gastric electrical stimulation system). The pulse generator delivers low-energy, high-frequency stimuli and has a battery life of 6–8 years [41]. This method is, at present, limited to a few centers.

Initial experience with gastric stimulators was obtained through 2 multicenter trials, the Gastric Electrical Mechanical Stimulation Study (GEMS) [42] and the Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS) [43]. GEMS was a multicenter open-labeled trial that documented improvement in nausea and vomiting in gastroparetic patients. WAVESS was a controlled double-blind sham stimulation trial that reaffirmed the efficacy of gastric stimulation and paved the way for FDA approval of the Enterra system.

All trials [40, 44–46] have produced encouraging results with patients experiencing 75–80% reduction in symptoms (table 7). While some initial studies showed conflicting results with regard to sustenance of improvement [40, 44], two subsequent studies have indicated long-term benefits lasting 3 and 4 years, respectively [45, 46]. Cutts et al. [47] were able to demonstrate that gastric stimulation therapy is superior to intensive medical treatment.

About 10% of patients, however, develop complications like infection, which invariably warrants removal of the device. Other adverse events noted include: lead dislodgement, wire breakage, penetration of the stomach and intestinal obstruction, all of which require surgical intervention [41].

New methods that involve electrodes that can be placed orally by endoscopy or through a percutaneous endoscopic gastrostomy [48] or by percutaneous techniques [49] are also being explored.

Gastric electric stimulation is not ready for prime time yet. Available devices need to undergo further refinement

and easier electrode implantation techniques that obviate the need for surgery are required. Long-term controlled studies involving larger numbers will be necessary for gastric electrical stimulation to be accepted as standard therapy [50, 51].

Surgery

Extreme cases may require surgical intervention, and operations like partial gastrectomy and pyloroplasty have been performed to treat resistant gastroparesis. The results are unproven so far.

Rarely, a venting gastrostomy may be placed to release the discomfort from gas and liquids [1].

Enteral and Parenteral Nutrition

Some patients with severe refractory gastroparesis may need enteral or parenteral modes of nutritional support. Enteral nutrition is usually indicated in patients with significant malnutrition (>10% weight loss over 6 months), evidence of mineral deficiencies and electrolyte imbalance and in those who require frequent hospitalizations [1].

Total parenteral nutrition maybe necessary in patients who have concomitant intestinal motility.

Psychological Support

Anxiety, depression and somatization are increasingly found in patients with severe gastroparesis and appropriate psychological support is necessary to improve the overall well-being of the patient. Psychotherapeutic measures like relaxation techniques have been useful. Some patients benefit from hypnosis and biofeedback [9].

Conclusion

Most therapeutic measures available to treat gastroparesis are less than ideal and patients may require a combination of measures depending on the severity of their condition. Table 8 summarizes the overall approach to the treatment of gastroparesis.

References

- Hasler WL: Gastroparesis: Symptoms, Evaluation, and Treatment. *Gastroenterol Clin N Am* 2007;36:619–647.
- Kong M-F, Horowitz M, Jones KL, et al: Natural history of diabetic gastroparesis. *Diabetes Care* 1998;22:503–507.
- Nowak TV, Johnson CP, Kalbfleisch JH, et al: Highly variable gastric emptying in patients with insulin dependent diabetes mellitus. *Gut* 1995;37:23–29.
- Moldovan C, Dumitrascu DL, Demian L, et al: Gastroparesis in diabetes mellitus: an Ultrasonographic study. *Rom J Gastroenterol* 2005;14:19–22.
- Horowitz M, Su YC, Rayner CK, et al: Gastroparesis: prevalence, clinical significance and treatment. *Can J Gastroenterol* 2001;15: 805–813.
- Soykan I, Sivri B, Saosiek 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.
- Hoogerwerf WA, Pasricha PJ, Kalloo AN, et al: Pain: the overlooked symptom in gastroparesis. *Am J Gastroenterol* 1999;94:1029–1033.
- Revicki DA, Rentz AM, Dubois D, et al: Development and validation of a patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. *Aliment Pharmacol Ther* 2003;18: 141–150.
- Abel TL, Bernstein RK, Cutts T, et al: Treatment of gastroparesis: a multidisciplinary clinical review. *Neurogastroenterol Motil* 2006;18:263–283.
- Parkman HP, Hasler WL, Fisher RS: American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. *Gastroenterology* 2004; 127: 1592–1622.
- McCallum RW, Ricci DA, Rakatansky H, et al: A multicenter placebo-controlled clinical trial of oral metoclopramide in diabetic gastroparesis. *Diabetes Care* 1983;6:463–467.
- Snape WJ Jr, Battle WM, Schwartz SS, Braunstein SN, Goldstein HA, Alavi A: Metoclopramide to treat gastroparesis due to diabetes mellitus: a double-blind, controlled trial. *Ann Intern Med* 1982;96:444–446.
- Perkel MS, Moore C, Hersh T, Davidson ED: Metoclopramide therapy in patients with delayed gastric emptying: a randomized, double-blind study. *Dig Dis Sci* 1979;24:662–666.
- Ricci DA, Saltzman MB, Meyer C, Callachan C, McCallum RW: Effect of metoclopramide in diabetic gastroparesis. *J Clin Gastroenterol* 1985;7:25–32.
- de Caestecker JS, Ewing DJ, Tothill P, Clarke BF, Heading RC: Evaluation of oral cisapride and metoclopramide in diabetic autonomic neuropathy: an eight-week double-blind crossover study. *Aliment Pharmacol Ther* 1989;3:69–81.
- Erbas T, Varoglu E, Erbas B, Tastekin G, Akalin S: Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis. *Diabetes Care* 1993;16: 1511–1514.
- Dumitrascu DL, Weinbeck M: Domperidone versus metoclopramide in the treatment of diabetic gastroparesis. *Am J Gastroenterol* 2000;95:316–317.
- Patterson D, Abell T, Rothstein R, Koch K, Barnett J: A double-blind multi-center comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. *Am J Gastroenterol* 1999;94:1230–1234.
- Ganzini L, Casey DE, Hoffman WL, et al: The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. *Arch Intern Med* 1993; 153:1469–1475.
- Horowitz M, Harding PE, Chatterton BE, Collins PJ, Sherman DJC: Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. *Dig Dis Sci* 1985;30:1–9.
- Peters TL: Erythromycin and other macrolides as prokinetic agents. *Gastroenterology* 1993;105:1886–1899.
- Maganti K, Onyemere K, Jones MP: Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am J Gastroenterol* 2003;98:259–263.

- 23 Fiorucci S, Distrutti E, Bassotti G, et al: Effect of erythromycin administration on upper gastrointestinal motility in scleroderma patients. *Scand J Gastroenterol* 1994;29:807–813.
- 24 Ramirez B, Eaker EY, Drane WE, et al: Erythromycin enhances gastric emptying in patients with gastroparesis after vagotomy and antrectomy. *Dig Dis Sci* 1994;39:2295–2300.
- 25 Richards RD, Davenport K, McCallum RW: The treatment of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. *Am J Gastroenterol* 1993;88:203–207.
- 26 Samsom M, Jebbink RJ, Akkermans LM, et al: Effects of oral erythromycin on fasting and postprandial antroduodenal motility in patients with type I diabetes, measured with an ambulatory manometric technique. *Diabetes Care* 1997;20:129–134.
- 27 Camilleri M: The current role of erythromycin in the clinical management of gastric emptying disorders. *Am J Gastroenterol* 1993;88:169–171.
- 28 Ray WA, Murray KT, Meredith S, et al: Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004;351:1089–1096.
- 29 McCallum RW, Cynshi O; US Investigative Team: Efficacy of mitemincin, a motilin agonist, on gastrointestinal symptoms suggesting diabetic gastropathy: a randomized, multi-center, placebo-controlled trial. *Aliment Pharmacol Ther* 2007;26:107–116.
- 30 Murray CD, Martin NM, Patterson M, et al: Ghrelin enhances gastric emptying in diabetic gastroparesis: a double blind, placebo controlled, crossover study. *Gut* 2005;54:1693–1698.
- 31 Sawhney MS, Prakash C, Lustman PJ, Clouse RE: Tricyclic antidepressants for persistent or recurrent vomiting in diabetic patients. *Gastroenterology* 2001;120:A243.
- 32 Bromer MQ, Friedenberg F, Miller LS, et al: Endoscopic pyloric injection of botulinum toxin A for the treatment of refractory gastroparesis. *Gastrointest Endosc* 2005;61:833–839.
- 33 Ezzeddine D, Jit R, Katz N, Gopalswamy N, Bhutani MS: Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. *Gastrointest Endosc* 2002;55:920–923.
- 34 Miller LS, Szych GA, Kantor SB, et al: Treatment of idiopathic gastroparesis with injection of botulinum toxin into the pyloric sphincter muscle. *Am J Gastroenterol* 2002;97:1653–1660.
- 35 Lacy BE, Crowell MD, Schettler-Duncan A, Mathis C, Pasricha PJ: The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus. *Diabetes Care* 2004;27:2341–2347.
- 36 Arts J, van GS, Caenepeel P, Verbeke K, Janssens J, Tack J: Influence of intrapyloric botulinum toxin injection on gastric emptying and meal-related symptoms in gastroparesis patients. *Aliment Pharmacol Ther* 2006;24:661–667.
- 37 Coleski R, Hasler W: Clinical and gastric functional predictors of symptom response to pyloric injection of botulinum toxin in patients with gastroparesis. *Neurogastroenterol Motil* 2005;17:268.
- 38 Arts J, Holvoet L, Caenepeel P, Bisschops R, Sifrim D, Verbeke K, Janssens J, Tack J: Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. *Aliment Pharmacol Ther* 2007;26:1251–1258.
- 39 Friedenberg FK, Palit A, Parkman HP, Nelson D: Randomized, placebo-controlled trial of botulinum toxin A for the treatment of delayed gastric emptying. *Gastroenterology* 2007;132:M1150.
- 40 Forster J, Sarosiek I, Delcore R, Lin Z, Raju GS, McCallum RW: Gastric pacing is a new surgical treatment for gastroparesis. *Am J Surg* 2001;182:676–681.
- 41 Maranki J, Parkman HP: Gastric electrical stimulation for the treatment of gastroparesis. *Curr Gastroenterol Rep* 2007;9:286–294.
- 42 Abell TL, Van Cutsem E, Abrahamsson H, Huizinga JD, Konturek JW, Galmiche JP, Voeller G, Filez L, Everts B, Waterfall WE, Domschke W, Bruley des Varannes S, Familoni BO, Bourgeois IM, Janssens J, Tougas G: Gastric electrical stimulation in intractable symptomatic gastroparesis. *Digestion* 2002;66:204–212.
- 43 Abell T, McCallum R, Hocking M, Koch K, Abrahamsson H, Leblanc I, Lindberg G, Konturek J, Nowak T, Quigley EM, Tougas G, Starkebaum W: Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology* 2003;125:421–428.
- 44 Forster J, Sarosiek I, Lin Z, et al: Further experiences with gastric stimulation to treat drug refractory gastroparesis. *Am J Surg* 2003;186:690–695.
- 45 Lin Z, Sarosiek I, Forster J, McCallum RW: Symptom responses, long-term outcomes and adverse events beyond 3 years of high frequency gastric electrical stimulation for gastroparesis. *Neurogastroenterol Motil* 2006;18:18–27.
- 46 Anand C, Al-Juburi A, Familoni B, Rashed H, Cutts T, Abidi N, Johnson WD, Minocha A, Abell TL: Gastric electrical stimulation is safe and effective: a long-term study in patients with drug-refractory gastroparesis in three regional centers. *Digestion* 2007;75:83–89.
- 47 Cutts TF, Luo J, Starkebaum W, Rashid H, Abell TL: Is gastric electrical stimulation superior to standard pharmacologic therapy in improving GI symptoms, healthcare resources, and long-term health care benefits? *Neurogastroenterol Motil* 2005;17:35–43.
- 48 Ayinala S, Batista O, Goyal A, et al: Temporary gastric electrical stimulation with orally or PEG-placed electrodes in patients with drug refractory gastroparesis. *Gastrointest Endosc* 2005;61:455–461.
- 49 Elfvin A, Anderson S, Abrahamsson H, et al: Percutaneous implantation of gastric electrodes—a novel technique applied to animals and in patients. *Neurogastroenterol Motil* 2007;19:103–109.
- 50 Yin J, Chen JZ: Implantable gastric electrical stimulation: ready for prime time? *Gastroenterology* 2008;134:665–667.
- 51 Ang D, Tack J: Gastric Electrical Stimulation for the treatment of gastroparesis: ready for prime time? *Digestion* 2007;75:80–82.