

# Diabetic Gastroparesis: A Review of Medical Treatments

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**Gastroparesis is a common complication of diabetes mellitus, producing symptoms of nausea, vomiting, early satiety, and abdominal discomfort. Etiology of diabetic gastroparesis is multifactorial, including autonomic neuropathy, enteric nervous system dysfunction, and altered neurotransmitter and hormone levels. Treatment of diabetic gastroparesis is based on symptom severity and relief and ranges from dietary to pharmaceutical intervention. Antiemetic therapies may reduce nausea and vomiting associated with gastroparesis but have unproven efficacy in patients with diabetic gastroparesis. Prokinetic therapies, such as motilin receptor agonists and 5-HT<sub>4</sub>-receptor agonists, enhance gastrointestinal motility but have limited use because of unfavorable adverse event profiles. In contrast, the prokinetic dopamine D<sub>2</sub>-receptor antagonist metoclopramide has been indicated for gastroparesis treatment for 30 years. A new orally disintegrating tablet formulation of metoclopramide is being developed and will be a valuable additional therapy for patients with nausea, vomiting or dysphagia and will contribute to increased compliance in patients with gastroparesis.**

## INTRODUCTION

**A**ccording to 2007 data from the National Institute of Diabetes and Digestive and Kidney Diseases, 23.6 million people—7.8% of the US population have diabetes (1). Also, diabetes incurred an estimated expenditure of \$174 billion in direct and indirect costs in 2007 (1). Part of this cost (estimated to be \$22.9 billion in 2006) can be attributed to the treatment of diabetes-related complications (2), including cardiovascular and nervous system disorders (1), renal failure (1), hypertension (1), blindness (1), amputation (1), and gastrointestinal (GI) dysfunction (3), which may be exacerbated by poor disease management.

Symptoms attributed to gastrointestinal dysfunction are common in patients with diabetes mellitus (DM) (3–6) and may result in decreased control of glucose levels and reduced overall quality of life (3). Three population-based studies (N = 114–15,000) have examined the prevalence of GI symptoms in patients with diabetes and found that these patients are more likely to experience GI symptoms than controls (4–6). These GI symptoms may (6–9) or may not (5) be related to other complications in diabetes such as neuropathy, but several studies report positive correlations between poor glycemic control and GI symptom prevalence (4,7,10). This is not surprising given that GI disorders such as gastroparesis may impair glucose absorption and thwart glycemic control in diabetics (11). In this review, we address the predominant gastric complication of DM, gastroparesis, and discuss medical treatments available in the United States for this disorder.

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## OVERVIEW

Gastroparesis is characterized by delayed gastric emptying in the absence of mechanical obstruction of the stomach (3) and may lead to symptoms of nausea, vomiting, early satiety, and abdominal discomfort and pain (3,11). In a retrospective chart review of 146 patients with gastroparesis, nausea, vomiting, abdominal bloating, and early satiety were present in 92%, 84%, 75%, and 60% of patients, respectively (12). Gastroparesis may also cause weight loss, malnutrition, and dehydration in severe cases as a result of reduced digestion and absorption by the stomach and GI tract (11). The prevalence of gastroparesis in the general population is unknown, but current published literature suggests that 20% to 40% of patients with diabetes experience gastroparesis; patients with long-standing type 1 diabetes are more likely to develop the disorder (13,14). An estimated 23.6 million people in the United States currently have diabetes (1); thus, up to 9.4 million people may develop diabetic gastroparesis. Taken together, these data emphasize the need for appropriate diagnosis and treatment of gastroparesis in patients with diabetes.

## ETIOLOGY

### Normal Gastric Emptying

The predominant function of the stomach is digestion of ingested materials to allow nutrient absorption in the small intestine (15). To accomplish this, the stomach stores, mixes, and grinds food into chyme before emptying it into the duodenum (15). All of these processes are coordinated by extrinsic and intrinsic nervous system activity, as well as endocrine and paracrine hormones (15,16).

During a meal, the fundus relaxes (“accommodation”) to receive the ingested food, a process controlled by vagal efferent fibers and nitric oxide pathways in the proximal stomach (15). The food is then broken up and mixed with stomach acid and digestive enzymes to generate chyme. This mixing occurs via gastric peristaltic contractions of the smooth muscle of the stomach, which in turn relies on interstitial cells of Cajal (ICC). The ICCs control the frequency of the gastric slow wave (3 cycles/min), which is programmed into the gastric smooth muscle cells. A gastric contraction occurs when

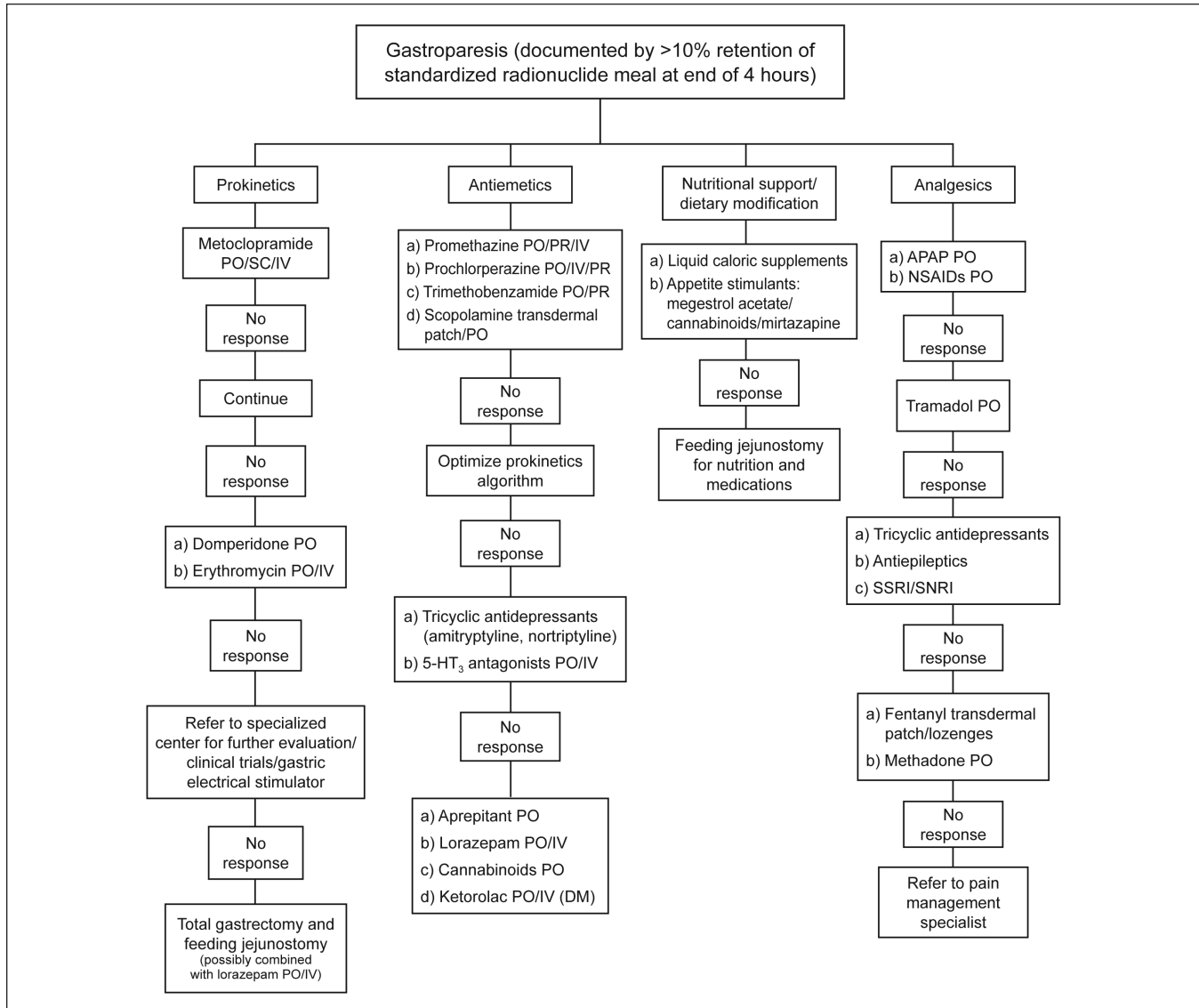
depolarization achieves an action potential and elicits electromechanical coupling. This intrinsic depolarization and repolarization allows coordination of peristalsis and proper mixing of food and digestive enzymes. Gastric emptying requires titration of food particles to a small diameter (<5 mm) to traverse the pylorus and pass into the duodenum. Gastric emptying takes a variable time depending on the caloric and physical characteristics of the food (liquid nutrients and carbohydrates empty quickly, whereas protein and fats leave more slowly) (17).

### Delayed Gastric Emptying (Gastroparesis)

The underlying mechanism of gastroparesis in patients with diabetes is poorly understood because of inconsistent links between symptomology and biological pathology (17). Although the cause of gastroparesis in patients with diabetes remains elusive, several mechanisms have been proposed, including autonomic neuropathy (alterations in vagal tone and increased sympathetic activity) (15,17,18), dysfunction of the enteric system (17), and dysfunction of hormonal and neurotransmitter control mechanisms (15,18).

Autonomic neuropathy was first associated with delayed gastric emptying because of similar radiographic findings in patients with gastroparesis and patients with gastric atony/hypomotility after surgical vagotomy (18). It should be noted, however, that some of these patients were said to have “gastroparesis diabeticorum.” Additional studies have postulated that neuropathy is common in patients with diabetes, affecting 60% of patients (16), and may include reductions in autonomic ganglia and unmyelinated nerves and loss of myelinated fibers in the vagal and sympathetic nerve trunks (18). However, the degree of diabetic neuropathy and the presence of gastroparesis do not necessarily correlate (15,18,19), indicating that neuropathy alone is not the cause of gastroparesis.

Loss of autonomic control of the GI system may reduce gastric transit in several ways, including abnormal fundic relaxation (15,18), uncoordinated peristaltic contractions (15), and loss of antroduodenal synchronization (15). Reductions in proper coordination of fundic, antral, and pyloric motor activity leads to food retention (15). Gastric dysrhythmias (15,16) and “pylorospasms” (uncoordinated pyloric contractions)



**Figure 1.** Treatment algorithm for gastroparesis. Management of gastroparesis focuses on alleviation of symptoms and improvement of delayed gastric emptying. The recommended course of treatment depends on symptom severity. Gastroparesis with mild, easily managed symptoms may be controlled with dietary modification. More persistent gastroparesis with moderate symptoms typically requires pharmacologic intervention (prokinetics, antiemetics, analgesics), with the prokinetic metoclopramide recommended as first-line treatment. Severe instances of gastroparesis may require surgical intervention, nutritional support, or both. APAP, acetaminophen; DM, diabetes mellitus; IV, intravenous; NSAIDs, nonsteroidal antiinflammatory drugs; PO, by mouth, PR, per rectum; SC, subcutaneous; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

(18) may be present in patients with DM and lead to nausea, fullness, abdominal pain, and bezoar formation (18).

Reductions in the number of ICCs have been reported in patients with gastroparesis (19,20), as well as in patients with severe DM (21). Because ICC cells

are responsible for originating the gastric slow wave, reduction in the number of these cells may cause tachygastria (>4 cycles/min) (19), leading to loss of electromechanical coupling and impaired gastric emptying.

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In addition to neurotransmitter alterations, hormonal mechanisms may be disrupted (15,18). Healthy individuals and patients with diabetes may experience reduced gastric emptying in states of hyperglycemia (15). Alterations in the release of other hormones, such as motilin, cholecystokinin, somatostatin, and glucagon, may also play a role in gastroparesis (18). Motilin increases the contractions of the proximal stomach; motilin levels may be normal or increased in patients with diabetic gastroparesis (18). Similarly, cholecystokinin (18) and glucagon (22) inhibit gastric motility and may be increased in patients with diabetic complications.

## TREATMENTS

Treatment of gastroparesis is based on controlling symptoms (particularly nausea and vomiting) and improving delayed gastric emptying (3). Mild gastroparesis with easily controlled symptoms is generally controlled with dietary modifications whereas moderate or severe gastroparesis requires prokinetic and antiemetic medications or surgical intervention,

respectively (Figure 1) (23). The altered nutritional and hydration status of patients with severe gastroparesis may also necessitate enteral or parenteral interventions to promote proper nutritional status and restore electrolyte balance (Figure 1).

## Dietary Modifications

Dietary recommendations include eating multiple small meals, avoiding indigestible solids and high-fat meals, and discontinuing medications that may inhibit GI motility, if possible (23). Also, maintenance of glucose levels with insulin, oral hypoglycemic medications, or diet is advisable to avoid the inhibitory effect of hyperglycemia (glucose levels >180 mg/dL) on gastric motility (23).

## Antiemetics

Antiemetics are efficacious in reducing nausea and vomiting in gastroparesis and may be beneficial in complementing prokinetics as combination therapy. However, there is limited literature discussing the use of antiemetics as the only management of gastroparesis (11). Thus, clinicians should take into account adverse effects and interactions with other medications when prescribing these therapies.

Antiemetics reduce vomiting by acting on a variety of receptor subtypes in the peripheral and central nervous system (Table 1) (11). The most commonly prescribed antiemetics are the phenothiazines (e.g., prochlorperazine, thiethylperazine), which are dopamine and cholinergic receptor antagonists believed to act primarily in the area postrema (11). Other antiemetics, including cholinergic muscarinic  $M_1$ -receptor antagonists (e.g., scopolamine patch) and histamine  $H_1$ -receptor antagonists, appear to operate on vestibular pathways, preventing nausea associated with motion sickness (11). However their importance in gastroparesis-related nausea is unproven (11). Benzodiazepines, tricyclic antidepressants, and  $NK_1$ -receptor antagonists may exhibit antiemetic effects through central mechanisms without exacerbating gastroparesis. Despite the potential use of these antiemetics for symptom relief in patients with diabetic gastroparesis, most of these therapies are not approved for this use (23).

**Table 1**  
**Commonly Used Antiemetics in Gastroparesis**

<i>Drug Category</i>	<i>Agent</i>
Dopamine $D_2$ -receptor antagonist	
With prokinetic activity	Metoclopramide Domperidone
Without prokinetic activity	Prochlorperazine Trimethobenzamide Thiethylperazine
Serotonin 5-HT <sub>3</sub> -receptor antagonist	Ondansetron Granisetron Dolasetron Tropisetron
Tricyclic antidepressants	Desipramine Nortriptyline Amitriptyline
Muscarinic $M_1$ -receptor antagonists	Scopolamine patch
Histamine $H_1$ -receptor antagonists	Dimenhydrinate Meclizine Promethazine
Cannabinoids	Tetrahydrocannabinol
Benzodiazepines	Lorazepam
Neurokinin $NK_1$ -receptor antagonists	Aprepitant

**Table 2**  
**Review of Randomized Studies on Oral Metoclopramide for Gastroparesis**

<i>Reference</i>	<i>Study Design</i>	<i>No. of Patients Receiving Metoclopramide</i>	<i>Diagnosis</i>
Perkel et al,1979 (41)	Randomized, double-blind, parallel-group, placebo-controlled	14	DM, GP PS GP ID GP
Snape et al,1982 (44)	Randomized, double-blind, crossover, placebo-controlled	10	DM, GP
McCallum et al,1983 (42)	Randomized, double-blind, multicenter, placebo-controlled	18	DM, GP
Ricci et al,1985 (45)	Randomized, double-blind, crossover, placebo-controlled	13 (symptom endpoint) 7 (gastric emptying endpoint)	DM, GP
Erbas et al,1993 (43)	Randomized, single-blind, crossover	13	DM, GP
Patterson et al, 1999 (39)	Randomized, double-blind, parallel-group, multicenter	45	DM, GP

DM, diabetes mellitus; GP, gastroparesis; ID, idiopathic; PS, postsurgical; t.i.d., three times daily; q.i.d., four times daily.

## Prokinetics

Prokinetics are used to enhance GI motility and thereby relieve symptoms of nausea and vomiting. These include motilin receptor agonists, 5-HT<sub>4</sub>-receptor agonists, and dopamine D<sub>2</sub>-receptor antagonists (17,18).

## Motilin Receptor Agonists

Motilin receptor agonists, such as erythromycin, azithromycin, clarithromycin, and the investigational drug mitemcinal (GM-611) are prokinetics that improve delayed gastric emptying by accelerating antroduodenal contractions (11). Several studies have demonstrated increased antral contractions (8,24–27) and symptom relief (28) in patients with diabetes after erythromycin administration. Despite the efficacy of erythromycin, it is not recommended as the prokinetic of choice because of problems with dose tolerance and tachyphylaxis (17) in addition to concerns regarding bacterial antibiotic resistance (29). In hopes of eliminating these concerns, several erythromycin derivatives were manufactured, such as mitemcinal (30). In a randomized, double-blind, placebo-controlled study of

106 patients with gastroparesis, mitemcinal (10 mg, 20 mg, or 30 mg b.i.d. or 20 mg t.i.d.) for 28 days accelerated gastric emptying, although the reduction in gastroparesis symptoms was not significant compared with placebo (31). Another antibiotic structurally related to erythromycin, azithromycin also demonstrates prokinetic activity and has been successfully used to reduce gastroparesis symptoms in one patient with diabetic gastroparesis unresponsive to other prokinetics (32).

## 5-HT<sub>4</sub>-Receptor Agonists

5-HT<sub>4</sub>-receptor agonists have prokinetic properties in the GI tract because they facilitate the release of acetylcholine from myenteric cholinergic nerves (11,14). Predominant in this category is cisapride, which, in addition to its prokinetic effects, effectively controls nausea and vomiting through weak antagonism of 5-HT<sub>3</sub> receptors (17). Cisapride increases the pressure of the lower esophageal sphincter and coordinates and increases antral, pyloric, and duodenal pressure waves (15,17). Unfortunately, because of more than 250 reported cases of cardiac arrhythmias associ-

<i>Metoclopramide Dose</i>	<i>Treatment Duration</i>	<i>Results</i>
10 mg q.i.d.	3 wk	<ul style="list-style-type: none"> <li>• Symptoms significantly improved after metoclopramide therapy compared with baseline (P &lt;0.01)</li> </ul>
10 mg q.i.d.	3 wk	<ul style="list-style-type: none"> <li>• Symptoms improved in 7 of 10 patients compared with baseline</li> <li>• Gastric emptying improved in 8 of 9 patients</li> <li>• Poor correlation between gastric emptying and symptoms</li> </ul>
10 mg q.i.d.	3 wk	<ul style="list-style-type: none"> <li>• Symptoms of abdominal fullness, nausea, vomiting, anorexia, meal intolerance, and early satiety were reduced compared with baseline</li> <li>• Gastric emptying 90 minutes after test meal improved by 25% vs baseline</li> </ul>
10 mg q.i.d.	3 wk	<ul style="list-style-type: none"> <li>• Overall symptom score improved by 53% vs pretreatment baseline</li> <li>• Gastric emptying improved but did not correlate with symptom improvement</li> </ul>
10 mg t.i.d.	3 wk	<ul style="list-style-type: none"> <li>• Symptom score improved in 10 of 11 patients vs pretreatment baseline</li> <li>• Gastric emptying 90 minutes after test meal improved by 24% vs baseline</li> </ul>
10 mg q.i.d.	4 wk	<ul style="list-style-type: none"> <li>• Total symptom score improved by 39% vs baseline</li> </ul>

ated with cisapride, it was withdrawn from the US market in 2000 (11,17,33). Cisapride is obtainable within the United States via a compassionate-use limited-access program from the manufacturer (11,33) but its toxicity, unclear long-term efficacy, and interactions with a large variety of other medications limits its use as a long-term solution for gastroparesis (17). Tegaserod, a partial 5-HT<sub>4</sub>-receptor antagonist that is primarily used for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome, has also been shown to improve gastric emptying in healthy subjects (34,35). In March of 2007, marketing of tegaserod was stopped by its manufacturer at the request of the US Food and Drug Administration (FDA). In a postmarketing safety analysis, it was shown that patients who received tegaserod were at a higher risk of ischemic events, including heart attack and stroke (36).

### Dopamine D<sub>2</sub>-receptor antagonists

Dopamine D<sub>2</sub>-receptor antagonists such as domperidone (not commonly available in United States) and metoclo-

pramide have been used with varying degrees of success in the treatment of gastroparesis (11,37). Domperidone antagonizes peripheral D<sub>2</sub>-receptors in the stomach, inhibiting fundic receptive relaxation and enhancing and coordinating stomach contractions. It does not cross the blood-brain barrier and lacks cholinergic adverse effects (18). A variety of studies have shown that domperidone alleviates symptoms (13,38,39) and enhances solid and liquid emptying (13) in patients with diabetic gastroparesis; however, one study has suggested that part of this effect may be temporary because domperidone was ineffective in stimulating solid emptying after one month of oral administration although liquid emptying remained enhanced (13). Clinical trials, including a double-blind study, indicate efficacy in diabetic gastroparesis (38). Domperidone is not currently approved by the FDA for use in gastroparesis, but it may be obtained through an FDA investigational new drug application for some patients (3).

The only D<sub>2</sub>-receptor antagonist approved for use in gastroparesis is metoclopramide (17). Metoclopramide is a central and peripheral D<sub>2</sub>-receptor antagonist that also acts as a 5-HT<sub>4</sub> agonist and 5-HT<sub>3</sub>

antagonist (15). It blocks dopaminergic inhibition of motor activity (17) thereby decreasing receptive relaxation and increasing antral contractions (15). Since 1979, metoclopramide has been approved for relief of symptoms associated with acute and recurrent diabetic gastric stasis (40). It also has been approved for prevention of postoperative and chemotherapy-induced nausea and vomiting as well as gastroesophageal reflux disease (40). We reviewed six randomized studies evaluating the efficacy of oral metoclopramide in the treatment of gastroparesis and found that all demonstrated moderate improvement in gastroparesis symptoms and gastric emptying (Table 2) (39,41–45). Two of these studies compared metoclopramide with other prokinetics (39,43). A double-blind, multicenter, randomized trial in patients with diabetic gastroparesis (N = 95) showed that domperidone and metoclopramide were equally effective in reducing the severity of gastroparesis symptoms (39). The incidence and severity of somnolence, akathisia, anxiety, and depression were significantly greater in patients who received metoclopramide compared with domperidone. A smaller, randomized, single-blind, crossover study in patients with diabetic gastroparesis (N = 13) demonstrated efficacy of both erythromycin and metoclopramide in ameliorating gastroparesis symptoms, although erythromycin was more effective and caused fewer adverse effects than metoclopramide (43).

Metoclopramide may be administered orally (i.e., tablet formulation, oral solution) or by injection (i.e., intramuscular, subcutaneous, intravenous routes). An orally disintegrating metoclopramide formulation is also currently being developed. Rapidly disintegrating oral drug formulations are available for other medications to improve compliance in patients with nausea, vomiting, difficulty swallowing, or gastroparesis, which impairs gastric emptying of conventional tablet formulations. For example, ondansetron (Zofran®; Glaxo-SmithKline, Research Triangle Park, NC) is available in an orally dissolving form, as is lansoprazol (Prevacid®; Takeda Pharmaceuticals, Deerfield, IL). According to a recent unpublished study comparing the pharmacokinetics of orally disintegrating metoclopramide and conventional metoclopramide tablet formulations, the plasma concentration–time profiles are similar and the two formulations are bioequivalent (Data on file, Salix Phar-

maceuticals, Inc). The orally disintegrating formulation may be more useful than traditional tablets in situations where swallowing is difficult or painful and where there is nausea, vomiting, or intolerance to drinking liquid to swallow a tablet. This may include patients with dysphagia (46,47), renal failure (46), odynophagia, nausea, vomiting, and painful heartburn, as well as stroke victims (46). In addition, an orally disintegrating formulation may be beneficial in situations where administration of a conventional formulation is physically difficult, such as in uncooperative patients (e.g., patients with psychiatric disturbances) (46), elderly patients (46,48), or pediatric populations (46,48).

### SUMMARY

Gastroparesis is common in patients with long-standing diabetes, particularly patients with type 1 DM. Treatment goals are to control symptoms and accelerate delayed gastric emptying. Dietary modifications and glucose control are beneficial, but prokinetics and antiemetics in combination may be the most effective. Metoclopramide, a dopamine D<sub>2</sub>-receptor antagonist, has been successfully used for controlling gastroparesis symptoms for 30 years. An orally disintegrating tablet formulation of metoclopramide is in development and, because of ease of administration, will be a welcome addition for patients with nausea, vomiting, or dysphagia. ■

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