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## Gastroparesis and Functional Dyspepsia: Excerpts from the AGA/ANMS Meeting

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### Abstract

Despite the relatively high prevalence of gastroparesis and functional dyspepsia, the etiology and pathophysiology of these disorders remain incompletely understood. Similarly, the diagnostic and treatment options for these two disorders are relatively limited despite recent advances in our understanding of both disorders. This manuscript reviews the advances in the understanding of the epidemiology, pathophysiology, diagnosis, and treatment of gastroparesis and functional dyspepsia as discussed at a recent conference sponsored by the American Gastroenterological Association (AGA) and the American Neurogastroenterology and Motility Society (ANMS). Particular focus is placed on discussing unmet needs and areas for future research.

### INTRODUCTION

Gastroparesis and functional dyspepsia, neuromuscular disorders of the stomach involving both motor and sensory dysfunctions, are increasingly recognized as a cause of chronic abdominal symptoms in patients and thus represent significant health care burden. While there has been considerable progress in understanding enteric neuromuscular dysfunctions and gastric sensorimotor dysfunctions in these conditions, our understanding of several aspects of these disorders, in particular the underlying etiology and the relationship between enteric neuromuscular dysfunctions, whole organ physiology, and symptoms is still limited. While gastroparesis and functional dyspepsia are generally considered two distinct disorders, the distinction between them is blurred by the considerable overlap in symptoms and the recognition that delayed gastric emptying can be seen in functional dyspepsia. New approaches are therefore needed to aid in the diagnosis and treatment of these disorders. Recent advances in the development of newer, less-invasive diagnostic techniques offers promise for understanding these conditions; whereas recent insights into abnormalities at the cellular and tissue level may lead to the identification of novel molecular and cellular targets for therapy.

This manuscript reviews advances in the understanding of the epidemiology, pathophysiology, diagnosis, and treatment of gastroparesis and functional dyspepsia, and also addresses unmet needs and proposes areas for future research. This article was derived from the presentations

at the AGA/ANMS meeting on Gastroparesis and Functional Dyspepsia held in Orlando, Florida in January 2009.

## EPIDEMIOLOGY AND DEFINITIONS

### Gastroparesis

Gastroparesis is a syndrome characterized by delayed gastric emptying in absence of mechanical obstruction (1). The main symptoms include postprandial fullness (early satiety), nausea, vomiting, and bloating. The etiology of gastroparesis is multifactorial; the main categories being diabetic, idiopathic, and postgastric surgical disorders. In one tertiary referral series, diabetes mellitus (DM) accounted for almost one third of cases of gastroparesis (2).

The prevalence of gastroparesis is not well defined in population-based studies, but the condition appears to be relatively common, affecting up to 5 million individuals in the United States. Women constitute the majority of patients with a female:male ratio of 4:1 and the mean age of onset is 34 years (3). The reason for the sex ratio imbalance remains unknown. There does appear to be a gender difference in gastric emptying with females having slower gastric emptying than males (4).

Symptoms attributable to gastroparesis are reported by 5 to 12% of patients with diabetes in the community. Higher rates of diabetic gastroparesis are generally reported in academic centers possibly suggesting referral bias of more severe patients (5,6). In a general population-based study from Olmsted County, MN, there was no significant difference in prevalence for nausea and/or vomiting or dyspepsia in type 1 or 2 diabetes relative to community controls (7). However, using a combined definition of delayed gastric emptying and symptoms, the cumulative incidence over 10 years in community type 1 DM was 4.8%, in type 2 DM, 1%, and in controls, 0.1% (8). Increased prevalence of gastroparesis was demonstrated for type 1 DM. Prevalence rates of gastrointestinal (GI) symptoms (rated often/very often) in Australians with diabetes (predominantly type 2 DM) were slightly higher than in controls (9).

Gastric emptying disturbances, particularly delayed gastric emptying, is thought to be responsible for the upper gastrointestinal (GI) symptoms in diabetic patients (10). In a Mayo Clinic, tertiary referral study of 129 patients with diabetes and upper GI symptoms undergoing scintigraphy, 42% had normal, 36% delayed, and 22% rapid gastric emptying (11). There were approximately an equal number of patients with type 1 and type 2 diabetes in each category. Insulin use was associated with a lower prevalence of rapid emptying compared to normal emptying among the symptomatic diabetics. Significant weight loss and neuropathy were risk factors for delayed and rapid GE, respectively.

Once true gastroparesis develops with delayed gastric emptying, symptoms can be severe with considerable morbidity and also mortality as gastroparesis can contribute to worsening glycemic control due to erratic and slow gastric emptying. In outpatient diabetics (predominantly type 2 DM), upper GI symptoms were associated with diabetic triopathy (retinopathy, nephropathy, neuropathy) (10). Self-reported poor glycemic control was associated with increased prevalence of upper GI symptoms. Interestingly, psychological distress is also linked to GI symptoms in diabetes mellitus, particularly nausea and early satiety (12).

Diabetic gastroparesis may impair quality of life independently of other factors commonly associated with impaired quality of life, e.g. age, tobacco, alcohol, and type of diabetes. Typically, gastroparesis develops after diabetes has been present for >10 years and patients have evidence for autonomic dysfunction. The increased mortality in patients with diabetic gastroparesis is usually related to other organ dysfunction (13). The median time of death was

6 years (range: 1–12) and major causes of death were cardiovascular or renal disease. In those patients who had died, the duration of diabetes and scores for autonomic neuropathy, retinopathy, and esophageal transit were greater than in the patients who were alive. Trends for gastroparesis-related hospitalizations in the United States between 1995 and 2004 suggest an increase in hospitalizations (14). Two recent papers demonstrate the impact of gastroparesis on morbidity, increased hospitalizations, emergency department visits and in one study, increased mortality (8,15). These new data on incidence, natural history, co-morbidity and impact of diabetic gastroparesis in patients in the United States should increase awareness of this disease and hopefully guide society, regulators, and pharmaceutical and device industry to increase their efforts to help patients with these unmet medical needs.

Much less is known about the epidemiology of idiopathic gastroparesis. In a tertiary referral series of patients with idiopathic gastroparesis (2), several subgroups were identified: 23% had a presentation consistent with a viral etiology and a small subset (8%) had onset of symptoms after cholecystectomy (8%). From a symptom standpoint, 48% had prominent abdominal pain; other subgroups included patients with predominant symptoms of gastroesophageal reflux disease or functional dyspepsia.

### Functional Dyspepsia

Functional dyspepsia (FD), a syndrome thought to originate from the gastroduodenal region, is one of the most prevalent “functional” GI disorders. When symptoms are present in the absence of underlying organic disease that is likely to explain the symptoms, determined by a negative upper GI endoscopy, the patient is considered to have FD (16). The epidemiology of uninvestigated dyspepsia has mainly been studied using the Rome II criteria (16). The prevalence rate is estimated to range between 5 and 12% when strict criteria are used, but liberal criteria may yield prevalences as high as 40% (17).

The Rome III criteria for FD specify four specific symptoms (postprandial fullness, early satiation, epigastric pain, and epigastric burning) which are thought to originate from the gastroduodenal region (18). In addition, a subdivision into two new diagnostic categories of 1) meal-induced dyspeptic symptoms (postprandial distress syndrome [PDS], characterized by postprandial fullness and early satiation) and 2) epigastric pain syndrome ([EPS], characterized by epigastric pain and burning) was proposed (18). The Rome III subdivision of FD was proposed based on the assumption that different underlying pathophysiological mechanisms would be present in each of the subgroups and, by consequence, that different treatment modalities would be most suitable for each subgroup: acid suppressive therapy in EPS, and prokinetic therapy for PDS (19). It is currently unclear whether these assumptions will hold up as we further understand the etiology of FD or whether targeted therapy will increase therapeutic success. Recent epidemiological studies addressed the validity of the Rome III subdivisions of FD. A population-based study in Olmsted County found support of the existence of both EPS and PDS-like symptom groupings in the population, with the overlap between the subgroups being less than expected (20). On the other hand, major overlap between EPS and PDS was found in patients referred for open access endoscopy, and several patients with dyspeptic symptoms were not classifiable (21). The Kalixanda study confirmed the existence of PDS and EPS in the general population, and provided evidence for differential association of PDS or EPS with putative pathophysiological factors, such as anxiety (22).

## ETIOLOGY AND PATHOGENESIS

### Diabetes, Neuropathy and Gastroparesis

The pathophysiology of gastric motor disturbances in diabetic gastroparesis is multifactorial including vagal parasympathetic dysfunction, hyperglycemia, loss of expression of neuronal

nitric oxide (nNOS), loss of enteric neurons, smooth muscle abnormalities and disruption of interstitial cell of Cajal (ICC) networks. GI disturbances caused by autonomic neuropathy can arise as a disabling complication of diabetes. Between 20% and 40% of patients with diabetes mellitus develop dysfunction of the autonomic nervous system (23). Autonomic functions can be evaluated by assessing sudomotor function (e.g., quantitative sudomotor axon reflex tests) and by assessing cardiovascular autonomic reflexes including the heart rate response to deep breathing and the blood pressure/heart rate responses to standing or Valsalva maneuver. While patients with diabetes and gastrointestinal dysmotility often have autonomic dysfunctions, non-gastrointestinal autonomic dysfunctions tests do not necessarily indicate that enteric manifestations are the result of autonomic neuropathy.

Metabolic abnormalities such as hyperglycemia and electrolyte imbalances contribute to the acute disruption of GI motility in patients with diabetes. Clinically, this is most apparent when diabetic ketoacidosis occurs and the typical features of anorexia, nausea, vomiting, or abdominal pain develop. As the acute metabolic derangements are controlled, GI symptoms often resolve. Acute hyperglycemia may cause delayed gastric emptying in both healthy individuals and individuals with diabetes, even when the autonomic nervous system is intact (24,25).

Rapid gastric emptying can be seen in subgroups of patients in the early stages of type 2 diabetes and neuropathy-free type 1 diabetes. Normally the rate of gastric emptying postprandially is tightly regulated, as a result of neural and hormonal feedback triggered by the interaction of nutrients with the upper and lower small intestine. This feedback is caloric load-dependent, relates to the length of small intestine exposed to nutrient, and regulates the overall rate of gastric emptying to about 2 to 3 kcal/min. The presence of nutrients in the small intestine is associated with relaxation of the gastric fundus, suppression of antral contractions, and stimulation of tonic and phasic pyloric contractions. The main hormones involved include cholecystikinin (CCK) from the upper small bowel and glucagon-like peptide-1 (GLP-1), peptide YY (PYY) from the distal small intestine, and amylin from the pancreas (26). In addition to these hormonal feedback mechanisms, there is neural feedback that involves both intrinsic (the enteric nervous system) and extrinsic (the autonomic and central nervous systems) components. Nitric oxide plays a role in the neural feedback pathway.

In diabetes, there is impaired meal-induced relaxation of the gastric fundus, increased pyloric motor activity, fewer antral contractions, and impaired antroduodenal coordination. Glucagon-like peptide (GLP-1) is an enterogastrone that inhibits antral contractility and stimulates pyloric motility both of which contributes to inhibition of gastric emptying and reduce food intake (26)

### **Gastroparesis and Dyspepsia as Hormonal Disorders**

Gastroparesis is a recognized complication of a number of endocrine disorders, particularly DM, but also including hypopituitarism, Addison's disease, hypothyroidism, hyperthyroidism and hyperparathyroidism. Numerous hormones secreted by the gut and adipose tissue, in both the fasted state (e.g. motilin, somatostatin, ghrelin, orexin A and B, melanin concentrating hormone) and in response to a meal (e.g. CCK, PYY, GLP-1, PP, oxyntomodulin, leptin, enterostatin, apolipoprotein AIV, amylin) may influence gastric motor and/or sensory function (26).

In the critically ill, of whom up to 50% have markedly delayed gastric emptying, which frequently causes intolerance of nasogastric feedings, exaggerated humoral inhibitory feedback on gastric emptying is likely to be important in the etiology of gastroparesis. In this group, fasting and nutrient-stimulated CCK and PYY are elevated, while fasting ghrelin is suppressed (27,28). In response to duodenal nutrients, the secretion of CCK and PYY is exaggerated,

particularly in patients with feed intolerance (28). Moreover, the rate of gastric emptying is inversely related to both fasting and postprandial CCK and PYY concentrations, so that levels are higher in those patients who have feed intolerance (28).

Only a limited number of studies have investigated the potential role of GI hormones on symptoms in functional dyspepsia (FD). In FD patients, perceptions of fullness, bloating and nausea induced by duodenal lipid infusion are reduced by concurrent administration of the CCK-1 receptor antagonist, dexloxiglumide (29). There is also evidence that the sensitivity to exogenous CCK-8 may be increased.

### **Gastroparesis and Functional Dyspepsia as Post-Infectious Disorders**

In contrast to the large number of prospective studies demonstrating that IBS can follow an infectious illness (30), only two studies have addressed post-infectious dyspepsia (PI-D). The first involved 677 cases infected with *Salmonella enteritidis* through food contamination (31), new onset dyspepsia was present in 17% of infected individuals at 3 months and 13.4% at 12 months compared with 2.6% among uninfected controls. The risk factors for developing PI-D were vomiting during the acute illness, the duration of pain, and female gender. A second study of infection with *Giardia intestinalis* which affected 1300 people documented ~2% PI-D after infection was eradicated (32); duodenal inflammation persisted, and a subgroup of 22 patients had reduced volume to satiation and delayed gastric emptying (33).

In a cross sectional study of 400 patients with FD, 98 described an acute onset, and 66 of these were presumed post-infectious as they had at least two of the following; fever, myalgia, diarrhoea or vomiting. Early satiety, weight loss and vomiting were significantly commoner in presumed PI-D. Pathophysiology was not significantly different in those with acute vs. non-acute onset except for a ~2 fold higher prevalence of impaired meal-related accommodation in presumed PI-D (34).

The role of common infectious agents in gastroparesis remains controversial. For example, *Helicobacter pylori* infection in the absence of peptic ulceration is asymptomatic and appears unrelated to GI dysmotilities (35,36,37,38,39). While acute *Rotavirus gastroenteritis* is associated with a delay in gastric emptying (39), the effect seems transient (<12 weeks). Similarly, healthy adults, experimentally infected with either the *Norwalk virus* or *Hawaiian virus* develop gastroparesis of unknown duration in about half the cases (40).

Cross-sectional studies of gastroparesis suggests that gastroparesis following acute infection is rare e.g. 7 of 103 cases of gastroparesis were associated with a viral infection (41). Patients had delayed gastric emptying or autonomic dysfunction. Although initially severe with marked weight loss, 5 of 7 recovered within 12 months and 2 showed partial recovery. In another series of 143 patients with idiopathic gastroparesis (42), 12 cases with acute onset showed slow resolution, 4 had antibodies to *Cytomegalovirus* (CMV), 2 to Epstein-Barr virus (EBV) and 6 were not tested. Gastroparesis might represent an autoimmune response to infection. Five individuals have been reported developing an acute onset gastroparesis: 3 following vaccination and 2 after Lyme disease (43).

Future studies are required to take advantage of modern, large scale microbial screening to determine the contribution of infection to the etiology of gastroparesis and FD.

### **Cellular Changes in Gastroparesis and Dyspepsia**

There are very limited data on the cellular pathology of functional dyspepsia. The few studies suggest increased gastric mast cell, eosinophil degranulation and afferent dysfunction (44, 45). However, the data are not robust and have not been replicated. The limited data is most likely due the lack of good animal models and to the need for an invasive procedure to obtain

a full thickness biopsy. Advances in endoscopic approaches to full thickness biopsies may enable such studies in the future (46).

Considerable progress in identifying cellular defects that underlie gastroparesis has been driven by the availability of animal models and by the increased availability of human tissue from the NIH-funded gastroparesis consortium. Cellular defects in gastroparesis are being increasingly recognized (47). These include loss of expression of nNOS (48,49,50), often not accompanied by neuronal loss and therefore potentially reversible (51). The most common cellular defect in gastroparesis is a disruption of ICC networks. Animal models show that loss of ICC is associated with loss of heme oxygenase 1, resulting in increased oxidative stress (52). Re-expression of heme oxygenase results in reversal of the ICC and normalizes gastric emptying suggesting that the loss of ICC is due to loss of heme oxygenase and subsequent increase in oxidative stress is central to the development of these motor abnormalities (52). Smooth muscle dystrophy with fibrosis can occur in severe diabetic gastroparesis and animal models suggest this is due to a decreased insulin and IGF-I availability with subsequent decrease in smooth muscle steel factor release leading to loss of ICC (53). Future studies will be needed at the genomic and protein level to build on the cellular findings, integrate them, as well as correlate the cellular findings with whole organ physiology and symptoms.

### **Visceral Hypersensitivity in Human Dyspepsia: from the Gut to the Brain**

In the absence of a detectable cause for symptoms in the GI tract, enhanced perception of physiological signals arising from the GI tract (“visceral hypersensitivity”) are considered a hallmark of functional GI disorders, including functional dyspepsia (54). In a subset of FD patients such hypersensitivity can be reproduced acutely by different types of mechanical gastric distension (55,56). It has not been possible to conclusively identify the site and mechanisms underlying visceral hypersensitivity in human FD patients, or to establish the translational validity of any animal model for human symptoms. Several functional brain imaging studies using controlled gastric distension have been reported for healthy control subjects and for patients with FD (57). Despite significant variability of results, activation of homeostatic afferent brain circuits in FD patients has been reported. Alterations in attentional mechanisms, in particular an increase in threat-related attention, associated hypervigilance and future-directed symptom related fears of sensations arising from the upper GI tract, have been suggested as important pathophysiological components of functional pain disorders, as well as in anxiety disorders (58).

In order to develop more effective therapies for patients with gastroparesis with and without symptoms of dyspepsia, it is important to clearly distinguish between patients with FD and with gastroparesis, and to better understand the relationship between alterations in gastric emptying, specific symptoms, and altered brain responses to gastric stimuli.

### **Gastroparesis and Functional Dyspepsia - Insights from Animal Models**

The lack of easy access of the enteric nervous system and associated cellular elements putatively involved in the disease process of gastroparesis and functional dyspepsia has necessitated the use of animal models to provide an alternative means to gain insight into these syndromes (47). Beginning with the seminal observation that *Nos1<sup>-/-</sup>* knockout mice develop grossly enlarged stomachs with gastric stasis (59), much animal work in gastroparesis has been focused on the role of this enzyme and its key product, the gaseous neurotransmitter, nitric oxide. Diabetic rodents have consistently shown defects in nitrinergic inhibitory activity and while most studies have examined changes in nNOS expression, recent work has also highlighted post-translational modifications of the enzyme including dimerization (crucial to its activity), and protein-protein interaction (60,61,62,63). These studies may provide insight into the biological basis of clinical phenomena such as the marked gender bias of gastroparesis

as well as identify other important molecules in the maintenance of nitrinergic expression and function such as vagal acetylcholine acting via nicotinic receptors, insulin and the nNOS cofactor, tetrahydrobiopterin (60,63,64).

Animal investigations have also attempted to identify the most important cellular elements involved in gastroparesis. While enteric neuronal loss is an attractive disease mechanism, it has been difficult to demonstrate this in the stomach and indeed recent human studies suggest that this may not be in fact be a significant component of the pathology. By contrast, loss, or phenotypic alteration, of ICC appears to be more important both in experimental models and the human condition (65,66). Finally, defects in smooth muscle function, both global and regional in nature, have also been noted in animal models (67,68). Emerging paradigms suggest cross-talk and linkage of the pathophysiological mechanisms involving these diverse but related cellular elements (53,69).

An important insight gained from animal studies has been the role of inflammation, particularly oxidative stress, in the pathogenesis of some of the above abnormalities. Candidate factors promoting such injury include advanced glycation end-products (AGEs) and their receptor, RAGE (70,71). At the same time, counter-regulatory mechanisms may be impaired, with one example being the loss of gastric macrophage expression of heme-oxygenase 1 (HO-1) activity (52). These findings have implications for novel therapeutic approaches such as hemin (an inducer of HO-1) and other forms of anti-oxidant therapies (52,72).

In contrast to gastroparesis, there is a marked paucity of true animal models of functional dyspepsia. Recently, a rat model, based on the neonatal irritation paradigm, has been described that appears to mimic both the sensory and the motor phenomena associated with human functional dyspepsia (73). It is hoped that further research with this model may provide insight into the molecular basis of this syndrome.

Animal models have been an important part of the research into gastroparesis. However, while it has been relatively simple to model diabetes (type 1 or 2) in rodents and establish gastrointestinal dysfunction, real breakthroughs in terms of identifying valid therapeutic targets has been difficult to date. This is because almost all research with animals has used motor abnormalities (gastric emptying, intestinal transit etc.) as the “read-out”. While these studies have identified key molecules (e.g. nitric oxide) or cell types (e.g. ICC) that mediate gastric motility, little progress has been made in the pathogenesis of the most bothersome symptoms of these syndromes, such as nausea, vomiting and pain, which have been difficult to model in rodents. This hiatus in our knowledge has been highlighted by recent research that emphasizes the poor correlation between gastric emptying and symptoms in patients. Future animal research therefore needs to incorporate relevant measures and outcomes in order for us to make rapid progress in the treatment of these conditions.

## DIAGNOSIS

Assessment of gastric emptying is commonly performed for the evaluation of nausea, vomiting and dyspepsia to assess for delayed gastric emptying. Limitations of this approach include the imperfect correlation of symptoms to rates of stomach emptying, and the relative lack of satisfactory treatments for abnormal gastric emptying. Nevertheless, emptying of triturated content is arguably the most important function of the stomach, and abnormalities associated in either accelerated or delayed emptying may be a marker for the underlying defect in the neuromuscular apparatus of the stomach that gives rise to symptoms (74,75). Of the imaging techniques, scintigraphy is widely available and the standard method for assessing gastric emptying in clinical practice. However, scintigraphy remains expensive and is associated with some radiation exposure. Wireless motility capsule and gastric emptying breath testing are newer noninvasive technologies that allow standardization among centers and these tests can

be performed in a gastroenterology practice. Other techniques, such as ultrasound, single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) are predominantly research tools for evaluating gastric volumes, contractility, gastric distribution of meals, and emptying. Tables 1 and 2 highlight strengths, limitations, and considerations for areas of research.

### **Gastric Emptying Scintigraphy**

Scintigraphic determination of the emptying rate of a solid meal from the stomach is regarded as the standard measurement technique for gastric emptying. Determination of emptying rates of liquid meals is less sensitive and generally reserved for the evaluation of dumping syndrome and post-surgical disorders.

For solid-phase testing, most centers use a  $^{99m}\text{Tc}$  sulfur colloid-labeled egg sandwich as a test meal (76) endorsed by a consensus statement from the ANMS and the Society of Nuclear Medicine (77). Extending scintigraphy to 4 hours improves the accuracy in determining the presence of delayed gastric emptying (78,79). Unfortunately, contrary to the evidence and consensus recommendations, many centers in the United States perform gastric emptying scintigraphy for merely 90 to 120 minutes instead of 4 hours postprandially, which substantially limits the clinical utility of this test (80).

Regional gastric emptying can assess intragastric meal distribution and transit from the proximal to distal portions of the stomach and may provide greater information regarding fundal and antral function (81). Studies have shown an association between symptoms of nausea, early satiety, abdominal distention with proximal gastric retention; whereas vomiting is associated more with delayed distal gastric retention (82,83).

Gastric mucosal labeling with intravenous technetium-99m followed by SPECT imaging allows assessment of gastric volumes. Gastric volumes, especially impaired accommodation, are important factors in symptom production in FD and gastroparesis. With scintigraphy and SPECT imaging, gastric volumes and emptying can be measured simultaneously (84,85) (Table 3).

### **Wireless Capsule Motility for Assessment of Gastric Emptying**

Wireless capsule motility uses an indigestible capsule containing miniaturized wireless sensor technology that measures pH, pressure and temperature as the capsule travels through the digestive tract. Gastric emptying is identified by the abrupt change from the acidic pH profile of the stomach to the alkaline pH of the duodenum. The SmartPill™ GI Monitoring System has been approved by the U.S. Food and Drug Administration (FDA) for the assessment of gastric pH, gastric emptying, and total GI transit time. Gastric emptying by the wireless capsule correlates with the T-90% for gastric emptying (86) better than with the T-50% and appears to empty with the phase III migrating motor complex signifying completion of the postprandial phase and return to the fasting condition (87). Using a 5 hour cutoff for gastric emptying, the capsule discriminated between normal or delayed gastric emptying with a sensitivity of 0.87 and a specificity of 0.92. As the capsule traverses the GI tract, the pH profile of the capsule can be used to measure small bowel and colonic transit (88). In addition, pressure measurements provide information about motor functions of the stomach, small intestine, and colon (89).

### **Gastric Emptying Breath Test**

Another alternative method for assessing gastric function includes the gastric emptying breath test (GEBT) using  $^{13}\text{C}$ , a stable (non-radioactive) isotope. Tests have used either with the eight-carbon saturated fatty acid, octanoic acid or the blue-green algae, *Spirulina platensis*. The  $^{13}\text{C}$  containing substrates empty from the stomach, are absorbed in the small intestine,



undergo catabolism in the liver, enter the body's bicarbonate pool, and then are excreted as  $^{13}\text{CO}_2$  in the breath, where  $^{13}\text{C}$  can be detected by mass spectrometry. The rate-limiting step in this process is the stomach emptying rate (90,91).

There have been numerous studies with simultaneous scintigraphy and breath test validating the breath test to measure gastric emptying. The best validated GEBT (by numbers and spectrum of gastric emptying disorders tested) is the shelf-stable 238 kcal meal consisting of freeze dried egg mix, saltine crackers, water and 100 mg of  $^{13}\text{C}$  *S. platensis* (92). Performance characteristics of this test meal were 89% sensitivity and 80% specificity in identifying delayed gastric emptying utilizing the breath sample values at 150 and 180 minutes, and 93% sensitivity and 80% specificity for identifying accelerated gastric emptying utilizing the breath sample values at 45 and 180 minutes (with scintigraphy as gold-standard). The test is not yet approved by the FDA.

### Ultrasonography: 2D and 3D

Transabdominal ultrasonography represents a relatively simple, non-invasive, inexpensive technique for the assessment of GI motor function. In the stomach, it can assess structural and functional abnormalities. Ultrasonography has now been used to study gastric distension/accommodation (93,94), antral contractility (95,96), mechanical deformation (strain) (97), transpyloric flow (96), and gastric emptying (98,99). Ultrasound (US) is uniquely suited for concurrently measuring antral contractility, pyloric opening, pyloric flow and perhaps gastric emptying (100,101). However, only a handful of centers have studied gastric motility by US, which requires considerable technical expertise.

2D ultrasound (2D-US) provides an indirect measurement of gastric emptying which is determined by quantifying changes in antral area over time (96). A probe is placed over the abdomen and a parasagittal image of the antrum is obtained in the region of the aorta and superior mesenteric vein (98). 2D-US has been used in studies in health and disease and validated in comparison to scintigraphy (98). Diseases have included functional dyspepsia which is frequently associated with increased antral area (both fasting and postprandial) (102), overall delayed gastric emptying with occasionally more rapid 'early' emptying (103), and impaired proximal stomach accommodation (104). In diabetes, both fasting and postprandial antral area are frequently increased (105), proximal stomach area reduced (106) and gastric emptying is delayed in ~50% of patients. 2D ultrasonography provides a simple and straightforward assessment of gastric emptying for clinical purposes. A limitation of 2D measurements of gastric emptying is that the technique uses liquid meals and relies on assumptions about the geometry of the stomach based on a single parasagittal antral image (98). Another limitation, present in all ultrasonographic techniques, is the inability of imaging through air.

3D ultrasonography offers the ability to assess intragastric meal distribution that is often disordered in functional dyspepsia and gastroparesis (24). Studies using 3D ultrasonography have confirmed that both fasting and postprandial antral volumes are increased in functional dyspepsia (94,107). Gastric accommodation, as assessed by changes in the ratio of the total/proximal gastric volume, are decreased in functional dyspepsia compared to healthy subjects (94,108) and assessment of proximal gastric volumes by 3D ultrasonography correlates closely with measurements made with the gastric barostat (94). While 3D ultrasonography provides much more information about gastric pathophysiology than 2D ultrasonography, it is a time-consuming technique that requires the skill of an experienced operator and relatively expensive equipment.

## MRI Assessment of GI Function

Magnetic resonance imaging (MRI) of GI function has been used in the past by only a handful of researchers but it is now rapidly developing and may soon be a clinically relevant tool. Once hindered by abdominal motion and long acquisition times, with the development and optimization of ultra-fast echo-planar MRI (109,110), researchers have gained the ability to acquire images of the body in a fraction of a second, thereby overcoming motion artifacts and moving organs. This has allowed several aspects of GI function to be imaged in real time. MRI provides detailed insights on anatomy and allows gaining complementary information about the tissues and the composition of gut contents. Multiple parameters can be assessed in subjects delineating gastric contents and measuring gastric volumes and emptying. Gastric emptying measurements using MRI were validated against simultaneous double marker indicator technique (111,112), and gamma scintigraphy for a liquid (112,113) and mixed solid/liquid meal (113). MRI measures gastric volumes with acceptable performance characteristics with good reproducibility (114,115).

MRI of GI function has recently started to be applied to the field of gastroparesis and functional dyspepsia and the effects of pharmacological intervention especially in diabetic gastroparesis. A study that assessed 10 gastroparesis patients (who received a 400 ml high caloric pudding) found reduced antral wave propagation speed and motility index (calculated as a product of velocity and deepness of contraction) in the gastroparesis group compared to 10 healthy volunteers (116). Intersubject and intrasubject variability in 8 functional dyspepsia and 8 healthy controls (106) showed excellent reproducibility between days in both groups in terms of meal volumes and gastric emptying times.

Gastric volumes measured by MRI and ultrasound are lower and more realistic than those measured by a barostat because the former do not distend the stomach (117,118). MRI has better temporal and spatial resolution and has been validated but less widely used than SPECT (114). In addition to measuring total gastric volume, MRI has the unique ability to discriminate between gastric air and fluid, and therefore assess gastric emptying and secretion concurrently. Rapid MRI imaging sequences can assess gastric contractility. MRI can also visualize intestinal fluid and caliber (119).

The advantages of functional GI MRI are high imaging speed, high image resolution, richness of contrast, three-dimensional coverage of the abdomen and spectroscopic capability to provide localized information on metabolites. MRI can also measure other parameters of pathophysiological interest such as intragastric distribution of food, intragastric flow, and intragastric dilution by secretion, as well as parameters reflecting gallbladder function, blood flow to the gut (110,112). It is 'patient-friendly', non-invasive and safe, thus allowing serial, dynamic studies and it can acquire many different parameters within a single session. Patients can be asked to score symptoms during the scans allowing direct comparison with the MRI parameters measured. However, MRI does have limitations. It is not suitable for patients with metal implants or a large body frame. The study is conducted supine, data processing is still a burden, there is a lack of standardization, and MRI scan time is expensive.

## PATIENT MANAGEMENT

Treatment is targeted at reducing symptoms, correcting fluid, electrolyte, and nutritional deficiencies along with correcting the precipitating cause, if possible (1).

### Nutrition Assessment and Dietary Treatment

There are no prospective, randomized controlled trials comparing dietary treatments in patients with gastroparesis. A low fat, low fiber diet of small portions and frequent feedings are often recommended. This is based on studies that demonstrate fat slows emptying in normal

volunteers. Fiber is limited due to the presumption that these patients are at risk for bezoar formation (120,121). Smaller, frequent meals are recommended as large volumes slow gastric emptying aggravating the early satiety often seen. Patients are also advised to chew foods well since the antrum's grinding capability is altered. Patients should remain upright in an effort to use of gravity to move food from fundus to antrum in order to decrease reflux after meals (122).

Unintentional weight loss is the most obvious marker of nutritional compromise. Five percent loss of usual body weight (UBW) over 3 months or 10% loss over 6 months is indicative of severe malnutrition (123). It is important to compare the patient's *usual* body weight with their *current* actual weight. An important consideration for this patient population when assessing weight changes is hydration status, particularly those admitted after several days of vomiting, diarrhea, or in diabetic ketoacidosis. An often overlooked patient population at high risk for gastroparesis is chronic hemodialysis patients. Weight fluctuations can occur in relationship to the dialysis sessions – either hemodialysis or peritoneal dialysis.

Oral nutrient drinks are often used for dietary supplementation. The clinician needs to be aware that many enteral formulas on the market also contain fructooligosaccharides which many patients may not tolerate.

In the malnourished patient, enteral feeding options may need to be considered for nutritional support. Nutrition support should be considered in patients who experience significant unintentional weight loss of 5–10% over 3–6 months respectively, have been unable to achieve the weight goal identified by the healthcare team, require gastric decompression, or have repeated hospitalizations for hydration, nutrition medication delivery (124).

Enteral feedings are given into the small intestine to bypass the dysfunctional stomach. Although various facilities have their favorite feeding modality (percutaneous endoscopic gastrostomy/jejunostomy, nasogastric-jejunal tube, surgical or laparoscopic jejunostomy, or both a gastrostomy *and* jejunostomy), there has yet to be a prospective controlled trial that demonstrates superiority of one over the other. In patients suspected as having dysmotility in the small bowel or colon, a 48 hour nasojejunal feeding trial to determine if enteral feedings are tolerated may be prudent prior to endoscopic or surgical placement. Venting gastrostomies have been successful in reducing hospitalizations for some patients (124). Some experts refute the benefit of gastric venting asserting that it may delay the recovery of gastric motility, but no data exists to support this concept.

During initiation of enteral feeding, some recommend strict 'nothing to eat' (NPO) status for at least the first 48 hours. This allows separating enteral intolerance from oral intolerance if problems with enteral infusions develop. Formula selection should begin with a standard polymeric, non-fiber containing formulas as fiber may cause or increase in gas, bloating and cramping. In those patients at risk for refeeding syndrome (125), caloric infusions are started slowly at 20 calories/kg until potassium, phosphorous, and magnesium, in particular, stabilize. Jejunal feeding is often given overnight so oral intake can continue as tolerated during the day. If diarrhea occurs with enteral feeding, medications should be reviewed, especially liquid formulations, as they often contain sugar alcohols such as sorbitol that may cause osmotic diarrhea. If the diarrhea continues, patients should be evaluated for *C. difficile* colitis and small intestinal bacterial overgrowth. Once infectious agents are ruled out, gut-slowing medications can be tried. If a fiber-containing formula is used, switching to one without fiber may prove beneficial. Other changes in the enteral formulation have been tried to decrease the enteral feeding-induced diarrhea. Modifying the enteral feeding regimen (e.g. dilution) may resolve the diarrhea which may be from the hyperosmolar nutrient fluid. In a subset of patients, the infusion rate can also be reduced with an increase in the concentration of the formula so total

calories per day do not change very much. In diabetic patients, careful control of glucose is important for two reasons: to maximize utilization of nutrients, and to avoid further aggravation of gastroparesis from hyperglycemia (126). Wide swings of glucose are especially problematic. Total parenteral nutrition should be reserved only for those patients who have failed an enteral feeding trial with several formulas.

There is a paucity of prospective, randomized clinical trials in the area of nutrition intervention in patients with gastroparesis. The clinician is left using presumptions of GI function based on trials of single meals or nutrients in normal patients or in small heterogeneous populations of patients with gastroparesis along with his or her best clinical judgment and the patient's preferences and overall goals.

## Treatment

Treatment has several goals: restoration of hydration, nutrition (enteral route being preferable), correction of electrolyte, glycemic imbalances, reducing vomiting with antiemetic agents, enhancing gastric emptying with prokinetic agents, and pain relief without narcotics. Recent reviews provide algorithms on the use of treatments based on severity of symptoms, degree of delay of gastric emptying, and ability to maintain hydration and nutrition by oral route (127, 128). Treatment must include not only relief of symptoms, but also restoration of nutritional status.

Initial treatment of diabetic gastroparesis should focus on blood glucose control. Even with mild symptoms, gastroparesis interferes with nutrient delivery to the small bowel and disrupts the relationship between glucose absorption and exogenous insulin administration. This may result in wide swings of glucose levels and unexpected episodes of postprandial hypoglycemia. Gastroparesis should be suspected in diabetic patients with erratic glucose control. It may, in its most troublesome form, cause chronic nausea and anorexia, punctuated by bouts of prolonged emesis requiring hospitalization for dehydration and uncontrolled hyperglycemia. Inexplicably, symptoms are variable and may fluctuate markedly over a period of weeks to months (129).

Drugs with anticholinergic potential that may further decrease gastric emptying should be reduced or withdrawn. Of particular concern, is the increased use in the treatment of diabetes of drugs that mimic or modify incretins which slow gastric emptying and may aggravate symptoms of gastroparesis. For example, amylin delays gastric emptying. Exenatide, a mimetic of GLP-I used in treatment of type II diabetes, delays gastric emptying. In contrast, inhibitors of the enzyme dipeptidyl peptidase 4 (DPP-4), which break down GLP-I, do not delay gastric emptying nor reduce food intake (130).

Oral metoclopramide and domperidone are useful in the treatment of gastroparesis (131,132). Domperidone and metoclopramide are equally effective in reducing symptoms of diabetic gastroparesis, particularly nausea and vomiting. However, adverse CNS effects are more severe and more common with metoclopramide, e.g. somnolence and reduction in mental acuity (132). Metoclopramide is available intravenously and useful for hospitalized patients. In February 2009, the FDA announced that manufacturers of metoclopramide must add a boxed warning to their drug labels about the risk of its long-term or high-dose use. Chronic use of metoclopramide has been linked to tardive dyskinesia, which may include involuntary and repetitive movements of the body. Domperidone is not approved, but it can be obtained by filing for an investigational new drug application to the FDA and obtaining local IRB approval. Some compounding pharmacies in the United States provide domperidone. The maximum dose should be no more than 20 mg QID.

Erythromycin, besides being an antibiotic, is a motilin receptor agonist. The effect of erythromycin in gastroparesis involves two different pathways activating motilin receptors on cholinergic neurons and muscle. It is the most effective i.v. prokinetic agent. Unfortunately, erythromycin is associated with tachyphylaxis, probably by 4 weeks of oral treatment (133).

Despite some initial enthusiasm for intrapyloric botulinum toxin injection into the pylorus (134,135), randomized, controlled trials of intrapyloric botulinum toxin type A showed little efficacy for relief of symptoms (136,137).

Endoscopic therapy or surgical procedures are mainly indicated for establishing venting gastrostomy or feeding jejunostomy or for the implantation of a gastric electrical stimulator. Feeding jejunostomy or venting gastrostomy tubes in upper GI motility disorders reduces hospitalization rate by factor of 5 during the year after placement (124). Enterra gastric electric stimulation is approved for humanitarian use device. The literature documents that Enterra gastric electric stimulation therapy leads to improvement in symptoms, reduced need for nutritional support documented in open-label studies of idiopathic, diabetic and postsurgical gastroparesis. The mechanism of symptom relief is unclear as gastric emptying, in many patients, is unchanged.

In some instances, near-total gastrectomy may be helpful for severe postsurgical gastric stasis with reduction in nausea, vomiting, and postprandial pain (127).

New experimental treatments include the following

- a. *New motilides*: Mitemincin enhances gastric emptying and postprandial glycemic control. The best subgroup to use mitemincin is unclear. Poor responders include obese diabetic patients with poor glucose control. Paradoxically, response rates were higher in patients with non-delayed gastric emptying than for those with delayed gastric emptying (138,139).
- b. *Ghrelin and ghrelin receptor agonists*: There is evidence that pharmacological doses of ghrelin accelerate gastric emptying and improve symptoms (140,141). Contraction of proximal stomach may conceivably aggravate postprandial symptoms.
- c. *5-HT<sub>4</sub> agonists*: Prucalopride and TD-5108 both accelerate gastric emptying and have dose selectivity for 5-HT<sub>4</sub> receptors over hERG channel and other receptors (142, 143,144,145). Prucalopride has recently been approved in Europe for chronic constipation. Neither agent has been tested in gastroparesis or dyspepsia.
- d. *Acotiamide*: Acotiamide (Z-338) is a muscarinic M1/M2 receptor antagonist that enhances acetylcholine release, may enhance gastric accommodation, and is associated with improvement of dyspeptic symptoms (146).
- e. *Iberogast* is a herbal preparation of nine herbs. Although more studies are needed, initial studies of Iberogast show promise in treatment of dyspeptic symptoms and for gastroparesis (147,148,149).

Future treatments may include stem cell transplantation, including of enteric nerves and ICCs (150). Transplanted neural stem cells survive in the pyloric wall of nNOS knockout mice, improve gastric emptying by increasing relaxation of the pyloric muscle through NO-dependent and neurally-mediated action.

### Management of Pain in Gastroparesis and Functional Dyspepsia

Pain often has been neglected in the management gastroparesis. In the only publication strictly focusing on pain in gastroparesis, the prevalence of pain [89%] was similar to that of nausea [93%] and early satiety [86%] and was greater than that of vomiting [68%] (151). Other case

series of gastroparesis report prevalence rates of pain ranging from 46 to 71% (2,152) and more than 90% of affected individuals state their pain is of moderate to severe intensity (152). Abdominal pain has variable characteristics as reported by patients with gastroparesis. Pain was characterized as crampy, burning, or vague in character and localized to the epigastrium in only 36% of cases (151). Meals exacerbated symptoms in 80% but provided relief in 15% of patients. Up to 80% of gastroparetic patients experienced some pain at night (151). Using the Patient Assessment of GI Symptoms [PAGI-SYM], upper abdominal pain scores in patients with gastroparesis averaged 2.21 on a scale from 0 to 5 (153). This value was similar to conditions more classically associated with pain including dyspepsia [2.27].

A limited number of investigations have addressed the underlying causes of pain in gastroparesis. The prevalence of pain has been found to be similar in symptomatic individuals with normal emptying compared to those with modest or severe degrees of gastric retention (152,154), or in patients with impaired gastric fundic accommodation (152). The prevalence of pain is higher in those with heightened perception of gastric distention versus those with normal sensation (152).

To date, no investigation has targeted pain relief in gastroparesis. Pain may be relieved through the prokinetic effect of drugs (155). Uncontrolled series with prokinetic treatments including cisapride, levosulpiride, domperidone have observed decreases in pain that closely track reductions in traditional symptoms of gastroparesis such as nausea, vomiting, and fullness (155,156). Studies of the effects of gastric electrical stimulation on pain in gastroparesis have yielded conflicting results (157,158,159). Other medication classes for treatment of pain including tricyclic and tetracyclic antidepressants and pain modulators such as gabapentin and pregabalin exhibit beneficial effects in reducing chronic abdominal pain of varied etiologies, but their effects on gastroparesis pain are unknown. These agents can also help improve nausea and vomiting. Investigations focusing on the specific effects of these and other treatment modalities on pain in gastroparesis are warranted.

Multiple mechanisms may be involved in the pathogenesis of visceral pain. A drug that selectively targets a specific mechanism may not be able to resolve pain alone. Severe visceral pain in gastroparesis may need to be managed in a multidisciplinary approach. Various approaches are available (160,161) including the following: 1) targeting coexistent dysmotility problems; 2) targeting inflammatory response; 3) targeting peripheral receptors and neuromodulators; 4) targeting central circuits; 5) targeting somatic hypervigilance and related conditions; and 6) targeting of all of the above. Table 4 provides a summary of the characteristics of some commonly used agents.

Careful use of opiates may need to be considered for treatment of pain in selected cases. The weak opiate agonist tramadol, which can also affect serotonin and norepinephrine reuptake, appears to be a reasonable first choice. The new kappa agonist asimadoline may become a good choice in this group of medications (162).

Antiepileptic agents have not been widely used in visceral pain, except for the gabapentinoids. Although each agent has different mechanisms of action, they all have some common features which include: sodium channel blockade, inhibition of glutamatergic transmission, and increasing GABA concentration. These agents have much less effect on GI motility and could be very valuable therapeutic options.

Acupuncture and biofeedback can also be very helpful in these conditions, and with few side effects (163,164). Possible future directions include the increased use of ketamine, dorsal cord stimulators, and repetitive transcranial magnetic stimulation (165).

## Gastric Electrical Stimulation Therapy

Gastric pacing uses high energy/low frequency to stimulate gastric slow waves at a frequency just above the intrinsic gastric slow wave frequency using a long pulse duration (300 milliseconds) system. Gastric pacing presently requires using external pulse generators due to the amount of energy required (166).

The clinical use of gastric electric stimulation (GES) as a possible treatment option for patients with gastroparesis was based on the experimental work performed by Familoni et al in the 1990's in animals and humans (167). These studies showed that electrical stimulation with a higher frequency than the intrinsic gastric slow wave frequency (3 cycles/min in humans) and shorter pulse duration (300 microseconds) improved nausea and vomiting, and also enhanced gastric emptying. However, these observations have not been confirmed or reproduced.

To date only one double-blind study (WAVESS study) evaluated the efficacy of the high frequency/low energy GES in patients with gastroparesis (157). Parameters used in this study were stimulation frequency of 12 cycles/minute, with 0.1 seconds 'on' and 5 seconds 'off' and trains of 14 Hz pulse frequencies with 5 mA strength. This study included 33 patients (17 diabetic and 16 idiopathic) who were initially subjected to 1 month each of stimulation ('ON' phase) or sham stimulation ('OFF' phase) in a double blinded phase of the study. GES achieved a significant reduction in weekly vomiting frequency and the majority patients preferred the ON month. In the next 12 months, 80% of patients reported a >50% improvement in vomiting and quality of life. While the majority of patients had improvement in gastric emptying, it still had not returned to normal. Based on the results of this study, the FDA approved this Enterra gastric electric stimulation therapy under the Humanitarian Device Exemption in April 2000 for patients with diabetic and idiopathic gastroparesis as a Human Use Device. Currently in the US, over 3,500 devices have been placed over the last 9 years.

Apart from this double-blind trial, all of the published literature on the efficacy of GES consists of open-label studies mainly from centers with substantial experience with this device. Follow-up data has been reported for periods of up to years after implanting the device which show improvement in symptoms over many years (166,168,169). Early improvement in symptoms in the first 3–6 months after placement of the device predicts a long term control of symptoms over many years. This open-label experience suggests that GES also improves quality of life, reduces requirement for health care utilization, improves glycemic control in diabetics, reduces dependence on enteral or parenteral nutrition and also improves nutritional status. A recent double-blind trial with GES in diabetic gastroparesis has been completed: GES produced a relatively rapid decrease in gastroparetic symptoms initially but the subsequent double blind crossover phase showed that GES ON was not significantly better than OFF (170). The mechanism of action of GES is an area of research that requires more attention.

Some of the complications related to GES placement include intestinal obstruction from the intraabdominal stimulating wires, infection of the pulse generator pocket site, pain, erosion of the pulse generator through the abdominal wall, and rarely detachment and/or displacement of the electrodes with possible penetration of the leads through the stomach wall into the lumen. About 5% of the devices have had to be removed due to these complications over a 5–10 year followup.

Alternative approaches are being explored and constitute exciting refinements that need to be fully validated:

- a. **Long-pulse and high-energy stimulation** with physiological frequencies (3 cycles/min) to achieve gastric pacing. In this method, the electrical stimulus is composed of repetitive single pulses with a pulse width in the order of milliseconds (10–600 ms),

and a stimulation frequency in the vicinity of the physiological frequency of the gastric slow wave.

- b. **Single-channel GES** with a pair of electrodes located in the mid-body of the stomach and using long pulses. This method is able to normalize gastric dysrhythmia and may improve gastric emptying in both patients with gastroparesis and animal models of gastroparesis.
- c. **Two or four-channel GES with long pulses** has been investigated and the preliminary results from several studies in both healthy and diseased canine models are promising. The results in patients with severe diabetic gastroparesis indicated that two-channel gastric pacing at 1.1 times the intrinsic frequency (pulse width: 10 to 300 ms and pulse amplitude: 0.5 to 3 mA) entrained gastric slow waves and normalized gastric dysrhythmia (171). After 6 weeks of GES, tachygastria was decreased, mean total symptom score was reduced and mean 4-hour gastric retention improved.
- d. **Temporary GES** can be performed with endoscopic placed stimulating wires or via a percutaneous approach. Temporary GES placed with upper endoscopy, has recently been developed. In a recent FDA IDE trial, 58 patients were randomized into the OFF/OFF and ON/OFF groups (172). Symptom improvement was rapid when the stimulator was ON and persisted even after the stimulator was turned OFF in the second half of the study. Improvement in gastric emptying was greater with permanent compared with temporary GES (173). Endoscopic mucosal EGG may predict who will respond to GES, and may help assess baseline neuromuscular status and predict response to permanent GES. Based on temporary GES, predictors of improvement in vomiting score after permanent GES include: younger patient age, higher baseline vomiting score and lower ratio of frequency to amplitude of mucosal EGG (174). Endoscopic temporary GES may be a useful screening tool to select patients likely to respond to permanent stimulation and to individualize stimulus parameters. Cross over device trials can be a problem as enteric remodeling occurs rapidly. GES may also be applicable to other non-gastroparetic disorders with nausea and vomiting.

## FUTURE TRENDS IN RESEARCH AND PATIENT CARE

### The NIH Gastroparesis Consortium

The NIDDK Gastroparesis Clinical Research Consortium (GpCRC) is a unique network of six clinical centers and one Data Coordinating Center (DCC) that are geared to further advance the understanding and management of gastroparesis. The Gastroparesis Clinical Research Consortium works cooperatively to conduct clinical research to elucidate the pathophysiology and develop better treatments for gastroparesis. The Gastroparesis Registry is the largest, well-characterized cohort of patients with gastroparesis with approximately 500 patients whom will be followed longitudinally. Treatment trials are also underway for idiopathic gastroparesis and diabetic gastroparesis.

### The National Commission on Digestive Diseases

The recent National Commission on Digestive Diseases report includes recommendations on future research for Digestive Diseases. The chapter on Functional Gastrointestinal Disorders and Motility Disorders presents relevant research goals to gastric motility disorders which include understanding the molecular and cellular events, the components and functional interactions of the peripheral (autonomic and enteric) and central nervous systems, peripheral and central pain and sensory pathways, noxious visceral signaling and the bi-directional brain-gut interactions; the factors in diabetes that lead to the development of GI and motility diseases and developing new technologies and therapeutic approaches to effectively treat patients with functional GI and motility disorders.



## Clinical Trials in Gastroparesis

Entry criteria for gastroparesis trials generally depend on gastric emptying and symptoms. Often there is a minimum level of symptom severity for entry. Gastric emptying tests are generally used in clinical trials for gastroparesis to determine eligibility criteria for patients to enter the study. Generally any delay in gastric emptying, which defines gastroparesis, is used. Using moderate to severe gastric emptying may allow better correlation of symptoms to gastric emptying but may cause difficulty in recruitment of these patients. The gastric emptying test result at enrollment could also serve as a covariate in analysis of symptom response to treatment.

The Gastroparesis Cardinal Symptom Index (GCSI) was developed as a patient reported outcome (PRO) measure of gastroparetic symptoms and was based on patient interviews, clinician recommendations and medical literature. The GCSI contains 9 symptoms covering three areas: nausea/vomiting (3 items); bloating (2 items); fullness/early satiety (4 items). The response scale is based on the symptom severity over the prior two weeks with responses from “none” (0) to “very severe” (5). The total score is the average of 3 subscale scores and ranges from 0 to 5. The GCSI has been used in treatment trials: gastric electric stimulation; botulinum toxin injection into the pylorus; and trials with prokinetic and antiemetic agents. For responsiveness to treatment of the GCSI, often a decrease in 0.5 is used.

To minimize patient recall effects using a two week symptom period, a GCSI daily diary (GCSI-DD) was developed (177). Qualitative interviews in patients with gastroparesis confirmed that the symptoms addressed in the GCSI are the main symptoms relevant to patients with gastroparesis. The daily diary form of the GCSI captures daily variability of those symptoms, and has psychometric properties consistent with a good PRO endpoint for gastroparesis clinical trials.

There is an overlap of the symptoms in patients with FD and patients with idiopathic gastroparesis. Generally, patients with FD have more abdominal pain whereas patients with idiopathic gastroparesis have more nausea and vomiting. The symptoms in the GCSI do not include abdominal pain, which would be more suggestive of FD.

Some have suggested the gastric emptying test also be performed during a treatment trial with the patient on treatment at the end of the study. This result often serves as a secondary endpoint. Further studies are needed to address whether a composite endpoint using both symptoms and gastric emptying provides additional value to assess patient outcomes in trials.

Areas that need to be explored in future studies include:

- Understanding differences between the spectrum of symptoms in idiopathic and diabetic gastroparesis patients.
- Appreciation that within the FD patient population up to 40% may have slow gastric emptying and therefore qualify for the term idiopathic gastroparesis. Differentiation between FD with delayed gastric emptying and idiopathic gastroparesis may be difficult and may need to be explored.
- The validity of gastric emptying measurement in the enhancement of clinical trials assessing symptoms in gastroparesis: eligibility criterion, covariate, secondary endpoint or as part of a composite endpoint with GCSI daily diary or other symptom instrument
- The identification of the predominant or most bothersome symptom as a primary or secondary endpoint in treatment trials of gastroparesis.

## Stem Cells and Regenerative Medicine as a Therapeutic Option

Although cell loss affecting the enteric nervous system, ICC and smooth muscle cells occurs in several GI neuromuscular disorders including diabetic and idiopathic gastroparesis (53, 178,179,180,181), current therapeutic strategies do not specifically target the cellular deficit. Recent advances in regenerative medicine promise to open new avenues for restoring tissue integrity in these disorders.

Stem cells (SC) can be defined functionally as uncommitted cells capable of asymmetric cell divisions resulting in daughter cells identical to their mother (self-renewal) and progeny that, through a series of increasingly more committed progenitors, culminate in terminally differentiated cells (182). The differentiation potential of SC is closely related to their developmental state. Differentiated cells can be experimentally reprogrammed into pluripotent SC and thus, theoretically, an infinite source of patient-specific replacement cells could be created (182).

The goal of regenerative medicine is to exploit SC for tissue repair or replacement. Besides restoration of tissue function by integration, SC can be used for the engineering of complex tissues/organs or as vehicles to deliver trophic, immunoregulatory, anti-inflammatory or angiogenic signals, as well as genetic material (183,184). Endogenous SC could also be activated by pharmacological treatment to improve tissue function (184). Key cell types of the GI muscle layers differ considerably in their ability to regenerate and may require different therapeutic strategies for repopulation. For example, ICC have considerable regenerative capacity and thus their networks could potentially be regenerated by pharmacological stimulation of their local progenitors recently identified in postnatal murine gastric muscles (185). In contrast, regeneration of enteric neurons is markedly limited and thus likely requires exogenous sources of replacement cells such as gut-derived neural crest SC (186), neural SC derived from the fetal central nervous system (187), or gut-like structures obtained from embryonic SC (188).

SC-based therapies promise to treat the root cause of degenerative and congenital GI neuromuscular disorders. Pioneering studies have laid the foundations for future progress. However, for the ultimate goal to be realized, the focus of research should shift from purely observational to mechanistic studies.

## SUMMARY

This review from the AGA/ANMS meeting on gastroparesis and functional dyspepsia has covered salient aspects in the present understanding of the epidemiology, pathophysiology, diagnosis, and treatment of gastroparesis and functional dyspepsia. In addition, this review has discussed unmet needs and some directions for future research are suggested. These disorders, gastroparesis and functional dyspepsia, are areas of active investigation because they are common, the current therapy is suboptimal, and existing treatments have not been well studied. A combination of approaches, i.e., basic research, clinical investigation, and controlled clinical trials will likely be needed to consolidate recent advances and to improve management of patients with these conditions.

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**Table 1**

## Comparison of Methods Used to Assess Gastric Emptying

	<b>Scintigraphy</b>	<b>Breath test</b>	<b>Capsule</b>
Mechanisms of gastric emptying	Antral motor activity	Antral motor activity	Antral motor activity and migrating motor complex activity
Validation Studies	Extensive	Modest	Modest
Radiation exposure	Yes	No	No
Reproducibility (CV%)	Inter – 24% intra – 12%	Inter - 24% intra - 12%	Not studied
Limitations for testing	None	Malabsorption, liver failure, pancreatic/ pulmonary disease	Obstruction
Assessment of antral contractility	Feasible	No	Yes
Assessment of small bowel and colonic transit	Yes	No	Yes

CV% - percentage coefficient of variation

Inter and intra – inter- and intra-individual coefficient of variation

**Table 2**

## Considerations for Future Research in Gastric Imaging Techniques

Scintigraphy	Categorization of patients with discrepant gastric emptying at 2 and 4 hours, utility of evaluating symptoms during GE, assessing gastric motility by dynamic scintigraphy
Gastric emptying breath test	Evaluate accuracy in malabsorption, bacterial overgrowth, pancreatic insufficiency, and COPD
Wireless Capsule Motility (SmartPill pH-pressure capsule)	Evaluate relationship between antral contractility and gastric emptying
Ultrasound	Extend availability to other centers
MRI	Validate MRI for studying mechanical properties, validate MRI versus manometry for evaluating gastric contractility and assess gastric contractility in disease.

**Table 3**

## Strengths and Limitations of Imaging Techniques for Measuring Gastric Volumes

Technique	Strengths	Limitations
SPECT	Extensively validated Can be combined with scintigraphy to assess gastric emptying	Radiation exposure Limited temporal and spatial resolution
Ultrasound	No radiation Can also assess antral contractility and pyloric flow	Presence of air may limit visualization, especially in the fundus Highly operator-dependent
MRI	No radiation Validated Can also assess gastric air and fluid volumes, contractility, secretion, and emptying	Expense and limited availability

**Table 4**

Effect of therapeutic agents used to treat pain in gastroparesis on receptors

	Neurotransmitter transporter blockade potency				Receptor blockade potency			
	NE	5-HT	DA	HI	Ach-musc.	Alpha 1-adrenergic	5-HT 2 and 3	
Amitriptyline	++	++++	+/-	+++++	++++	+++	0	
Desipramine	++++	++	+/-	++	++	++	0	
Venlafaxine	++	++++	+/-	+/-	+	0	0	
Duloxetine	++++	+++++	+	+/-	+/-	+/-	0	
Mirtazapine	+++	+++	0	++++	++	++	+++	