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Nausea and Vomiting in Gastroparesis: Similarities and Differences in Idiopathic and Diabetic Gastroparesis

The NIDDK Gastroparesis Clinical Research Consortium (GpCRC)*

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Abstract

Nausea and vomiting are classic symptoms of gastroparesis. It is unclear if characteristics of nausea and vomiting are similar in different etiologies of gastroparesis. **Aims:** Describe characteristics of nausea and vomiting in patients with gastroparesis; and determine if there are differences in nausea and vomiting in diabetic (DG) and idiopathic gastroparesis (IG). **Methods:** Gastroparetic patients enrolling in the NIDDK Gastroparesis Registry underwent assessment

with history and questionnaires assessing symptoms, quality of life, and a questionnaire characterizing nausea and vomiting. **Key Results:** Of 159 gastroparesis patients (107 IG, 52 DG), 96% experienced nausea while 65% experienced vomiting. Nausea was predominant symptom in 28% and vomiting was predominant in 4%. Nausea was severe or very severe in 41%. PAGI-SYM nausea/vomiting subscore was greater with increased vomiting severity, but not nausea severity in DG than IG. Nausea was related to meals in 71%; lasting most of the day in 41%. Increasing nausea severity was related to decreased quality of life. Nausea often preceded vomiting in 82% of patients and vomiting often relieved nausea in 30%. Vomiting was more common in DG (81%) compared to IG (57%; p=0.004). Diabetic patients more often had vomiting in the morning before eating, during the night, and when not eating. **Conclusions & Inferences:** Nausea is present in essentially all patients with gastroparesis irrespective of cause and associated with decreased quality of life. In contrast, vomiting was more prevalent, more severe, and occurred more often in DG than IG. Thus, characteristics of vomiting differ in idiopathic versus diabetic gastroparesis.

Keypoints

- Nausea and vomiting are classic symptoms in patients with gastroparesis. Most studies combine nausea and vomiting into one symptom complex; there may be different characteristics relating to nausea as compared vomiting. There may be different characteristics of these symptoms in diabetic compared to idiopathic gastroparesis.
- Nausea is present in essentially all patients with gastroparesis irrespective of cause. Nausea is associated with decreased quality of life in patients with gastroparesis. Vomiting was more prevalent, more severe, and occurred more often in diabetic compared to idiopathic gastroparesis.
- The characteristics of vomiting differ in idiopathic versus diabetic gastroparesis.

Introduction

Nausea and vomiting are classic symptoms in patients with gastroparesis (1). While most patients experience some degree of nausea, only some gastroparesis patients have vomiting with some studies suggest vomiting is seen in less than 50% of patients with gastroparesis (2). Studies have suggested that nausea and vomiting symptoms correlate with worse quality of life in gastroparesis patients (3,4). Despite the importance of nausea and vomiting in gastroparesis, the characteristics of these symptoms have not been well described.

Nausea and vomiting may have different manifestations in different etiologies of gastroparesis. Some studies have suggested that nausea and vomiting are more severe in diabetic gastroparesis (DG) than idiopathic gastroparesis (IG) (3,4,5). Most studies combine nausea and vomiting into one symptom complex; there may be different characteristics relating to nausea as compared vomiting. There may be different characteristics of these symptoms in diabetic compared to idiopathic gastroparesis. The potential differential perception of nausea in diabetic versus idiopathic gastroparesis might be due to different pathophysiological mechanisms as well as the effects of diabetes on neuronal function. This has important treatment implications for nausea and vomiting in patients with diabetic and idiopathic gastroparesis.

The aims of this study were to describe characteristics of nausea as compared to vomiting in patients with gastroparesis and determine if there are differences between two etiologies of gastroparesis - DG and IG. We also aimed to better understand the relationship between nausea and vomiting in gastroparesis, determine if nausea and vomiting impact on the impaired quality of life in gastroparesis, and investigate the relationship of nausea and vomiting with gastric emptying.

Methods

Overview

The NIDDK Gastroparesis Clinical Research Consortium is a cooperative network of eight academic motility centers and one Data Coordinating Center (DCC) (5,6). The Gastroparesis Registry 2 (ClinicalTrials.gov Identifier: NCT01696747) was implemented as an observational study of patients with gastroparesis enrolled prospectively at eight centers. This study uses data from the second gastroparesis registry (GpR2), which was designed, in part, to enhance the understanding of symptoms and physiologic dysfunction in patients with

gastroparesis. There was a special emphasis to look at the symptoms of nausea and vomiting through a Nausea and Vomiting Questionnaire which was designed to assess the clinical characteristics of both nausea and vomiting.

Study Patients

Gastroparetic patients were enrolled at 8 centers into the NIH Gastroparesis Registry from September 2012 to August 2015. Enrolled patients met specific entry criteria being 18 years or older with symptoms of at least 12 weeks duration, delayed gastric emptying scintigraphy (GES) within 6 months of enrollment, and no structural abnormality as seen by upper endoscopy within one year of enrollment.

This report focuses on patients with either idiopathic or diabetic gastroparesis. The diabetic patients could have either Type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) as defined by the physician and/or patient. The diagnosis of patients with the idiopathic etiology was based on no previous gastric surgery, no diabetes history (before or after the onset of gastroparesis at enrollment), a normal hemoglobin $A1_C$, and no other known etiologies.

All studies were approved by the Institutional Review Board at each Clinical Center and at the Data Coordinating Center.

Study Protocol

During face-to-face interviews with each subject, the study physicians or coordinators at each Clinical Center completed case report forms including data relating to gastroparesis disease onset, symptoms, disease profile, associated medical conditions, including diabetes, and medication and supplemental therapies. The study physicians performed a comprehensive physical examination. Laboratory measures were obtained, including hemoglobin $A1_C$ values, antinuclear antibody (ANA), and erythrocyte sedimentation rate (ESR).

The clinical severity of gastroparesis was graded on a scale originally proposed by Tack et al and reported in the American Neurogastroenterology and Motility Society (ANMS) review on treatment of gastroparesis (7). The severity was graded as grade 1: mild gastroparesis (symptoms relatively easily controlled and able to maintain weight and nutrition on a regular diet); grade 2: compensated gastroparesis (moderate symptoms with only partial control with use of daily medications, able to maintain nutrition with dietary adjustments); grade 3: gastroparesis

with gastric failure (refractory symptoms that are not controlled as shown by the patient having ER visits, frequent doctor visits or hospitalizations and/or inability to maintain nutrition via an oral route).

Each patient filled out the 20 item Patient Assessment of Upper Gastrointestinal Symptoms (PAGI-SYM) questionnaire which assesses symptoms of gastroparesis, dyspepsia, and gastroesophageal reflux disease (8); it includes the nine symptoms of the Gastroparesis Cardinal Symptom Index (GCSI) which asks about nausea, retching, vomiting, stomach fullness, inability to finish a meal, excessive fullness, loss of appetite, bloating, and abdominal distension (9). The GCSI equals the mean of the nausea/vomiting subscore, postprandial fullness/early satiety subscore, and bloating subscore where: Nausea/vomiting subscore = mean of the scores for nausea, retching, and vomiting; Postprandial fullness/early satiety sub-score = mean of the scores for stomach fullness, inability to finish meal, excessive fullness, and loss of appetite; and Bloating subscore = mean of the scores for bloating and large stomach. The PAGI-SYM also inquires about symptoms of gastroesophageal reflux including daytime heartburn, heartburn lying down, daytime chest discomfort, nighttime chest discomfort, daytime reflux, nighttime reflux, and bitter taste. In the PAGI-SYM, patients are asked to assess the severity of their symptoms during the previous two weeks using a 0 to 5 scale where no symptoms = 0, very mild = 1, mild = 2, moderate = 3, severe = 4, and very severe = 5.

Disease-specific quality of life was assessed by the Patient Assessment of Upper Gastrointestinal Disorders Quality of Life (PAGI-QOL) survey, which scores 30 factors from 0 (none of the time) to 5 (all of the time) (10). Patients were asked how often gastrointestinal problems they may be experiencing have affected different aspects of their quality of life and well-being in the past two weeks. Overall PAGI-QOL scores were calculated by taking means of all subscores after reversing item scores; thus a mean PAGI-QOL score of 0 represents poor quality of life while 5 reflects the best life quality.

The Medical Outcomes Study 36-Item Short-Form Health Survey version 2 (SF-36v2) was additionally used to assess the patients' views of overall physical and mental health in the past 4 weeks (standard recall form). The 8 subscales were standardized to the 1998 U.S. general population with a mean (±SD) of 50±10. Physical and mental health summary measures were computed. A higher score reflects higher quality of life (11).

A Nausea and Vomiting Questionnaire was designed to assess the clinical characteristics of both nausea and vomiting. Part of this questionnaire is a modification of the Nausea Profile characterizing nausea in three dimensions: somatic distress, GI distress, and emotional distress (12). This questionnaire had previously been modified for capturing nausea related to gastroparesis (3).

Gastric Emptying Scintigraphy

Gastric emptying scintigraphy was performed using a low-fat, egg white meal with imaging at 0, 1, 2, 4 hours after meal ingestion, as described by a published multicenter protocol (13) and endorsed by the Society of Nuclear Medicine and ANMS (14). This protocol ensures standardized information about gastric emptying across sites. In addition, liquid gastric emptying in the presence of solids was assessed using Indium-111 (15).

Patients were instructed to stop medications that could affect gastrointestinal motility for the 72 hours prior to the study and to come to the Nuclear Medicine Section in the morning after fasting overnight with nothing to eat after midnight, that is, an 8 hour fast. Gastric emptying scintigraphy was performed using a standard low-fat, Eggbeaters® meal to measure solid emptying (13,14). The meal consisted of the equivalent of two large eggs radiolabeled with Tc-99m sulfur colloid served with two pieces of white bread and jelly. In addition, patients were given 120 ml water radiolabeled with In-111 DTPA (diethylene triamine pentacetic acid) for the measurement of liquid gastric emptying. Following ingestion of the meal, imaging was performed at 0, 1, 2, 3 and 4 hrs with the patient upright for measuring gastric emptying of Tc-labeled solids and 111-In-labeled liquids. In between imaging, patients generally sat in the nuclear medicine waiting area.

Gastric emptying was analyzed as the percent of radioactivity retained in the stomach over time using the geometric center of the decay-corrected anterior and posterior counts for each time point. Gastric retention of Tc-99m >60 % at 2 hrs and/or >10% at 4 hrs was considered evidence of delayed gastric emptying of solids. Delayed gastric emptying was graded according to the gastric retention at 4 hours: mild (≤20% gastric retention at 4 hours), moderate (>20 to 35%), and severe (>35%) (14,16). Delayed gastric emptying of liquids in the presence of solids is greater than 50% retention of In-111 at 1 hr emptying (15).

Statistical Methods

Descriptive statistics (means, standard deviations, frequencies, and percentages) were used to compare subgroups of gastroparesis patients. Enrollment characteristics such as demographics, medical history, gastroparesis history, symptom severity, and quality of life were compared by etiology (idiopathic compared to diabetic). P-values were determined from Fisher's exact tests for categorical variables and t-tests for continuous variables. Enrollment characteristics were also compared by the subgroups of nausea severity score on the PAGI-SYM instrument (none/very mild/mild, moderate, and severe/very severe) and the subgroup of vomiting severity score on the PAGI-SYM instrument (none, very mild/mild/moderate, and severe/very severe). P-values were determined from a Cochran-Armitage test for trend in nausea or vomiting subgroups for binary variables, a Mantel-Haenszel chi-square test for trend in nausea or vomiting subgroups for categorical variables, and a non-parametric Cuzick test for trend in nausea or vomiting subgroups for continuous variables (17). Multiple logistic models were selected based on Akaike Information criteria (AIC) using forward selection of all possible models derived from a candidate set of 16 enrollment variables (see table 1) (18,19). The resulting model for severe nausea included etiology, age, solid gastric emptying percent at 4 hours, PAGI-SYM satiety/fullness sub-score, SF-36 mental score, SF-36 physical score, and PAGI-QOL score. The resulting model for severe vomiting included etiology, age, race, PAGI-QOL score, HbA1c%, and the following PAGI-SYM measures: satiety/fullness sub-score, bloating sub-score, and GERD sub-score. All p-values are two-sided; values <0.05 were considered statistically significant. Analyses were performed using methods described in SAS version 9.3 (SAS Institute) or Stata version 13.1 (StataCorp) (20).

Results

Patient characteristics

159 patients with gastroparesis were evaluated: 107 patients with idiopathic gastroparesis and 52 patients with diabetic gastroparesis (35 with T1DM, 17 with T2DM). Average age was 44.7±13.3 years. Females comprised the majority of patients (84.9%). Table 1 contains other demographic information. The majority of patients had compensated (grade 2) gastroparesis (66.0%) with moderate severity of symptoms of gastroparesis (GCSI score of 2.7±1.1). However, 13.8% of patients were graded as having gastric failure with 27.7% of these patients

having been hospitalized within last year. Symptoms prompting evaluation for gastroparesis included nausea (30.2%), vomiting (14.5%), and abdominal pain (22.0%). At the time of enrollment in the registry, the predominant symptoms were nausea in 27.7% of patients, upper abdominal pain in 13.2% and vomiting in 4.4% of patients. Antinausea medications were being used by 81.1% of the patients, prokinetics agent use in 35.2%, and narcotic analgesics by 36.5%. Other treatments included gastric electric stimulator in 9.4% of patients, use of G tube in 1.9%, use of J tube in 1.9%, and presence of a central line in 2.7%. Overall the gastric emptying was moderately delayed with 30.0% retention at 4 hours, being more delayed in diabetic gastroparesis (37.1% retention) than idiopathic gastroparesis (26.5% retention; p=0.0009). For the diabetic patients, the average HgbA1c was 8.3±2.0% with 53.9% of the diabetic patients having HgbA1c $\geq$8.0%. There was a decreased quality of life in the patients with gastroparesis most prominently with the SF-36 physical score being 33.7 compared to normal of 50.

Nausea/Vomiting severity using PAGI-SYM

Table 1 compares the PAGI-SYM symptom severity between diabetic and idiopathic patients. The nausea/vomiting subscore of the PAGI-SYM (average of nausea, retching, and vomiting severity) was greater in diabetic (2.3±1.5; p=0.006) than idiopathics (1.6±1.2) with increased vomiting severity in diabetic (1.9±1.8; p=0.0001) than idiopathic (0.9±1.4) and increased retching severity in diabetics (1.8±1.7) than idiopathic (1.1±1.5; p=0.01). Nausea severity was not different between IG and DG (3.0±1.6 for diabetic vs 2.9±1.6 for idiopathic (p=0.64).

Table 2 shows characteristics of patients with gastroparesis according to their nausea severity as assessed using the PAGI-SYM. Nausea severity was severe or very severe in 65 of 159 (41%) patients (42 of 107 [40%] IG and 23 of 52 [45%] IG; p=0.77). The severity of retching and vomiting increased as nausea severity increased. The severity of other symptoms of gastroparesis also tracked with the severity of nausea: satiety/fullness subscore (p<0.0001), bloating subscore (p=0.002), upper abdominal pain subscore (p<0.0001), and GERD subscore (p=0.03).

Increasing nausea was related to decreased quality of life by PAGI-QOL (p=0.005), especially in the activity subscore (p<0.001), diet subscore (p=0.005), and relationship subscore

(p=0.01). Increasing nausea was associated with decreased quality of life using the SF-36: SF-36 physical (p=0.01) and mental (p=0.03) measures.

There was a trend for increasing antiemetic use (p=0.04) and narcotic use (p=0.06) with increasing nausea severity. In the diabetic patients, there were similar HgbA1c values across the different severities of nausea.

Severe or very severe nausea patients had increased gastric retention at 4 hours on the gastric emptying scintigraphy test (34.6% retention for severe/very severe compared to 23.5% for moderate, and 29.5% none/mild; p=0.09). Severity of nausea was not related to retention of liquids (p=0.36).

Table 3 shows characteristics of patients according to their vomiting severity. Vomiting was present at the time of enrollment in 75 of 159 patients (48%), being present more often in diabetic gastroparesis (65%) than in idiopathic gastroparesis (38%; p=0.002). Percentage wise, more patients with diabetic gastroparesis (11 of 52 or 21%) had severe/very severe vomiting compared to idiopathic gastroparesis (12 of 107 or 11%; p=0.15). As expected, increasing retching and nausea severity were seen with increasing vomiting severity. Increasing vomiting severity tracked with other symptoms of gastroparesis; satiety subscore (p<0.001), bloating subscore (p=0.002), upper abdominal pain subscore (p<0.001), and GERD subscore (p=0.03). Increasing vomiting severity was associated with worsening quality of life on the PAGI-QOL (p=0.005), especially activity (p<0.001), relationship (p=0.01) subscores. Increasing vomiting was associated with decreased SF-36 physical component (p=0.01) and mental component (p=0.03). In diabetic patients, HgbA1c tended to be higher in those with more severe vomiting (9.0±1.9%), but the trend was not significant (p=0.81). Use of prokinetic agents, antiemetic agents, and narcotic analgesics increased with increasing vomiting severity. Retention at 4 hours on gastric emptying scintigraphy differed, but not statistically significantly, in the vomiting severity subgroups (p=0.09): with 39.8% retention in those with severe/very severe vomiting, compared to 26.6% retention for those with mild/moderate vomiting, and 29.4% retention for those with no vomiting.

We further looked at the relationship of gastroparetic symptoms with delayed gastric emptying (Supplemental Table 1). Gastric retention at 4 hours was greater in diabetic than idiopathic gastroparesis. More patients with diabetic gastroparesis had severe gastric retention than idiopathic gastroparesis. Stomach fullness and postprandial fullness, but not nausea and

vomiting, were significantly increased with increasing gastric retention at 4 hours using symptoms captured at enrollment. We also collected symptoms at time of the gastric emptying test. As with surveys obtained on enrollment, symptom severities measured at the time of the gastric emptying test showed no significant relation of nausea or vomiting to gastric retention rates. Increasing stomach fullness was associated with increasing gastric retention. Use of antiemetics, but not prokinetic or narcotic analgesics, was associated with more severe retention during gastric emptying testing.

The gastroparesis patients were also compared according to the 2 and 4 hr gastric emptying data by dividing the patients in three groups: 1) Delayed at 2 hr, normal at 4 hr; 2) Delayed at 2 hr, delayed at 4 hr; and 3) Normal at 2 hr, delayed at 4 hr. The severity of nausea, retching, early satiety and upper abdominal pain were similar among these groups.

Most patients had nausea. There were 24 patients scoring no nausea on the PAGI-SYM, 84 patients with no vomiting on the PAGI-SYM, and 23 patients with no nausea or vomiting. Using the nausea and vomiting form, there were 6 with no nausea, 56 with no vomiting, and 6 with no nausea or vomiting. The patients with no nausea or vomiting on the PAGI-SYM had a higher BMI than patients with nausea and/or vomiting (32±11 vs 27±7; p=0.004). There were also significantly less other gastroparesis symptoms on the PAGI-SYM including satiety subscore (2.3±1.4 vs 3.5±1.1; p<0.0001) and upper abdominal pain (1.8±1.8 vs 3.0±1.4; p=0.001). There were similar percentages of diabetic/idiopathic patients and similar percent retention at 2 hours and 4 hours between these two groups.

Logistic regression analysis was used to look at independent predictors of nausea and vomiting severity (Tables 4 and 5). Severe/very severe nausea according to the PAGI-SYM was associated with younger age, increased satiety subscore, decreased mental SF-36 score, and decreased SF-36 physical score (Table 4). Severe vomiting was associated with non-white race, increased satiety subscore, decreased bloating subscore, and increased GERD subscore (Table 5).

Characteristics of nausea/vomiting

The characteristics of nausea and vomiting are shown Supplemental Table 2. Overall 153 of 159 patients (96.2%) experienced nausea as a symptom (97.2% of idiopathics and 94.2% of diabetic patients). The nausea was lasting most of the day (41.2%) or at least several hours of the day (27.5%); whereas in 31.4% of the patients, the nausea lasted for about an hour or less.

Nausea was related to meals in 71.2%, but felt by patients to be unrelated to eating in 28.8%. Nausea was worse in the morning before eating in 27.5% of patients and worse in the evening in 26.1% of patients. Other factors that were related to increasing nausea included high fat meals (44.4% of patients), dairy (32.0% of patients), being hungry (26.3%), riding in a car (25.7%). There were no significant differences in these characteristics of nausea between patients with diabetic gastroparesis and idiopathic gastroparesis. Nausea increasing during or after meals tended to be more frequently reported by IG (52.4%) compared to DG (32.7%; p=0.06).

The nausea profile was compared between patients with idiopathic and diabetic gastroparesis. The total nausea profile was not significantly different between idiopathic and diabetic patients (46.4 vs 46.5; p=0.99); with similar values for the somatic, GI distress, and emotional distress subscales

The characteristics of vomiting are also shown in Table 6. Overall 64.8% of patients experienced vomiting as a symptom, being experienced more in diabetic (80.8%) compared to idiopathic patients (57.0% of idiopathic patients; p=0.004). Vomiting lasted for several minutes in 51.0% of patients, about 30 minutes to several hours in 32.4%, and most of the day in 16.7% of patients; tending to be more prolonged in diabetic than idiopathic patients (p=0.11). Vomiting often was related to eating (72.8% of patients), being unrelated to eating in 27.2%. The vomitus was described as partial digested food in 45.4% or undigested food in 34.0%. Vomiting occurred in the morning before eating more often in diabetic (69.0%) than idiopathic patients (44.3%; p=0.04). The vomiting could wake patients up at night in 55.4% of patients, being more prevalent in DG than IG (p=0.02). Nausea often preceded vomiting in 81.6% of patients; whereas vomiting often relieved nausea in 30.1%. Vomiting could occur even if no food or drink was take in 35.0% of patients, being more common in diabetic (45.2%), then idiopathic patients (27.9%; p=0.008).

Discussion

This study has carefully detailed the characteristics of both nausea and vomiting in patients with gastroparesis; two important, and often considered classical symptoms of gastroparesis. This study finds that nausea is present in nearly all (96%) patients with gastroparesis. Nausea was the predominant symptom in 28% of the patients, the most common of the single individual symptoms. Nausea was present for many hours in the majority of

patients. The characteristics of nausea (severity, timing) were similar in diabetic and idiopathic patients. Vomiting was present in approximately half the patients but was considered the predominant symptoms in only a small percentage (4%) of the patients. In contrast to nausea, vomiting was more prevalent and severe in diabetic than in idiopathic gastroparesis.

This study documents the decreased quality of life in patients with gastroparesis. The SF-36 physical score was 33.7 compared to normal of 50. There was less effect on the mental quality of life with SF-36 of 42.4. Increasing nausea and vomiting were both related to decreased quality of life using the disease specific instrument PAGI-QOL. Using logistic regression analysis, nausea severity, but not vomiting severity, was independently associated with the SF-36 QOL scores. Thus, gastroparesis has an increased clinical burden as demonstrated objectively by decreased quality of life, and nausea severity is associated with this decreased quality of life. Other smaller studies have shown that nausea and vomiting symptoms are associated with impaired quality of life (3,4), but this study importantly separates the characteristics of nausea and vomiting.

Nausea was present in nearly all patients with gastroparesis, irrespective of the etiology. Nausea was generally present for many hours in the majority of patients. The characteristics of nausea (severity, timing) were similar in diabetic and idiopathic patients. In contrast, vomiting was less prevalent, being present in roughly half of patients with gastroparesis, with significant differences in the characteristics of vomiting among the diabetic and idiopathic patients. Vomiting was more common and more severe in patients with diabetic than idiopathic gastroparesis. Interestingly, diabetic patients more often had vomiting occurring in the morning before eating, during the night, and could occur even if the patient did not eat. Clinically, many patients state they do not want to vomit and limit their intake and change diet so that do not have vomiting. On the other hand, some patients find that vomiting helps to relieve the nausea. Our prior study also suggested that nausea and vomiting were more severe in diabetic than idiopathic gastroparesis (21). This study expands this by showing it is the vomiting characteristics that appear to be different between diabetic and idiopathic gastroparesis with the nausea being somewhat similar between the two. The vomiting data was assessed by PAGI-SYM and our nausea and vomiting questionnaire. In the PAGI-SYM, vomiting severity is graded by the patient. More recent measures of vomiting have assessed the frequency and duration of vomiting episodes, instead of the severity of vomiting. Future studies should take these aspects into

consideration in assessing vomiting severity. We did not find a relationship of worsening glucose control in diabetic patients with different severities of nausea or with vomiting. Autonomic dysfunction sometimes present in diabetic patients may be related to the presence of vomiting. Vagal and non-vagal pathways as well as several brainstem nuclei participate in vomiting in response to different emetic stimuli (22). Physiologic differences between idiopathic and diabetic gastroparesis may relate to worse vagal impairments in diabetics (23,24).

Each of the symptoms of the nausea/vomiting subscore (nausea, retching, vomiting) tracked with each other. In addition, increasing nausea and increasing vomiting were related to increasing satiety/fullness subscore and upper abdominal pain; this is not surprising as these are the symptoms of gastroparesis. Satiety severity associated with nausea severity suggests a vagal neuropathy as a possible cause. We also found that as nausea and vomiting increased, there was an increased use of antiemetic agents as expected but also the use of narcotic analgesics. Narcotics can delay gastric emptying as well as cause nausea and vomiting as a side effect. Our study demonstrates a relationship of narcotics with symptoms but not with delayed gastric emptying. The relation of narcotic analgesics with nausea might be related to the central effects of opiates rather than their peripheral effects in slowing gastric emptying.

The results of the study show that nausea and vomiting severity varies by gastric emptying but are not linearly related. Our study showed increased severity of nausea among severely delayed gastric emptying. However, the statistical trend test for both nausea and vomiting showed no significant systematic relationship with gastric emptying ($p=0.09$ for both). In a previous study from our GpCRC, we did not show a significant relationship between nausea severity and delay of gastric emptying (25). The current study included assessment of gastric emptying using liquids as well; however, we found that the liquid results were consistent with the solid results— we did not find a relationship between retention of liquids and symptom severity of nausea or vomiting. The symptom assessment at enrollment was not on the same day as the gastric emptying test (median separation of 13 days, IQR 0-95 days); however, even when symptoms at the time of gastric emptying were assessed, only stomach fullness, but not nausea or vomiting, appeared to be associated with increasing delay in gastric emptying.

In conclusion, this study demonstrates that nausea and vomiting are important symptoms of gastroparesis. The severity of nausea is related to the decrease in quality of life that is present in patients with gastroparesis. Characteristics of nausea appeared similar between diabetic and

idiopathic gastroparesis. Vomiting, however, was more prevalent and severe in DG than in IG, occurred more often in the morning in DG, during the night and when not eating. Thus, although characteristics of nausea appear to be similar between diabetic and idiopathic gastroparesis, the characteristics of vomiting differ in idiopathic versus diabetic gastroparesis. Symptoms of nausea and vomiting are important symptoms that need to be specifically addressed, perhaps individually, in treating patients with gastroparesis.

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Table 1: Characteristics of patients with idiopathic or diabetic gastroparesis

Characteristic	Etiology		Total (n=159)	p-value*
	Idiopathic (n=107)	Diabetic (n=52)		
Demographics				
Gender: females	97 (90.7%)	38 (73.1%)	135 (84.9%)	0.008
Age (years)	43.6 ± 14.0	46.9 ± 11.8	44.7 ± 13.3	0.14
Hispanic	9 (8.4%)	13 (25.0%)	22 (13.8%)	0.007
Race: white	98 (91.6%)	42 (80.8%)	140 (88.1%)	0.07
Gastroparesis history				
Duration of symptoms (years)	6.0 ± 6.5	8.1 ± 7.8	6.7 ± 7.0	0.08
Onset of gastroparesis symptoms				0.50
Acute	46 (43.0%)	20 (38.5%)	66 (41.5%)	
Insidious or gradual	59 (55.1%)	32 (61.5%)	91 (57.2%)	
Predominant symptom prompting gastroparesis evaluation				0.26
Nausea	37 (34.6%)	11 (21.2%)	48 (30.2%)	
Vomiting	15 (14.0%)	8 (15.4%)	23 (14.5%)	
Abdominal pain	24 (22.4%)	11 (21.2%)	35 (22.0%)	
Other	31 (29.0%)	22 (42.3%)	53 (33.3%)	
Nature of gastroparesis symptoms:				0.70
Chronic, but stable	20 (18.9%)	6 (11.5%)	26 (16.5%)	
Chronic, but progressive worsening	22 (20.8%)	11 (21.2%)	33 (20.9%)	
Chronic, but some improvement	10 (9.4%)	8 (15.4%)	18 (11.4%)	
Chronic with periodic exacerbations	37 (34.9%)	17 (32.3%)	54 (34.2%)	
Cyclic pattern	16 (15.1%)	9 (17.3%)	25 (15.8%)	

Asymptomatic	1 (0.9%)	1 (1.9%)	2 (1.3%)	
Gastroparesis severity:				0.47
Mild (grade 1)	20 (18.7%)	12 (23.1%)	32 (20.1%)	
Compensated (grade 2)	74 (69.2%)	31 (59.6%)	105 (66.0%)	
Gastric failure (grade 3)	13 (12.2%)	9 (17.3%)	22 (13.8%)	
Weight history				
BMI (kg/m^2)	26.5 ± 8.2	29.3 ± 6.7	27.4 ± 7.8	0.03
Medical history				
Diabetes				
Type 1		35 (67.3%)		
Type 2		17 (32.7%)		
Hospitalization for gastroparesis in the past year	22 (20.6%)	22 (42.3%)	44 (27.7%)	0.004
Number of hospitalizations for gastroparesis in the past year	2.4 ± 1.7	7.0 ± 11.0	4.7 ± 8.2	0.06
Use of G tube	3 (2.8%)	0 (0.0%)	3 (1.9%)	0.55
Use of J tube	2 (1.9%)	1 (1.9%)	3 (1.9%)	1.00
Presence of central line	0 (0.0%)	4 (7.7%)	4 (2.7%)	0.01
Presence of gastric stimulator	5 (4.7%)	10 (19.2%)	15 (9.4%)	0.007
Use of prokinetics	34 (31.8%)	22 (42.3%)	56 (35.2%)	0.19
Use of Botox (ever)	28 (26.2%)	19 (36.5%)	47 (29.6%)	0.20
Use of antinausea medications	87 (81.3%)	42 (80.8%)	129 (81.1%)	1.00
Use of narcotics	87 (35.5%)	20 (38.5%)	58 (36.5%)	0.72
Use of alternative medications	53 (49.5%)	12 (23.1%)	65 (40.9%)	0.002
PAGI-SYM symptom severity (0-5) ¶				
Nausea score	2.9 ± 1.6	3.0 ± 1.6	2.9 ± 1.6	0.64
Vomiting score	0.9 ± 1.4	1.9 ± 1.8	1.2 ± 1.6	0.0001
Retching score	1.1 ± 1.5	1.8 ± 1.7	1.4 ± 1.6	0.01
Nausea sub-score	1.6 ± 1.2	2.3 ± 1.5	1.8 ± 1.4	0.006
Satiety sub-score	3.3 ± 1.2	3.3 ± 1.3	3.3 ± 1.2	0.88
Bloating sub-sore	3.1 ± 1.6	3.0 ± 1.7	3.0 ± 1.6	0.88

Cardinal symptom index (GCSI)	2.7 ± 1.1	2.9 ± 1.1	2.7 ± 1.1	0.27
Upper abdominal pain sub-score	2.8 ± 1.6	2.8 ± 1.5	2.8 ± 1.5	0.93
GERD sub-score	1.8 ± 1.3	1.8 ± 1.5	1.8 ± 1.4	0.89
Predominant symptom of PAGI-SYM				0.15
Nausea	31 (29.0%)	13 (25.0%)	44 (27.7%)	
Vomiting	5 (4.7%)	2 (3.9%)	7 (4.4%)	
Upper abdominal pain or discomfort	18 (16.8%)	3 (5.8%)	21 (13.2%)	
Other	53 (49.5%)	34 (65.4%)	87 (54.7%)	
PAGI-QOL (0-5) §				
Activity sub-score	2.6 ± 1.2	2.9 ± 1.2	2.7 ± 1.2	0.29
Clothing sub-score	2.9 ± 1.7	3.0 ± 1.9	2.9 ± 1.7	0.58
Diet sub-score	1.6 ± 1.3	2.2 ± 1.4	1.8 ± 1.3	0.006
Relationship sub-score	3.4 ± 1.2	3.3 ± 1.5	3.3 ± 1.3	0.56
Psychology sub-score	3.3 ± 1.3	3.1 ± 1.5	3.2 ± 1.4	0.39
Total PAGI-QOL	2.8 ± 1.0	2.9 ± 1.3	2.8 ± 1.1	0.47
SF-36v2 Health Survey (past 4 weeks) ‡				
Physical health summary measure	33.7 ± 9.7	33.8 ± 11.4	33.7 ± 10.2	0.94
Mental health summary measure	43.0 ± 13.5	41.1 ± 13.8	42.4 ± 13.6	0.41
Solid gastric scintigraphy				
Percent retention at 1 hour	79.3 ± 13.8	80.8 ± 12.6	79.8 ± 13.3	0.51
Percent retention at 2 hours	63.0 ± 16.3	64.7 ± 19.0	63.6 ± 17.2	0.58
Percent retention at 4 hours	26.5 ± 16.5	37.1 ± 22.3	30.0 ± 19.1	0.0009
Liquid gastric scintigraphy				
Percent retention at 30 minutes	63.1 ± 17.3	68.6 ± 17.4	65.0 ± 17.4	0.19
Percent retention at 1 hour	49.1 ± 16.6	50.8 ± 19.7	49.7 ± 17.6	0.66

Data are means ± standard deviations or number (percents).

^Nausea/vomiting severity is a subscale from the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM). It is the average of the nausea, retching, and vomiting severity scores.

*The significance of difference in categorical variables between groups was tested with a chi-square test or Fisher's exact test. Continuous variables were analyzed with a t-test. All P values are two-sided.

§ Subscales derived from the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL). Scales have been recoded so that a higher score reflects a higher QOL.

‡ Scores on the Medical Outcomes Study 36-Item Short-Form Health Survey V2 (SF-36v2) standard recall were normalized to the 1998 U.S. general population with a mean (±SD) of 50±10. A higher score reflects higher QOL or better health outcome.
¶ Subscales derived from the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM). A higher score reflects a greater severity.

Table 2: Characteristics of patients with idiopathic or diabetic gastroparesis by nausea severity

	Nausea severity on PAGI-SYM^				
Characteristic	None/Very mild/Mild (n=51)	Moderate (n=43)	Severe/Very Severe (n=65)	Total (n=159)	p-value*
Etiology					0.77
Idiopathic	34 (66.7%)	31 (72.1%)	42 (64.6%)	107 (67.3%)	
Diabetic	17 (33.3%)	12 (27.9%)	23 (35.4%)	52 (32.7%)	
Demographics					
Gender: females	45 (88.3%)	35 (81.4%)	55 (84.6%)	135 (84.9%)	0.62
Age (years)	48.3 ± 13.8	43.0 ± 13.4	41.0 ± 12.1	44.7 ± 13.3	0.001
Hispanic	11 (21.6%)	3 (7.0%)	8 (12.3%)	22 (13.8%)	0.18
Race: white	49 (96.1%)	38 (88.4%)	53 (81.5%)	140 (88.1%)	0.02
Gastroparesis history					
Nature of gastroparesis symptoms:					0.95
Chronic, but stable	10 (19.6%)	7 (16.3%)	9 (14.1%)	26 (16.5%)	
Chronic, but progressive worsening	6 (11.8%)	11 (25.6%)	16 (25.0%)	33 (20.9%)	
Chronic, but some improvement	11 (21.6%)	4 (9.3%)	3 (4.7%)	18 (11.4%)	
Chronic with periodic exacerbations	15 (29.4%)	13 (30.2%)	26 (40.6%)	54 (34.2%)	
Cyclic pattern	7 (13.7%)	8 (18.6%)	10 (15.6%)	25 (15.8%)	
Asymptomatic	2 (3.9%)	0 (0.0%)	0 (0.0%)	2 (1.3%)	
Gastroparesis severity:					<0.0001

Mild (grade 1)	22 (43.1%)	3 (7.0%)	7 (10.8%)	32 (20.1%)	
Compensated (grade 2)	27 (52.9%)	34 (79.1%)	44 (67.7%)	105 (66.0%)	
Gastric failure (grade 3)	2 (3.9%)	6 (14.0%)	14 (21.5%)	22 (13.8%)	
Medical history					
BMI (kg/m^2)	27.8 ± 8.8	28.3 ± 6.4	26.5 ± 7.9	27.4 ± 7.8	0.30
Use of prokinetics	14 (27.5%)	17 (39.5%)	25 (38.5%)	56 (35.2%)	0.24
Use of antiemetics	37 (72.6%)	35 (81.4%)	57 (87.7%)	129 (81.1%)	0.04
Use of narcotics	15 (29.4%)	13 (30.2%)	30 (46.2%)	58 (36.5%)	0.06
Laboratory results					
HbA1c, if diabetic (%)	8.3 ± 2.0	8.2 ± 2.4	8.3 ± 1.8	8.3 ± 2.0	0.91
HbA1c≥8.0%, if diabetic	11 (64.7%)	5 (41.7%)	12 (52.2%)	28 (53.9%)	0.48
ANA negative, if idiopathic	26 (76.5%)	29 (93.6%)	36 (85.7%)	91 (85.1%)	0.30
ESR, if idiopathic	15.6 ± 13.0	15.3 ± 10.3	12.8 ± 12.6	14.4 ± 12.0	0.28
ESR elevated>30mm, if idiopathic	6 (17.7%)	4 (12.9%)	2 (5.0%)	12 (11.4%)	0.09
PAGI-SYM symptom severity (0-5)¶					
Nausea score	0.9 ± 0.9	3.0 ± 0.0	4.4 ± 0.5	2.9 ± 1.6	<0.001
Vomiting score	0.4 ± 0.9	1.2 ± 1.3	1.9 ± 1.9	1.2 ± 1.6	<0.001
Retching score	0.4 ± 0.8	1.3 ± 1.2	2.1 ± 1.8	1.4 ± 1.6	<0.001
Nausea/vomiting sub-score	0.5 ± 0.7	1.8 ± 0.7	2.8 ± 1.2	1.8 ± 1.4	<0.001
Satiety/fullness sub-score	2.5 ± 1.3	3.3 ± 0.9	3.9 ± 1.0	3.3 ± 1.2	<0.001
Bloating sub-sore	2.4 ± 1.8	3.2 ± 1.4	3.4 ± 1.5	3.0 ± 1.6	0.002
Cardinal symptom index (GCSI)	1.8 ± 1.0	2.8 ± 0.7	3.4 ± 0.8	2.7 ± 1.1	<0.001
Upper abdominal pain sub-score	2.0 ± 1.7	2.7 ± 1.2	3.4 ± 1.4	2.8 ± 1.5	<0.001
GERD sub-score	1.4 ± 1.4	2.1 ± 1.3	2.0 ± 1.4	1.8 ± 1.4	0.03
Predominant symptom from the PAGI-SYM					0.08
Nausea	2 (3.9%)	12 (27.9%)	30 (46.2%)	44 (27.7%)	
Vomiting	1 (2.0%)	1 (2.3%)	5 (7.7%)	7 (4.4%)	
Upper abdominal pain or	6 (11.8%)	4 (9.3%)	11 (16.9%)	21 (13.2%)	

discomfort					
Other	42 (82.4%)	26 (60.5%)	19 (29.2%)	87 (54.7%)	
PAGI-QOL (0-5) §					
Activity sub-score	3.2 ± 1.1	2.6 ± 1.1	2.3 ± 1.2	2.7 ± 1.2	<0.001
Clothing sub-score	3.2 ± 1.8	2.8 ± 1.5	2.8 ± 1.9	2.9 ± 1.7	0.27
Diet sub-score	2.3 ± 1.5	1.7 ± 1.2	1.5 ± 1.2	1.8 ± 1.3	0.005
Relationship sub-score	3.7 ± 1.3	3.2 ± 1.3	3.1 ± 1.3	3.3 ± 1.3	0.01
Psychology sub-score	3.4 ± 1.3	3.3 ± 1.2	2.9 ± 1.5	3.2 ± 1.4	0.09
Total PAGI-QOL	3.2 ± 1.1	2.7 ± 1.0	2.5 ± 1.1	2.8 ± 1.1	0.005
SF-36v2 Health Survey (past 4 weeks) ‡					
Physical health summary measure	36.3 ± 10.9	34.4 ± 9.8	31.3 ± 9.5	33.7 ± 10.2	0.01
Mental health summary measure	44.7 ± 13.5	44.1 ± 12.9	39.4 ± 13.7	42.4 ± 13.6	0.03
Solid gastric scintigraphy					
Percent retention at 2 hours	63.6 ± 17.2	59.7 ± 15.6	66.2 ± 18.0	63.6 ± 17.2	0.27
Percent retention at 4 hours	29.5 ± 19.8	23.5 ± 14.2	34.6 ± 20.4	30.0 ± 19.2	0.09
Percent retention at 4 hours, diabetic patients only	37.1 ± 26.7	32.7 ± 19.3	39.5 ± 20.7	37.1 ± 22.3	0.33
Percent retention at 4 hours, idiopathic patients only	25.7 ± 14.4	20.0 ± 9.9	31.9 ± 20.0	26.5 ± 16.5	0.17
Liquid gastric scintigraphy					
Percent retention at 30 minutes	64.1 ± 16.9	67.3 ± 14.8	63.8 ± 20.0	65.0 ± 17.4	0.83
Percent retention at 1 hour	49.2 ± 19.0	52.2 ± 13.6	48.1 ± 19.4	49.7 ± 17.6	0.36

Data are means ± standard deviations or number (percents).

^Nausea severity is a score from the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM).

*The significance of difference in binary variables between groups was tested with a Cochran-Armitage trend test, the significance of difference in categorical variables between groups was tested with a Mantel-Haenszel chi-square test, and the significance of difference in continuous variables between groups was tested with a non-parametric Cuzick test for trend. All P values are two-sided.

§ Subscales derived from the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL). Scales have been recoded so that a higher score reflects a higher QOL.

‡ Scores on the Medical Outcomes Study 36-Item Short-Form Health Survey V2 (SF-36v2) standard recall were normalized to the 1998 U.S. general population with a mean (±SD) of 50±10. A higher score reflects higher QOL or better health outcome.

¶ Subscales derived from the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM). A higher score reflects a greater severity.

Table 3: Characteristics of patients with idiopathic or diabetic gastroparesis by vomiting severity

Characteristic	Vomiting severity^ None (n=84)	Very mild/Mild/ Moderate (n=52)	Severe/Very severe (n=23)	Total (n=159)	p-value*
Etiology					0.003
Idiopathic	66 (78.6%)	29 (55.8%)	12 (52.2%)	107 (67.3%)	
Diabetic	18 (21.4%)	23 (44.2%)	11 (47.8%)	52 (32.7%)	
Demographics					
Gender: females	75 (89.3%)	41 (78.9%)	19 (82.6%)	135 (84.9%)	0.20
Age (years)	45.4 ± 14.1	45.2 ± 12.4	41.0 ± 12.5	44.7 ± 13.3	0.001
Hispanic	11 (13.1%)	7 (13.5%)	4 (17.4%)	22 (13.8%)	0.65
Race: white	77 (91.7%)	47 (90.4%)	16 (69.6%)	140 (88.1%)	0.01
Medical history					
Nature of gastroparesis symptoms:					0.17
Chronic, but stable	19 (22.6%)	6 (11.8%)	1 (4.4%)	26 (16.5%)	
Chronic, but progressive worsening	14 (16.7%)	13 (25.5%)	6 (26.1%)	33 (20.9%)	
Chronic, but some improvement	8 (9.5%)	9 (17.7%)	1 (4.4%)	18 (11.4%)	
Chronic with periodic exacerbations	31 (36.9%)	14 (27.5%)	9 (39.1%)	54 (34.2%)	
Cyclic pattern	10 (11.9%)	9 (17.7%)	6 (26.1%)	25 (15.8%)	
Asymptomatic	2 (2.4%)	0 (0.0%)	0 (0.0%)	2 (1.3%)	
Gastroparesis severity:					<0.0001
Mild (grade 1)	25 (29.8%)	6 (11.5%)	1 (4.4%)	32 (20.1%)	

Compensated (grade 2)	54 (64.3%)	37 (71.2%)	14 (60.9%)	105 (66.1%)	
Gastric failure (grade 3)	5 (6.0%)	9 (17.3%)	8 (34.8%)	22 (13.8%)	
Medical history					
BMI (kg/m^2)	27.7 ± 8.6	28.1 ± 6.9	24.8 ± 6.3	27.4 ± 7.8	0.30
Use of prokinetics	21 (25.0%)	21 (40.4%)	14 (60.9%)	56 (35.2%)	0.0009
Use of antiemetics	63 (75.0%)	45 (86.5%)	21 (91.3%)	129 (81.1%)	0.04
Use of narcotics	21 (25.0%)	23 (44.2%)	14 (60.9%)	58 (36.5%)	0.0005
Laboratory results					
HbA1c, if diabetic (%)	8.5 ± 1.7	7.8 ± 2.1	9.0 ± 1.9	8.3 ± 2.0	0.81
HbA1c≥8.0%, if diabetic	12 (66.7%)	9 (39.1%)	7 (63.6%)	28 (53.9%)	0.64
ANA negative, if idiopathic	54 (81.8%)	25 (86.2%)	12 (100.0%)	91 (85.1%)	0.12
ESR, if idiopathic	15.6 ± 12.9	12.0 ± 10.0	13.7 ± 11.6	14.4 ± 12.0	0.39
ESR elevated>30mm, if idiopathic	9 (13.9%)	2 (6.9%)	1 (9.1%)	12 (11.4%)	0.41
PAGI-SYM symptom severity (0-5) ¶					
Nausea score	2.3 ± 1.7	3.3 ± 1.2	4.4 ± 0.9	2.9 ± 1.6	<0.001
Vomiting score	0.0 ± 0.0	1.8 ± 0.8	4.4 ± 0.5	1.2 ± 1.6	<0.001
Retching score	0.4 ± 0.9	2.1 ± 1.4	3.3 ± 1.4	1.4 ± 1.6	<0.001
Nausea/vomiting sub-score	0.9 ± 0.7	2.4 ± 0.9	4.0 ± 0.6	1.8 ± 1.4	<0.001
Satiety/fullness sub-score	3.0 ± 1.3	3.5 ± 0.9	3.9 ± 1.2	3.3 ± 1.2	<0.001
Bloating sub-sore	2.8 ± 1.6	3.3 ± 1.5	3.4 ± 1.7	3.0 ± 1.6	0.002
Cardinal symptom index (GCSI)	2.2 ± 1.0	3.1 ± 0.8	3.8 ± 0.9	2.7 ± 1.1	<0.001
Upper abdominal pain sub-score	2.4 ± 1.6	3.2 ± 1.3	3.2 ± 1.5	2.8 ± 1.5	<0.001
GERD sub-score	1.5 ± 1.3	2.0 ± 1.4	2.6 ± 1.5	1.8 ± 1.4	0.03
Predominant symptom from the PAGI-SYM					0.13
Nausea	20 (23.8%)	15 (28.9%)	9 (39.1%)	44 (27.7%)	
Vomiting	0 (0.0%)	0 (0.0%)	7 (30.4%)	7 (4.4%)	
Upper abdominal pain or discomfort	12 (14.3%)	8 (15.4%)	1 (4.4%)	21 (13.2%)	
Other	52 (61.9%)	29 (55.8%)	6 (26.1%)	87 (54.7%)	

PAGI-QOL (0-5) §					
Activity sub-score	2.9 ± 1.1	2.6 ± 1.2	2.1 ± 1.1	2.7 ± 1.2	<0.001
Clothing sub-score	3.1 ± 1.7	2.8 ± 1.7	2.6 ± 2.1	2.9 ± 1.7	0.27
Diet sub-score	1.9 ± 1.4	1.8 ± 1.3	1.3 ± 1.1	1.8 ± 1.3	0.005
Relationship sub-score	3.6 ± 1.2	3.1 ± 1.5	2.9 ± 1.4	3.3 ± 1.3	0.01
Psychology sub-score	3.4 ± 1.2	3.1 ± 1.5	2.7 ± 1.5	3.2 ± 1.4	0.09
Total PAGI-QOL	3.0 ± 1.0	2.7 ± 1.1	2.3 ± 1.1	2.8 ± 1.1	0.005
SF-36v2 Health Survey (past 4 weeks) ‡					
Physical health summary measure	35.5 ± 9.6	32.0 ± 11.1	31.1 ± 9.8	33.7 ± 10.2	0.01
Mental health summary measure	42.7 ± 13.3	42.8 ± 14.5	40.2 ± 12.5	42.4 ± 13.6	0.03
Solid gastric scintigraphy					
Percent retention at 1 hour	79.9 ± 14.4	80.6 ± 10.6	77.8 ± 15.1	79.8 ± 13.3	0.69
Percent retention at 2 hours	64.8 ± 16.9	61.2 ± 16.5	64.7 ± 20.1	63.6 ± 17.2	0.27
Percent retention at 4 hours	29.4 ± 19.4	26.6 ± 14.7	39.8 ± 24.2	30.0 ± 19.1	0.09
Percent retention at 4 hours, diabetic patients only	40.0 ± 28.9	33.5 ± 16.7	39.9 ± 21.1	37.1 ± 22.3	0.78
Percent retention at 4 hours, idiopathic patients only	26.5 ± 14.9	21.0 ± 10.3	39.7 ± 27.6	26.5 ± 16.5	0.65
Liquid gastric scintigraphy					
Percent retention at 30 minutes	64.1 ± 16.7	67.3 ± 13.6	62.8 ± 24.7	65.0 ± 17.4	0.83
Percent retention at 1 hour	48.2 ± 17.3	50.7 ± 13.4	51.5 ± 25.7	49.7 ± 17.6	0.36

Data are means ± standard deviations or number (percents).

^Vomiting severity is a score from the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM).

* The significance of difference in binary variables between groups was tested with a Cochran-Armitage trend test, the significance of difference in categorical variables between groups was tested with a Mantel-Haenszel chi-square test, and the significance of difference in continuous variables between groups was tested with a non-parametric Cuzick test for trend. All P values are two-sided.

§ Subscales derived from the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QOL). Scales have been recoded so that a higher score reflects a higher QOL.

‡ Scores on the Medical Outcomes Study 36-Item Short-Form Health Survey V2 (SF-36v2) standard recall were normalized to the 1998 U.S. general population with a mean (±SD) of 50±10. A higher score reflects higher QOL or better health outcome.

¶ Subscales derived from the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM). A higher score reflects a greater severity.

Table 4: Logistic Regression Analyses of Enrollment Characteristics as Predictors of Severe Nausea* in Idiopathic and Diabetic Gastroparetics (n=159)

	Unadjusted Analyses			Adjusted Analyses		
Enrollment chracteristic	**OR**	**CI**	**P†**	**OR**	**CI**	**P‡**
Etiology (diabetic vs idiopathic)	1.23	(0.63, 2.40)	0.55	1.12	(0.48, 2.61)	0.80
Age, years	0.96	(0.94, 0.99)	0.004	0.96	(0.93, 0.99)	0.005
Solid gastric emptying scintigraphy, percent retention at 4 hours	1.02	(1.00, 1.04)	0.01	1.02	(0.99, 1.04)	0.14
PAGI-SYM, satiety/fullness sub-score	2.58	(1.76, 3.77)	<0.001	2.83	(1.80, 4.44)	<0.001
SF-36, mental score	0.97	(0.95, 1.00)	0.02	0.94	(0.90, 0.98)	0.006
SF-36, physical score	0.96	(0.93, 0.99)	0.01	0.95	(0.90, 0.99)	0.02
PAGI-QOL score	0.70	(0.52, 0.94)	0.02	1.75	(0.95, 3.20)	0.07

* Severe nausea defined as ‘severe’ or ‘very severe’ nausea score on the PAGI-SYM instrument

† Unadjusted odds ratios, 95% confidence limits, P values determined from logistic regression models of severe nausea on each predictor

‡ Adjusted odds ratios, 95% confidence limits, P values were determined from a multiple logistic regression analyses of severe nausea using all baseline predictors indicated. This model was determined from Akaike Information criteria (AIC) with forward selection using a candidate set of baseline variables: gender, age at enrollment, etiology, race, SF-36 physical score, SF-36 mental score, PAGI-QOL total score, solid GES 2 hour retention percent, solid GES 4 hour retention percent, HbA1c, ESR, gastroparesis severity, and the following PAGI-SYM items: satiety sub-score, bloating sub-score, upper abdominal pain sub-score, and GERD sub-score. Etiology was forced into the model.

Table 5: Logistic Regression Analyses of Enrollment Characteristics as Predictors of Severe Vomiting* in Idiopathic and Diabetic Gastroparetics (n=159)

	Unadjusted Analyses			Adjusted Analyses		
Enrollment characteristic	**OR**	**CI**	**P†**	**OR**	**CI**	**P‡**
Etiology (diabetic vs idiopathic)	2.12	(0.87, 5.21)	0.10	1.02	(0.19, 5.59)	0.98
Age, years	0.98	(0.94, 1.01)	0.16	0.97	(0.93, 1.01)	0.16
Race (white vs non-white)	0.22	(0.08, 0.64)	0.006	0.20	(0.05, 0.80)	0.02
PAGI-SYM, satiety sub-score	1.95	(1.18, 3.21)	0.009	2.17	(1.19, 3.95)	0.01
PAGI-SYM, bloating sub-score	1.19	(0.89, 1.60)	0.24	0.62	(0.41, 0.95)	0.03
PAGI-SYM, GERD sub-score	1.60	(1.15, 2.22)	0.005	1.77	(1.16, 2.72)	0.009
PAGI-QOL score	0.63	(0.42, 0.95)	0.03	0.71	(0.42, 1.20)	0.20
HbA1c, %	1.28	(1.04, 1.59)	0.02	1.29	(0.85, 1.95)	0.24

* Severe vomiting defined as ‘severe’ or ‘very severe’ vomiting score on the PAGI-SYM instrument

† Unadjusted odds ratios, 95% confidence limits, P values determined from logistic regression models of severe vomiting on each predictor

‡ Adjusted odds ratios, 95% confidence limits, P values were determined from a multiple logistic regression analyses of severe nausea using all baseline predictors indicated. This model was determined from Akaike Information criteria (AIC) with forward selection using a candidate set of

baseline variables: gender, age at enrollment, etiology, race, SF-36 physical score, SF-36 mental score, PAGI-QOL total score, solid GES 2 hour retention percent, solid GES 4 hour retention percent, HbA1c, ESR, gastroparesis severity, and the following PAGI-SYM items: satiety sub-score, bloating sub-score, upper abdominal pain sub-score, and GERD sub-score. Etiology was forced into the model.

Supplemental Table 1: Baseline characteristics of patients with idiopathic or diabetic gastroparesis by four hour gastric retention

	Percent of gastric retention of solids at 4 hours				
Characteristic	≤20% (n=62)	20.1-35% (n=46)	>35% (n=51)	Total (n=159)	p-value*
Etiology					0.002
Idiopathic	48 (77.4%)	34 (73.9%)	25 (49.0%)	107 (67.3%)	
Diabetic	14 (22.6%)	12 (26.1%)	26 (51.0%)	52 (32.7%)	
PAGI-SYM closest to enrollment¶					
Median days from PAGI-SYM to enrollment (IQR)	12 (8-20)	16 (9-31)	14 (9-28)	13 (8-27)	0.09
Nausea/vomiting sub-score	1.8 ± 1.2	1.5 ± 1.2	2.2 ± 1.6	1.8 ± 1.4	0.40
Nausea score	2.9 ± 1.4	2.6 ± 1.7	3.2 ± 1.8	2.9 ± 1.6	0.17
Retching score	1.2 ± 1.4	1.2 ± 1.5	1.6 ± 1.8	1.4 ± 1.6	0.34
Vomiting score	1.3 ± 1.6	0.8 ± 1.2	1.6 ± 1.8	1.2 ± 1.6	0.53
Satiety/fullness sub-score	3.1 ± 1.3	3.1 ± 1.2	3.7 ± 1.1	3.3 ± 1.2	0.02
Stomach fullness score	3.3 ± 1.2	3.3 ± 1.4	3.9 ± 1.2	3.5 ± 1.3	0.01
Inability to finish meal score	3.2 ± 1.7	3.1 ± 1.5	3.7 ± 1.3	3.3 ± 1.6	0.15
Postprandial fullness score	3.4 ± 1.5	3.4 ± 1.4	4.0 ± 1.1	3.6 ± 1.4	0.03
Loss of appetite score	2.6 ± 1.6	2.5 ± 1.6	3.1 ± 1.6	2.7 ± 1.6	0.10

Bloating sub-score	3.0 ± 1.6	3.0 ± 1.5	3.2 ± 1.7	3.0 ± 1.6	0.33
Bloating score	3.1 ± 1.7	3.1 ± 1.6	6.4 ± 1.6	6.2 ± 1.6	0.31
Stomach visibly larger score	2.8 ± 1.8	2.9 ± 1.6	3.1 ± 1.9	2.9 ± 1.8	0.45
GCSI	2.6 ± 1.1	2.5 ± 1.0	3.0 ± 1.1	2.7 ± 1.1	0.06
Upper abdominal pain sub-score	2.8 ± 1.6	2.5 ± 1.4	3.1 ± 1.6	2.8 ± 1.5	0.30
Upper abdominal pain score	2.6 ± 1.8	2.3 ± 1.5	2.9 ± 1.7	2.6 ± 1.7	0.36
Upper abdominal discomfort score	2.9 ± 1.5	2.7 ± 1.6	3.3 ± 1.6	3.0 ± 1.6	0.29
GERD sub-score	1.6 ± 1.3	2.0 ± 1.5	1.9 ± 1.4	1.8 ± 1.4	0.30
PAGI-SYM closest to scintigraphy¶					
Median days from PAGI-SYM to scintigraphy (IQR)	1 (0-74)	15 (0-78)	45 (0-117)	13 (0-95)	0.15
Nausea/vomiting sub-score	2.1 ± 1.3	1.8 ± 1.2	2.4 ± 1.5	2.1 ± 1.4	0.26
Nausea score	3.3 ± 1.3	3.0 ± 1.7	3.5 ± 1.6	3.3 ± 1.5	0.26
Retching score	1.4 ± 1.5	1.5 ± 1.6	1.8 ± 1.9	1.5 ± 1.7	0.26
Vomiting score	1.5 ± 1.8	1.0 ± 1.3	2.0 ± 2.0	1.5 ± 1.8	0.21
Satiety/fullness sub-score	3.3 ± 1.2	3.4 ± 1.1	3.7 ± 1.2	3.5 ± 1.2	0.10
Stomach fullness score	3.5 ± 1.4	3.7 ± 1.0	3.9 ± 1.3	3.7 ± 1.3	0.04
Inability to finish meal score	3.4 ± 1.7	3.4 ± 1.4	3.6 ± 1.5	3.5 ± 1.5	0.53
Postprandial fullness score	3.7 ± 1.4	3.8 ± 1.2	4.0 ± 1.4	3.8 ± 1.4	0.11
Loss of appetite score	2.8 ± 1.5	2.8 ± 1.5	3.1 ± 1.6	2.9 ± 1.5	0.25
Bloating sub-score	3.3 ± 1.6	3.1 ± 1.5	3.1 ± 1.6	3.2 ± 1.6	0.43
Bloating score	3.4 ± 1.7	3.1 ± 1.6	3.3 ± 1.7	3.3 ± 1.6	0.63
Stomach visibly larger score	3.2 ± 1.8	3.0 ± 1.6	3.0 ± 1.6	3.1 ± 1.7	0.35
GCSI	2.9 ± 1.1	2.8 ± 1.0	3.1 ± 1.1	2.9 ± 1.0	0.37
Upper abdominal pain sub-score	3.1 ± 1.5	3.0 ± 1.5	3.2 ± 1.5	3.1 ± 1.5	0.85
Upper abdominal pain score	2.9 ± 1.7	2.9 ± 1.5	3.1 ± 1.6	3.0 ± 1.6	0.77
Upper abdominal discomfort score	3.3 ± 1.5	3.1 ± 1.6	3.3 ± 1.5	3.3 ± 1.5	0.99
GERD sub-score	1.6 ± 1.3	2.1 ± 1.4	1.9 ± 1.3	1.9 ± 1.3	0.16

Medical history					
BMI (kg/m^2)	27.2 ± 7.0	27.5 ± 7.7	27.6 ± 8.9	27.4 ± 7.8	0.96
Use of prokinetics	20 (32.3%)	16 (34.8%)	20 (39.2%)	56 (35.2%)	0.44
Use of antiemetics	43 (69.4%)	41 (89.1%)	45 (88.2%)	129 (81.1%)	0.008
Use of narcotics	20 (32.3%)	16 (34.8%)	22 (43.1%)	58 (36.5%)	0.24

Data are means ± standard deviations or number (percents).

* The significance of difference in binary variables between groups was tested with a Cochran-Armitage trend test and the significance of difference in continuous variables between groups was tested with a non-parametric Cuzick test for trend. All P values are two-sided.

¶ Subscales derived from the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM). A higher score reflects a greater severity.

Supplemental Table 2: Nausea and vomiting profile of patients with idiopathic or diabetic gastroparesis

	Etiology			
Characteristic	Idiopathic (n=107)	Diabetic (n=52)	Total (n=159)	p-value*
Nausea and vomiting profile				
Experiences nausea as a symptom	104 (97.2%)	49 (94.2%)	153 (96.2%)	0.39
If nausea is a symptom:				
How long nausea lasts				0.88
Several minutes to about 1 hour	32 (30.8%)	16 (32.7%)	48 (31.4%)	
Several hours	30 (28.9%)	12 (24.5%)	42 (27.5%)	
Most of the day	42 (40.4%)	21 (42.9%)	63 (41.2%)	
Nausea worse in the morning before eating				0.52
Yes	27 (30.0%)	15 (30.6%)	42 (27.5%)	
No	35 (33.7%)	12 (24.5%)	47 (30.7%)	
Sometimes	42 (40.4%)	22 (44.9%)	64 (41.8%)	

Nausea worse in the evening				0.22
Yes	30 (28.9%)	10 (20.4%)	40 (26.1%)	
No	23 (22.1%)	17 (34.7%)	40 (26.1%)	
Sometimes	51 (49.0%)	22 (44.9%)	73 (47.7%)	
Nausea typically occurs				0.42
During eating or within 60 minutes after eating	31 (29.8%)	10 (20.4%)	41 (26.8%)	
1-3+ hours after eating	12 (11.5%)	6 (12.2%)	18 (11.8%)	
All of the above	35 (33.7%)	15 (30.6%)	50 (32.7%)	
Unrelated to eating	26 (25.0%)	18 (36.7%)	44 (28.8%)	
High fat meal provokes nausea	47 (45.2%)	21 (42.9%)	68 (44.4%)	0.86
Dairy provokes nausea	35 (33.7%)	14 (28.6%)	49 (32.0%)	0.58
Vegetables or high-fiber meal provokes nausea	39 (37.5%)	17 (34.7%)	56 (36.6%)	0.86
Spicy meal provokes nausea	39 (37.5%)	23 (46.9%)	62 (40.5%)	0.29
Nausea increases during and/or after eating				0.06
Yes	54 (52.4%)	16 (32.7%)	70 (46.1%)	
No	17 (16.5%)	10 (20.4%)	27 (17.8%)	
Sometimes	32 (31.1%)	23 (46.9%)	55 (36.2%)	
Nausea increases when hungry				0.38
Yes	30 (29.1%)	10 (20.4%)	40 (26.3%)	
No	43 (41.8%)	26 (53.1%)	69 (45.4%)	
Sometimes	30 (29.1%)	13 (26.5%)	43 (28.3%)	
Nausea decreases when hungry				0.55
Yes/sometimes	24 (23.3%)	14 (28.6%)	38 (25.0%)	
No	79 (76.7%)	35 (71.4%)	114 (75.0%)	
Nausea increases when riding in a car or bus				0.92
Yes	27 (26.2%)	12 (24.5%)	39 (25.7%)	
No	51 (49.5%)	26 (53.1%)	77 (50.7%)	

Sometimes	25 (24.3%)	11 (22.5%)	36 (23.7%)	
Nausea profile **	46.4 ± 19.9	46.5 ± 23.0	46.4 ± 20.9	0.99
Somatic sub-scale	46.9 ± 24.9	44.9 ± 27.7	46.3 ± 25.7	0.66
GI distress sub-scale	73.0 ± 21.9	70.0 ± 26.8	72.1 ± 23.5	0.47
Emotional distress sub-scale	23.8 ± 25.5	28.4 ± 25.9	25.2 ± 25.6	0.30
Experiences vomiting as a symptom	61 (57.0%)	42 (80.8%)	103 (64.8%)	0.004
If vomiting is a symptom:				
How long vomiting lasts				0.11
Several minutes	34 (56.7%)	18 (42.9%)	52 (51.0%)	
About 30 minutes to several hours	20 (33.3%)	13 (31.0%)	33 (32.4%)	
Most of the day	6 (10.0%)	11 (26.1%)	17 (16.7%)	
Vomiting occurs in the morning before eating				0.04
Yes	10 (16.4%)	9 (21.4%)	19 (18.5%)	
No	34 (55.7%)	13 (31.0%)	47 (45.6%)	
Sometimes	17 (27.9%)	20 (47.6%)	37 (35.9%)	
Wakes up at night vomiting				0.02
Yes	15 (24.6%)	4 (9.5%)	19 (18.5%)	
No	30 (49.2%)	16 (38.1%)	46 (44.7%)	
Sometimes	16 (26.2%)	22 (52.4%)	38 (36.9%)	
Vomiting typically occurs				0.27
During eating or within 60 minutes after eating	15 (24.6%)	11 (26.2%)	26 (25.2%)	
1-3+ hours after eating	17 (27.9%)	6 (14.3%)	23 (22.3%)	
All of the above	16 (26.2%)	10 (23.8%)	26 (25.2%)	
Unrelated to eating	13 (21.3%)	15 (35.7%)	28 (27.2%)	
Predominant material vomited				0.12
Water or yellow/green liquid that tastes bitter	8 (14.0%)	12 (30.0%)	20 (20.6%)	
Partially digested food	26 (45.6%)	18 (45.0%)	44 (45.4%)	

Undigested food	23 (40.4%)	10 (25.0%)	33 (34.0%)	
Retching or dry heaving before, during or after vomiting				0.84
Always/often	30 (49.2%)	19 (45.2%)	49 (47.6%)	
Sometimes/never	31 (50.8%)	23 (54.8%)	54 (52.4%)	
Experiences nausea before vomiting				0.44
Always/often	48 (78.7%)	36 (85.7%)	84 (81.6%)	
Sometimes/never	13 (21.3%)	6 (14.3%)	19 (18.5%)	
Vomiting relieves nausea				0.52
Always/often	20 (32.8%)	11 (26.2%)	31 (30.1%)	
Sometimes/never	41 (67.2%)	31 (73.8%)	72 (69.9%)	
Vomits even if no food or drink all day				0.008
Yes	17 (27.9%)	19 (45.2%)	36 (35.0%)	
Sometimes	16 (26.2%)	16 (38.1%)	32 (31.1%)	
No	28 (45.9%)	7 (16.7%)	35 (34.0%)	
Vomits if only had water				0.11
Yes	20 (32.8%)	21 (50.0%)	41 (39.8%)	
Sometimes	17 (27.9%)	12 (28.6%)	29 (28.2%)	
No	24 (39.3%)	9 (21.4%)	33 (32.0%)	
Vomiting is worsened by eating				0.47
Yes	29 (47.5%)	19 (45.2%)	48 (46.6%)	
Sometimes	32 (37.7%)	13 (31.0%)	36 (35.0%)	
No	9 (14.8%)	10 (23.8%)	19 (18.5%)	
Vomiting improves with eating				0.64
Yes/sometimes	13 (21.3%)	11 (26.2%)	24 (23.3%)	
No	48 (78.7%)	31 (73.8%)	79 (76.7%)	
Smell of food makes patient vomit				0.16
Yes/sometimes	31 (50.8%)	28 (66.7%)	59 (57.3%)	
No	29 (50.9%)	12 (30.8%)	41 (42.7%)	
High fat meal provokes vomiting	31 (50.8%)	22 (52.4%)	53 (51.5%)	1.00
Dairy provokes vomiting	24 (39.3%)	13 (31.0%)	37 (35.9%)	0.41

Vegetables or high-fiber meal provokes vomiting	25 (41.0%)	16 (38.1%)	41 (39.8%)	0.84
Spicy meal provokes vomiting	24 (39.3%)	14 (33.3%)	38 (36.9%)	0.68
Number of times patient vomited in last 24 hours	0.9 ± 1.9	0.5 ± 1.0	0.8 ± 1.6	0.27
Severity of vomiting in last 24 hours				0.89
None	35 (57.4%)	23 (54.8%)	58 (56.3%)	
Mild	12 (19.7%)	10 (23.8%)	22 (21.4%)	
Moderate/severe/very severe	14 (23.0%)	9 (21.4%)	23 (22.3%)	

Data are means ± standard deviations or number (percents).

*The significance of difference in categorical variables between groups was tested with a Fisher's exact test. Continuous variables were analyzed with a t-test. All p-values are two-sided.

**Subscales are derived from the Nausea Profile. A higher score reflects greater severity.