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Psychological Dysfunction Is Associated With Symptom Severity but Not Disease Etiology or Degree of Gastric Retention in Patients With Gastroparesis

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Abstract

OBJECTIVES—Gastroparesis patients may have associated psychological distress. This study aimed to measure depression and anxiety in gastroparesis in relation to disease severity, etiology, and gastric retention.

METHODS—Beck Depression Inventory (BDI) and State–Trait Anxiety Inventory (STAI) scores for state (Y1) and trait (Y2) anxiety were obtained from 299 gastroparesis patients from 6 centers of the National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium. Severity was investigator graded as grades 1, 2, or 3 and patient reported by

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CONFLICT OF INTEREST

Guarantor of the article: William L. Hasler, MD.

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Gastroparesis Cardinal Symptom Index (GCSI) scores. Antiemetic/prokinetic medication use, anxiolytic and antidepressant medication use, supplemental feedings, and hospitalizations were recorded. BDI, Y1, and Y2 scores were compared in diabetic vs. idiopathic etiologies and mild ($\leq 20\%$) vs. moderate ($>20\text{--}35\%$) vs. severe ($>35\text{--}50\%$) vs. very severe ($>50\%$) gastric retention at 4h.

RESULTS—BDI, Y1, and Y2 scores were greater with increasing degrees of investigator-rated gastroparesis severity ($P<0.05$). BDI, Y1, and Y2 scores were higher for GCSI >3.1 vs. $\pi 3.1$ ($P<0.05$). Antiemetic and prokinetic use and ≥ 6 hospitalizations/year were more common with BDI ≥ 20 vs. <20 ($P<0.05$). Anxiolytic use was more common with Y1 ≥ 46 ; antidepressant use and ≥ 6 hospitalizations/year were more common with Y2 ≥ 44 ($P<0.05$). BDI, Y1, and Y2 scores were not different in diabetic and idiopathic gastroparesis and did not relate to degree of gastric retention. On logistic regression, GCSI >3.1 was associated with BDI ≥ 20 and Y1 ≥ 46 ; antiemetic/prokinetic use was associated with BDI ≥ 20 ; anxiolytic use was associated with Y1 ≥ 46 ; and antidepressant use was associated with Y2 ≥ 44 .

CONCLUSIONS—Higher depression and anxiety scores are associated with gastroparesis severity on investigator- and patient-reported assessments. Psychological dysfunction does not vary by etiology or degree of gastric retention. Psychological features should be considered in managing gastroparesis.

INTRODUCTION

Symptoms in gastroparesis range from mild in severity, requiring only minor degrees of dietary modification, to disabling, leading to multiple visits to outpatient and inpatient health care providers and necessitating enteral or intravenous fluids or nutrition. Determinants of symptom severity in gastroparesis have been poorly delineated. Gastroparesis most commonly is diagnosed in a symptomatic individual when there is prolonged retention of a solid meal on gastric emptying scintigraphy. However, several studies show poor correlation of symptom severity with the magnitude of delay in gastric emptying, suggesting that other factors in addition to gastric motor function may be important (1,2).

Psychological dysfunction is prevalent in functional bowel disorders such as irritable bowel syndrome (IBS). Using validated surveys, increases in depression, anxiety, neuroticism, somatization, hypochondriasis, and stress are present in this condition (3–6). Similarly, emotional disorders are common in functional dyspepsia (7–9). Psychological abnormalities in other conditions presenting with nausea and vomiting are less well characterized. However, increases in anxiety and/or depression are reported in cyclic vomiting syndrome, chemotherapy-induced emesis, and nausea and vomiting of pregnancy (10–14). Diabetics with nausea and vomiting showed increases in psychiatric illness in one study, but patients without gastroparesis were not specifically excluded (15). No investigation has rigorously measured depression and anxiety in gastroparesis patients with standardized gastric emptying scintigraphy using validated survey instruments.

The aims of this investigation were to relate measures of depression and anxiety to (i) gastroparesis severity as graded by investigators and reported by patients, (ii) correlates of gastroparesis severity including use of prokinetic and antiemetic medications, use of anxiolytic and antidepressant agents, need for supplemental enteral or parenteral nutrition, and hospitalizations, (iii) etiology of gastroparesis, and (iv) the degree of gastric retention on scintigraphy. Study population included gastroparesis patients enrolled at several US academic institutions with comprehensive evaluation including standardized gastric emptying scintigraphy. Subjects completed surveys to assess gastroparesis symptom profiles and severity, associated disorders, medication use, and psychological dysfunction. The Beck Depression Inventory (BDI) was chosen to measure depression, whereas the State–Trait

Anxiety Inventory (STAI) was used to measure anxiety. Multiple logistic regression analysis was performed to identify predictors of higher scores of depression and anxiety in patients with gastroparesis. Through these analyses, we hoped to gain insight into psychological abnormalities relating to gastroparesis severity.

METHODS

Patient populations

Two hundred ninety-nine patients with diabetic or idiopathic gastroparesis were recruited by the six centers of the NIH Gastroparesis Clinical Research Consortium into a multicenter Gastroparesis Registry from January 2007 through August 2009 (ClinicalTrials.gov Identifier: NCT00398801). To be eligible for Registry enrollment, subjects at least 18 years of age must have experienced symptoms of gastroparesis for ≥ 12 weeks that were not necessarily contiguous, with varying degrees of nausea, vomiting, abdominal pain, early satiety, and postprandial fullness. All subjects completed a 4-h gastric scintiscan using a standardized low fat meal within 6 months of Registry enrollment (16). For this investigation, all patients exhibited delayed emptying with $>10\%$ meal retention at 4h and/or $>60\%$ retention at 2h. Exclusion criteria included the presence of other conditions potentially explanatory of symptoms (e.g., mechanical obstruction, active inflammatory bowel disease, eosinophilic gastroenteritis, neurologic disease, acute liver or kidney disease); and prior fundoplication, gastric resection or pyloroplasty; and normal gastric scintigraphy values at 2 and 4 h.

The Gastroparesis Registry protocol and consent statements were approved by the institutional review board at each clinical center and at the data coordinating center. Written informed consent statements were obtained from all Registry participants before enrollment in the study.

Data acquisition and analysis

Data collection and extraction—On Registry enrollment, subjects completed several questionnaires, which characterized symptoms and quantified symptom severity. Psychological functioning was assessed using the BDI and the STAI. The BDI survey is comprised of 21 multiple-choice questions that relate to depression, cognition, and physical well-being and is extensively used to quantify depression in a range of clinical conditions (17). The STAI consists of 20 questions relating to state anxiety (a temporary state varying in intensity) and 20 questions pertaining to trait anxiety (a general propensity to be anxious) and has been well validated (18). However, the STAI does not confer a diagnosis of an anxiety disorder. During face-to-face interviews with each subject, the study physicians or coordinators at each clinical center completed case-report forms to collect information on symptoms, disease profile, associated medical conditions, and medication and supplemental therapies. The study physicians also performed a comprehensive physical examination. Results from the laboratory tests as well as previously performed upper endoscopy within the prior 12 months and gastric emptying scintigraphy done within the prior 6 months were recorded.

Data from questionnaires completed during Registry screening were used in analyses. An investigator-graded measure of gastroparesis severity at the time of enrollment was queried on the Baseline Medical History form. Grade 1 severity was defined by symptoms that were relatively easily controlled; subjects with grade 1 disease maintained weight on a regular diet. Grade 2 severity was defined by the presence of moderate symptoms that were only partly controlled by daily medications; such individuals were able to maintain nutrition with dietary modification. Grade 3 severity was defined if medication-refractory symptoms were

present, subjects made frequent visits to outpatient physicians or emergency departments, several hospitalizations for gastroparesis were required, and/or nutrition through an oral route was not possible. This disease stratification has been proposed by a consensus panel of experts in care of gastroparesis (19). A patient-reported measure of gastroparesis severity was obtained by extracting the Gastroparesis Cardinal Symptom Index (GCSI) from the Patient Assessment of Upper Gastrointestinal Disorders Symptoms Severity Index questionnaire completed on enrollment. The GCSI is a validated instrument, which quantifies nine symptoms relating to gastroparesis on a scale from 0 (no symptoms) to 5 (most severe) (20). A mean GCSI score from the nine symptoms was calculated for each subject. Scores for GCSI subscales relating to nausea and vomiting (three symptoms), bloating (two symptoms), and postprandial fullness (four symptoms) were also quantified. The percentages of patients who were on prokinetic (azithromycin, bethanechol, clarithromycin, domperidone, erythromycin, metoclopramide, or pyloric injection of botulinum toxin (within the past 4 weeks)), antiemetic (prochlorperazine, promethazine, trimethobenzamide, meclizine, ondansetron, granisetron, palonosetron, dolasetron, aprepitant, dronabinol), anxiolytic (lorazepam, alprazolam, buspirone, librium, diazepam, oxazepam, clonazepam, halazepam), and antidepressant (amitriptyline, nortriptyline, desipramine, imipramine, bupropion, venlafaxine, duloxetine, fluoxetine, paroxetine, sertraline, citalopram, escitalopram, mirtazapine, trazodone) medications at the time of enrollment were calculated from data collected on the Baseline Medical History form. Likewise, the percentages of patients receiving nutrition through a gastrostomy tube, a jejunostomy tube, or as total parenteral nutrition and percentages of patients reporting ≥ 6 hospitalizations within the past year were calculated from data collected on the Baseline Medical History. Disease etiology was determined based on the clinical assessment by the study physicians at each Clinical Center. One hundred patients were determined to have gastroparesis as a consequence of diabetes mellitus, whereas 199 patients were considered to have gastroparesis of an idiopathic nature based on a lack of prior gastric surgery, no personal history of diabetes, a normal hemoglobin A1c value at the time of Registry enrollment, and the absence of other potential etiologies.

Associations between psychological function and gastroparesis severity, etiology, and degree of gastric retention—Scores from BDI survey and the state (Y1) and trait (Y2) anxiety scores from the STAI survey were compared with baseline patient characteristics at the time of Registry enrollment. Mean BDI, Y1, and Y2 scores were calculated for investigator-determined grades 1, 2, and 3 severity. For some analyses, BDI, STAI Y1 and Y2, and GCSI scores were dichotomized using either clinically accepted cut points (e.g., BDI) or, when such measures were not available, the median value was used as the cut point as an objective measure of categorization. Scores for depression were categorized as BDI < 20 vs. BDI ≥ 20 , to compare gastroparesis patients with none-to-mild depression to those with moderate-to-severe depression. STAI Y1 scores were dichotomized at the median value of 46 and the STAI Y2 was dichotomized at the median value of 44. For patient-reported disease severity, the GCSI score was dichotomized at the median value of 3.1. Mean BDI, Y1, and Y2 scores were compared in those with GCSI ≤ 3.1 vs. subjects with GCSI > 3.1 to relate parameters of depression and anxiety in subjects with mildly to moderately severe gastroparesis symptoms to those with severe or very severe disease manifestations. Percentages of patients on prokinetic and/or antiemetic, anxiolytic, and antidepressant medications were calculated for those with a BDI score < 20 vs. ≥ 20 , below a median Y1 score (< 46) vs. above (≥ 46), and below a median Y2 score (< 44) vs. above (≥ 44). Separate analyses were performed relating to current and past use of metoclopramide, a medication with prokinetic and antiemetic properties that has been associated with increased depression and anxiety. Similar calculations were performed relating percentages of patients on supplemental nutrition and percentages of patients with ≥ 6 hospitalizations in

the past year to BDI, Y1, and Y2 scores. Mean BDI, Y1, and Y2 scores were calculated for patients with diabetic vs. idiopathic gastroparesis. Finally, BDI, Y1, and Y2 scores were related to degrees of scintigraphic gastric retention at 4 h after meal ingestion. Gastric retention was classified as mild ($\leq 20\%$ retention at 4h; this group included 18 individuals with $<10\%$ retention at 4h but $>60\%$ retention at 2h) vs. moderate ($>20\text{--}35\%$) vs. severe ($>35\text{--}50\%$) vs. very severe ($>50\%$). This stratification is a modification of the cutoffs recommended by a consensus panel and an expert in the field and includes a criterion for very severe retention included in recent consensus guidelines published by the American Neurogastroenterology and Motility Society and Society of Nuclear Medicine (19,21,22). The very severe gastric retention category was added in this study to the consensus opinion values to exclude the possibility that profound delays in emptying selectively associate with altered psychological profiles.

Statistical analysis

All data are reported as mean $\pm$ s.d. or number (%). Baseline clinical, demographic, and psychological scores were compared across groups, using either χ^2 tests (for categorical variables), Fisher's exact test (for categorical variables with small expected numbers: Hispanic ethnicity and race), or analysis of variance for continuous variables, to test statistical significance. Nominal, two-sided *P* values were used and were considered to be statistically significant if *P* < 0.05; no adjustments for multiple comparisons were made. Univariate logistic regression models (one model per factor without adjustments for other factors) were used to assess the individual associations between the outcome measure and the baseline patient characteristics. Three separate outcome measures were analyzed: BDI ≥ 20 vs. <20 , STAI Y1 ≥ 46 vs. <46 , and STAI Y2 ≥ 44 vs. <44 . The following baseline patient characteristics were tested individually in the univariate models: etiology (diabetic vs. idiopathic), investigator-rated gastroparesis severity (grades 1, 2, and 3; two indicator variables), GCSI median score (>3.1 vs. ≤ 3.1), gastric retention at 4h ($\leq 20\%$, $>20\text{--}35\%$, $>35\text{--}50\%$, $>50\%$), use of prokinetic/antiemetic medications, use of anxiolytic medications, use of antidepressant medications, supplemental enteral or parenteral feedings, and hospitalizations in the past year (≥ 6 vs. <6). Then, backwards stepwise logistic regression was used to select independent factors from among the set of all candidate factors listed above. Three separate backwards stepwise logistic regression analyses were performed for each of the outcome measures (BDI, STAI Y1, and STAI Y2). The *P* value for elimination from the model was <0.05 and age at enrollment (years), gender, and race (white, black, or other; two indicator variables) were controlled for in the model. The Hosmer–Lemeshow goodness-of-fit test was used to measure overall model fit. All analyses were performed using SAS statistical software (version 9.1, SAS Institute, Cary, NC) and Stata (Release 10.0, Stata Corporation, College Station, TX) (23,24).

RESULTS

Demographics

Two hundred ninety-nine gastroparesis patients satisfied inclusion and exclusion criteria (Table 1). One hundred patients exhibited gastroparesis of a diabetic etiology, whereas 199 were idiopathic in nature. The mean age was 43.0 ± 13.5 years; the mean age of diabetics was greater than that of the idiopathic patients (*P*=0.005). Women represented the majority of patients in both groups; however, the female predominance of the idiopathic group was greater than that of the diabetics (*P*=0.002). In all, 87.4% of all patients were Caucasian; the racial composition of the diabetic group was different from that of the idiopathic group, with a relatively higher percentage of African-Americans and a relatively lower percentage of Caucasians (*P*=0.009).

Psychological scoring related to gastroparesis severity

Scores from tests of psychological function including the BDI and STAI were related to grades of gastroparesis severity as assessed by the study physicians (Table 2). BDI scores showed increases from 14.8 ± 10.6 in those with grade 1 severity to 19.1 ± 10.8 in grade 2 severity to 20.5 ± 10.5 in individuals with grade 3 severity disease ($P=0.01$). STAI scores showed similar increases with worsening gastroparesis severity. Y1 state anxiety scores increased from 41.5 ± 12.9 with grade 1 to 47.2 ± 14.0 with grade 3 disease ($P=0.02$), whereas Y2 trait anxiety scores increased from 40.6 ± 12.2 to 46.4 ± 13.3 ($P=0.01$).

Scores from the BDI and STAI were also related to measures of gastroparesis severity rated by the patients with gastroparesis (Table 2). BDI scores were higher in subjects with mean GCSI scores of >3.1 compared with those with GCSI scores ≤ 3.1 ($P<0.0001$). Y1 scores were greater in individuals with GCSI >3.1 vs. GCSI ≤ 3.1 ($P=0.004$). Similarly, Y2 scores were increased in patients with GCSI >3.1 compared with subjects with GCSI ≤ 3.1 ($P=0.004$).

Depression and anxiety scores were related to the different subscales of the GCSI to ascertain if selected symptoms of gastroparesis were associated with depression or anxiety (Table 3). Nausea and vomiting subscale scores were greater for BDI ≥ 20 vs. BDI <20 ($P=0.003$) and showed trends to increases for Y1 scores ≥ 46 vs. <46 ($P=0.09$) and Y2 scores ≥ 44 vs. <44 ($P=0.09$). Bloating subscale scores were greater for BDI ≥ 20 vs. <20 ($P<0.0001$), Y1 ≥ 46 vs. <46 ($P=0.001$), and Y2 ≥ 44 vs. <44 ($P=0.03$). Likewise, postprandial fullness subscale scores were greater for BDI ≥ 20 vs. <20 ($P=0.002$), Y1 ≥ 46 vs. <46 ($P=0.045$), and Y2 ≥ 44 vs. <44 ($P=0.03$).

Psychological scoring related to other clinical factors in gastroparesis

BDI and STAI scores were related to other clinical factors that reflect gastroparesis severity, including percentages of patients using prokinetic and/or antiemetic medications, percentages of patients on anxiolytic and antidepressant medications, percentages of patients requiring supplemental enteral or parenteral nutrition, and hospitalizations in the year before enrollment in the Gastroparesis Registry (Table 4). Percentages of patients on prokinetic and/or antiemetic drugs were higher in subjects with BDI scores ≥ 20 vs. those with BDI scores <20 ($P=0.001$). Percentages of patients with ≥ 6 hospitalizations in the past year were greater with BDI scores ≥ 20 compared with individuals with BDI <20 ($P=0.04$). There was a trend to more frequent anxiolytic use with BDI ≥ 20 vs. <20 ($P=0.07$). Percentages of patients on antidepressants ($P=0.12$) and supplemental feedings ($P=0.44$) were similar with BDI scores ≥ 20 and <20 . Percentages of patients on anxiolytics were higher with Y1 scores ≥ 46 vs. <46 ($P=0.01$). In contrast, percentages of patients on prokinetic and antiemetic medications ($P=0.11$), on antidepressants ($P=0.16$), receiving supplemental nutrition ($P=0.64$), and being hospitalized ≥ 6 times in the past year ($P=0.07$) did not differ in individuals with Y1 state anxiety scores ≥ 46 vs. <46 . Percentages of patients on antidepressant medications ($P=0.003$) and with ≥ 6 hospitalizations in the past year ($P=0.02$) were higher with Y2 scores ≥ 44 vs. <44 . Percentages on prokinetic and antiemetic drugs ($P=0.49$), on anxiolytics ($P=0.38$), and on supplemental feedings ($P=0.12$) were similar with Y2 trait anxiety scores ≥ 44 compared with <44 .

Metoclopramide use was analyzed separately because of its propensity to elicit increases in depression and anxiety. BDI scores were nearly identical for individuals currently taking metoclopramide (19.1 ± 9.7) compared with those not on metoclopramide (19.0 ± 11.1) ($P=0.60$). Likewise, BDI scores for those with and without past metoclopramide use were similar ($P=0.66$). Anxiety scores were also nearly identical for individuals taking metoclopramide and those not on metoclopramide. The mean Y1 score for those currently

taking metoclopramide was 45.3 ± 11.7 compared with 45.3 ± 13.9 for those not currently on metoclopramide ($P=0.98$) and the mean Y2 score was 44.6 ± 10.9 for those currently on metoclopramide compared with 44.2 ± 12.6 for those not on the drug ($P=0.83$). Similarly, the mean Y1 and Y2 scores were not significantly different for past metoclopramide use ($P=0.75$ and $P=0.81$, respectively).

Psychological scoring related to gastroparesis etiology

BDI and STAI scores were compared in patients with gastroparesis of an idiopathic nature vs. secondary to diabetes (Table 5). Mean BDI scores were similar in patients with diabetic and idiopathic gastroparesis ($P=0.50$). Similarly, Y1 state anxiety scores were not different in gastroparesis of diabetic and idiopathic etiology ($P=0.89$). Y2 trait scores were similar in diabetic and idiopathic gastroparesis ($P=0.27$).

Psychological scoring related to gastric retention

BDI and STAI anxiety scores lastly were related to the degree of gastric retention on standardized gastric scintigraphy (Table 6). Patients were stratified into those with mild ($\leq 20\%$), moderate ($>20\text{--}35\%$), severe ($>35\text{--}50\%$), and very severe ($>50\%$) retention of a solid meal at 4h. BDI scores were not different in gastroparetics with mild, moderate, severe, and very severe gastric retention ($P=0.25$). Y1 state anxiety scores were similar in mild, moderate, severe, and very severe gastric retention ($P=0.37$). Likewise, Y2 trait anxiety scores were no different in patients with mild, moderate, severe, and very severe retention ($P=0.18$).

Multiple logistic regression analysis to identify predictors of depression and anxiety

Backwards stepwise multiple logistic regression models including baseline clinical parameters were used to identify factors, which were predictive of significant degrees of depression and state and trait anxiety (Table 7). A GCSI score >3.1 was predictive of a BDI score ≥ 20 with an odds ratio of 2.76 (95% confidence interval (CI): 1.63–4.69, $P<0.0001$). Likewise, a GCSI score >3.1 was predictive of an Y1 state anxiety score ≥ 46 with an odds ratio of 1.78 (95% CI: 1.08–2.95, $P=0.02$). Use of antiemetic/prokinetic medications was predictive of a BDI score ≥ 20 with an odds ratio of 2.12 (95% CI: 1.05–4.30, $P=0.04$). Use of anxiolytic medications was predictive of an Y1 state anxiety score ≥ 46 with an odds ratio of 1.91 (95% CI: 1.03–3.54, $P=0.04$), whereas use of antidepressant medications was predictive of an Y2 trait anxiety score ≥ 44 with an odds ratio of 2.14 (95% CI: 1.28–3.57, $P=0.004$). Although age at enrollment, gender, and race were forced to be included in the models, male gender was found to be associated with an Y1 state anxiety score ≥ 46 with an odds ratio of 2.00 (95% CI: 1.02–3.89, $P=0.04$) and older age at enrollment was associated with a decreased odds of Y2 trait anxiety score ≥ 44 with an odds ratio of 0.98 (95% CI: 0.96–1.00, $P=0.03$).

DISCUSSION

Gastroparesis commonly presents with nausea, vomiting, bloating, postprandial fullness, early satiety, and abdominal pain. Symptoms in gastroparesis may be mild, needing only dietary restrictions. Alternatively, symptoms may be disabling leading to extensive health care utilization and requiring surgical therapies or supplemental nutrition (19). One advance relates to use of validated symptom scales to grade gastroparesis severity. The GCSI, a component of the Patient Assessment of Upper Gastrointestinal Disorders Symptoms Severity Index, has been widely applied and is comprised of nine symptoms in three subscales (nausea and vomiting, bloating, and postprandial fullness/early satiety) (20). With the development of standardized gastroparesis severity, ratings have become renewed interest in understanding factors associated with symptom severity. Gastroparesis is

diagnosed in symptomatic patients by demonstrating delayed gastric emptying, yet older studies show poor correlation of symptoms with degrees of scintigraphic gastric retention (1). Even in newer preliminary investigations using the GCSI, there is little relation of symptoms to gastric emptying rates at 2 and 4 h, suggesting that factors other than prolonged meal retention contribute to the severity of the clinical presentation (2,25).

Psychiatric illness is common in functional bowel disorders such as IBS and functional dyspepsia and has been proposed to contribute to symptom development. Abnormalities in IBS include depression, anxiety, neuroticism, somatization, hypochondriasis, and stress (3–6) IBS patients more often seek mental health care for depression and anxiety and often are prescribed antidepressants. Older studies report that psychiatric conditions or anxiety-provoking situations precede the onset of bowel symptoms in many patients, suggesting possible causation. Some investigations suggest that comorbid emotional illness is a major factor in seeking care of IBS symptoms, but others have observed increased psychiatric disease even in those who manage their gut symptoms at home (5). Anxiety scores are higher in IBS patients who fail to improve on follow-up, whereas individuals with less depression respond better to fiber therapy (26). There is also an increase in psychiatric disorders in functional dyspepsia, most prominently anxiety, which may affect up to 70% of patients (7–9). Investigators report elevations both in state anxiety, or that occurring momentarily, and trait anxiety, a stable personality trait, in functional dyspepsia (7). Furthermore, improvements in dyspepsia with prokinetic therapy correlate strongly with reductions in depression and anxiety as measured by the Minnesota Multiphasic Personality Inventory and Millon Behavioral Health Inventory (27,28).

The prevalence of emotional illness in gastroparesis is unknown, but others have characterized psychiatric conditions in other disorders with prominent nausea and vomiting. Anxiety is common in cyclic vomiting syndrome and may precipitate attacks; two thirds of adult cyclic vomiting patients report panic attacks (10,11). Likewise, 84% of adults with cyclic vomiting reported depression in one study (11). Some but not all investigators have observed increases in state and trait anxiety in chemotherapy-induced emesis and with anticipatory nausea and vomiting before chemotherapy (12,13). One group has noted reduced anticipatory nausea with anxiolytic therapy (29). Depression has been correlated with the severity of first trimester nausea and vomiting (14). Finally, in 114 diabetics with clinical manifestations suggesting upper gut motor dysfunction, symptoms were more associated with psychiatric illness than with measures of peripheral neuropathy (15). Likewise, symptoms correlated poorly with autonomic neuropathy. However, this investigation did not focus on diabetics with gastroparesis.

This study represents the first detailed report relating symptoms in gastroparesis to measures of psychiatric illness. Its strengths are its large size, its multicenter nature, the strict standardization of entry criteria including scintigraphic determinants of delayed emptying, and use of a broad range of validated survey instruments. Although other measures of depression and anxiety are available such as the hospital anxiety and depression scale and the center for epidemiologic studies depression scale, the BDI and STAI were chosen to compare findings of this investigation to those of other studies of upper gut functional disorders that used the same instruments (7,8,13). The BDI is the most widely used measure of depression in patient populations; the STAI was chosen over the hospital anxiety and depression scale by virtue of its ability to quantify both state and trait anxiety. Significantly, scores for depression as well as state (a temporary condition) and trait (a general propensity) anxiety were increased with more severe gastroparesis as rated by investigators and patients. Analysis of GCSI subscale scores showed that higher degrees of depression and state and trait anxiety were associated with greater bloating and postprandial fullness. Nausea and vomiting were higher in those with greater depression scores and showed trends to increase

with greater anxiety scores. This indicates that no one symptom profile relates to psychologic dysfunction in gastroparesis. Greater numbers of patients with depression scores, indicating moderate–severe depression received prokinetic or antiemetic drugs. Higher percentages of those with greater degrees of state anxiety were on anxiolytic agents, whereas more patients with higher trait anxiety were taking antidepressants. Higher percentages of patients with ≥ 6 hospitalizations per year noted increased depression and trait anxiety. In contrast, these parameters did not correlate with state anxiety; needs for supplemental feeding did not relate to depression or anxiety. Analyses of current or past use of metoclopramide showed no increase in depression or anxiety scores, indicating that this drug did not contribute to the abnormal psychological profiles of gastroparesis patients. Depression and anxiety were similar with gastroparesis secondary to diabetes vs. idiopathic disease. The degree of gastric retention was not associated with differences in depression or anxiety. On multiple logistic regression analysis, elevated GCSI scores were associated with increased depression and state anxiety scores, antiemetic/prokinetic use related to increased depression, anxiolytic use related to elevated state anxiety, and antidepressant use associated with increased trait anxiety.

Levels of depression in this study were significant. BDI scores from 0 to 13 reflect none-to-minimal depression, scores from 14 to 19 represent mild depression, scores from 20 to 28 indicate moderate depression, and scores >29 reflect severe depression (16). Nearly half of the patients showed moderate-to-severe depression ($\text{BDI} \geq 20$). Despite this, only 40% of patients with significant depression received antidepressant medication therapy raising the possibility that this comorbidity may be underrecognized in many individuals. Likewise, state and trait anxiety were prominently elevated. Mean Y1 and Y2 scores were greater than that observed in the general population (scores 34–39) (7,17). Anxiety scores >39 –49 are found with clinically significant anxiety. Considerably, more than half of the patients in this study exhibited state and trait scores above this level. Indeed, many patients approached or exceeded scores in outpatients receiving mental health care for anxiety (scores 50–80) (7,17).

Although these findings profile and quantify depression and anxiety in gastroparesis, they cannot determine whether these psychological abnormalities are a cause or a consequence of severe gastrointestinal symptoms. Surveys completed on initial enrollment in the Gastroparesis Registry did not provide a temporal description of when gastrointestinal manifestations occurred in relation to the onset of the emotional disturbance. Future investigations relating longitudinal evolution of gastroparesis symptoms to changes in psychological function may provide insight into this question. Such data are currently being acquired, as subjects in the Gastroparesis Registry are queried for depression and anxiety in detail yearly after enrollment.

Nevertheless, findings in other conditions permit speculation regarding mechanisms by which depression or anxiety could worsen symptoms in gastroparesis. Gastric function can be affected by psychological disturbances in some settings. In healthy subjects, experimental anxiety reduces pressure thresholds for pain during gastric distention and lowered gastric compliance, suggesting effects both on gastric sensory and motor function (30). Inducing experimental anxiety to STAI scores (49 ± 3) similar to those in this study increases satiety, fullness, and bloating during nutrient satiety testing (29). In functional dyspepsia patients hypersensitive to gastric distention, the degree of state anxiety negatively correlates with compliance and discomfort and pain thresholds during balloon distention (7). Experimentally induced stress and anxiety exert variable modulatory effects on antral contractions and gastric emptying (31). This study showed no correlation of parameters of psychological dysfunction with gastric retention supporting conclusions of other

investigations that delayed gastric emptying has only a limited function in the clinical impact of gastroparesis (1,2).

Other factors may be influenced by psychological profiles. Histopathologic studies report inflammatory infiltrates in gastric specimens from patients with refractory gastroparesis (32). Mucosal inflammatory cell populations may be increased in IBS patients with significant depression and anxiety (3). The presence of anxiety or depression at the time of acute gastroenteritis predisposes to development of postinfectious IBS (3). Genetic markers relating affective disorders to symptoms in gastroparesis are unexplored, but certain serotonin transporter genotypes are enriched in IBS patients with prior depression, an increased susceptibility to depression in response to stress, and poor response to serotonin reuptake inhibitor antidepressants (33). Both type 1 and type 2 diabetes have been associated with increases in depression vs. other medically ill patients (34). Depression is a predictor of hospitalization in diabetics (35). Coexistent depression worsens insulin resistance and promotes hyperglycemia in diabetics (36). Meta-analyses associate depression with diabetic complications including neuropathy, retinopathy, nephropathy, microvascular disease, and sexual dysfunction (37). Likewise, anxiety is increased in both type 1 and type 2 diabetes and is associated with poor glycemic control (38). Anxiolytic therapy reduces glucose levels in anxious diabetics (39). However, in this study, depression and anxiety were not greater in diabetics with gastroparesis vs. those with idiopathic disease, suggesting that factors contributing to psychological dysfunction in the idiopathic subset are as great as those affecting diabetics.

Concerns can be raised relating to data generated by patients referred to the tertiary academic centers participating in the Gastroparesis Registry. Subject cohorts from such centers commonly are comprised of increased numbers of anxious patients (3). Furthermore, it has been reported earlier that anxious individuals show increased tendencies to participate in research studies (40). Patients with significant health care seeking behaviors exhibit increased psychological dysfunction (41). These observations suggest that community patients with gastroparesis might not exhibit such significant psychological impairment.

Other issues warrant further comment. The racial and ethnic composition of the study population of this study does not precisely mirror that of US society in general; this is especially evident for the idiopathic gastroparesis subset, which was comprised of predominantly white subjects with few subjects of Hispanic ethnicity or black race. Further, population-based investigations are warranted to determine whether these findings reflect a referral bias of the patients recruited into the Gastroparesis Registry or if selected ethnic or racial groups are more susceptible to development of this disease. Second, this study specifically aimed to investigate psychological abnormalities in gastroparesis patients with objective delays in gastric emptying as determined by a standardized gastric scintigraphy method. Therefore, individuals enrolled in the Gastroparesis Registry that had normal gastric emptying with <10% retention of a solid meal at 4h were excluded from this study.

Future analyses will determine whether symptomatic non-gastroparetic individuals exhibit similar psychological abnormalities as patients with well-defined gastroparesis. Third, the standardized scintigraphy method only evaluated overall gastric emptying; a more detailed method assessing intragastric distribution conceivably could relate particular psychological profiles to proximal or distal impairments. Finally, we stratified patients into groups of nearly equal size for analytic purposes. Concerns might be raised that the cutoffs have limited clinical relevance. However, the chosen values do provide important disease-related comparisons. The GCSI cutoff of 3.1 distinguishes subjects with mild-to-moderate symptoms from those with severe symptoms, and the BDI cutoff of 20 separates those with none-to-mild depression from patients with moderate or severe impairments (17,20).

Definitions of anxiety severity are less clearly provided by the STAI, but the cutoffs for this study separated those with scores similar to patients requiring mental health intervention from those with milder disease (7,17).

In conclusion, measures of depression and anxiety correlate with gastroparesis severity as determined by investigator-graded and patient-reported assessments. Psychological dysfunction does not vary by disease etiology or by the magnitude of gastric retention. Future longitudinal evaluations will provide insight into the function of psychological dysfunction in the genesis of symptoms in gastroparesis and if directed, therapy of depression and anxiety reduce gastrointestinal manifestations of this disorder. Nevertheless, findings of this study suggest that both physical and psychological features should be considered in developing individualized treatment plans for gastroparesis.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Symptoms correlate poorly with rates of gastric emptying in gastroparesis, suggesting participation of other factors.
- ✓ Psychological dysfunction is prevalent in the functional bowel disorders and conditions with nausea and vomiting.
- ✓ No investigations have related depression or anxiety to gastroparesis severity, etiology, or gastric retention.

WHAT IS NEW HERE

- ✓ Depression and anxiety scores related to physician- and patient-rated gastroparesis severity and hospitalizations.
- ✓ Antiemetic and prokinetic drug use was more prevalent with higher depression scores.
- ✓ The prevalence of anxiolytic use was higher with increased state anxiety scores, whereas the prevalence of antidepressant use was greater with higher trait anxiety scores.
- ✓ Depression and anxiety scores did not relate to gastroparesis etiology or gastric retention rates.
- ✓ Psychological features should be considered in the management of gastroparesis.

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APPENDIX

Members of the Gastroparesis Clinical Research Consortium as of March 2010

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Stanford University, Stanford, CA: Pankaj Jay Pasricha, MD (Principal Investigator); Linda Nguyen, MD; Nighat Ullah, MD

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Mayo Clinic College of Medicine, Rochester, MN: Gianrico Farrugia, MD; Cheryl Bernard; Matt Lurken (2007–2009)

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Table 1

Demographic characteristics of gastroparesis patients

	Diabetic (<i>n</i> = 100)	Idiopathic (<i>n</i> = 199)	Total (<i>n</i> = 299)	<i>P</i> value
Age at enrollment (years)	46.1 ± 12.7	41.4 ± 13.7	43.0 ± 13.5	0.005
Female gender	72 (72.0%)	173 (86.9%)	245 (81.9%)	0.002
Hispanic ethnicity	7 (7.0%)	6 (3.0%)	13 (4.4%)	0.14
<i>Race</i>				
White	77 (79.4%)	180 (91.4%)	257 (87.4%)	0.009
Black	16 (16.5%)	11 (5.6%)	27 (9.2%)	
Other	4 (4.1%)	6 (3.1%)	10 (3.4%)	

Values are presented as mean ± s.d. or *n* (%). *P* values are derived from χ^2 (gender), Fisher's exact test (Hispanic ethnicity and race), or analysis of variance (age at enrollment).

Table 2

Psychological scoring related to investigator- and patient-rated severity

Test	Investigator rated			Patient rated		
	Grade 1 (n = 38)	Grade 2 (n = 163)	Grade 3 (n = 97)	GCSI ≤ 3.1 (n = 148)	GCSI > 3.1 (n = 149)	P value
Beck Depression score	14.8 ± 10.6	19.1 ± 10.8	20.5 ± 10.5	15.9 ± 9.3	22.2 ± 11.2	< 0.0001
STAI state score (Y1)	41.5 ± 12.9	45.2 ± 12.7	47.2 ± 14.0	43.2 ± 12.7	47.6 ± 13.5	0.004
STAI trait score (Y2)	40.6 ± 12.2	44.0 ± 11.2	46.4 ± 13.3	42.3 ± 12.2	46.4 ± 11.9	0.004

GCSI, Gastroparesis Cardinal Symptom Index; STAI, State-Trait Anxiety Inventory.

All results are presented as mean ± s.d. P values are derived from analysis of variance. Data from two patients who did not complete the question relating to postprandial fullness on the GCSI are not included in this table.

Table 3
Psychological scoring related to nausea and vomiting, bloating, and postprandial fullness subscales of the GCSI

GCSI subscale	Depression score			State anxiety score			Trait anxiety score		
	BDI < 20 (n = 175)	BDI ≥ 20 (n = 124)	P value	Y1 < 46 (n = 149)	Y1 ≥ 46 (n = 150)	P value	Y2 < 44 (n = 145)	Y2 ≥ 44 (n = 154)	P value
Nausea and vomiting (range, 0–15)	6.9 ± 4.5	8.4 ± 4.2	0.003	7.1 ± 4.5	8.0 ± 4.3	0.09	7.1 ± 4.5	8.0 ± 4.3	0.09
Bloating (range, 0–10)	5.2 ± 3.3	6.9 ± 2.8	<0.0001	5.3 ± 3.4	6.5 ± 3.0	0.001	5.5 ± 3.3	6.3 ± 3.1	0.03
Postprandial fullness (range, 0–20)	12.7 ± 4.7	14.4 ± 4.2	0.002	12.9 ± 4.7	14.0 ± 4.4	0.045	12.8 ± 4.9	14.0 ± 4.2	0.03

BDI, Beck Depression Inventory; GCSI, Gastroparesis Cardinal Symptom Index.

All results are presented as mean ± s.d. P values are derived from analysis of variance.

Table 4
Psychological scoring related to medication use, supplemental feeding requirements, and hospitalizations

Severity parameter	Depression score		P value	State anxiety score		P value	Trait anxiety score		P value
	BDI < 20 (n = 175)	BDI ≥ 20 (n = 124)		Y1 < 46 (n = 149)	Y1 ≥ 46 (n =150)		Y2 < 44 (n = 145)	Y2 ≥ 44 (n = 154)	
No. taking antiemetic/prokinetic medications	127 (72.6%)	109 (87.9%)	0.001	112 (75.2%)	124 (82.7%)	0.11	112 (77.2%)	124 (80.5%)	0.49
No. taking anxiolytic medications	30 (17.1%)	32 (25.8%)	0.07	22 (14.8%)	40 (26.7%)	0.01	27 (18.6%)	35 (22.7%)	0.38
No. taking antidepressant medications	58 (33.1%)	52 (41.9%)	0.12	49 (32.9%)	61 (40.7%)	0.16	41 (28.3%)	69 (44.8%)	0.003
No. needing supplemental feeding	24 (13.7%)	21 (16.9%)	0.44	21 (14.1%)	24 (16.0%)	0.64	17 (11.7%)	28 (18.2%)	0.12
≥6 Hospitalizations in past year	18 (10.3%)	23 (18.6%)	0.04	15 (10.1%)	26 (17.3%)	0.07	13 (9.0%)	28 (18.2%)	0.02

BDI, Beck Depression Inventory.

All values are presented as n (%). P values are derived from χ^2 or Fisher's exact test (supplemental feeding and hospitalizations).

Table 5

Psychological scoring related to gastroparesis etiology

Test	Diabetic (<i>n</i> = 100)	Idiopathic (<i>n</i> = 199)	<i>P</i> value
Beck depression score	19.6 ± 10.7	18.7 ± 10.8	0.50
STAI state score (Y1)	45.5 ± 12.7	45.2 ± 13.6	0.89
STAI trait score (Y2)	45.4 ± 12.0	43.8 ± 12.2	0.27

STAI, State-Trait Anxiety Inventory.

All results are presented as mean ± s.d. *P* values are derived from analysis of variance.

Table 6

Psychological scoring related to degree of gastric retention

Test	Mild $\leq 20\%$ retained at 4 h (n = 118)	Moderate $> 20\text{--}35\%$ retained at 4 h (n = 80)	Severe $> 35\text{--}50\%$ retained at 4 h (n = 43)	Very severe $> 50\%$ retained at 4 h (n = 57)	P value
Beck Depression score	19.0 $\pm$ 10.7	17.2 $\pm$ 10.4	20.7 $\pm$ 11.4	20.4 $\pm$ 10.9	0.25
STAI state score (Y1)	45.0 $\pm$ 13.9	43.5 $\pm$ 13.3	47.2 $\pm$ 13.2	46.9 $\pm$ 11.9	0.37
STAI trait score (Y2)	44.0 $\pm$ 12.6	42.5 $\pm$ 12.0	44.7 $\pm$ 11.4	47.1 $\pm$ 12.0	0.18

STAI, State-Trait Anxiety Inventory.

All results are presented as mean $\pm$ s.d. P values are derived from analysis of variance. Note: Data from one patient with $> 60\%$ retention at 2 h who vomited the test meal and did not undergo scanning at 4 h after meal ingestion is not included in this table.

Table 7

Analysis of factors for individual and independent associations with depression and state and trait anxiety

Factor	BDI ≥ 20						Y1 ≥ 46						Y2 ≥ 44					
	Individual ^a			Independent ^b			Individual ^a			Independent ^b			Individual ^a			Independent ^b		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P	Odds ratio	95% CI	P	Odds ratio	95% CI	P	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Age (per year)	0.99	0.97–1.01	0.18	0.99	0.97–1.01	0.26	0.99	0.97–1.00	0.09	0.99	0.97–1.01	0.17	0.98	0.96–1.00	0.03	0.98	0.96–1.00	0.03
Gender																		
Female	1.00		0.85	1.00		0.27	1.00		0.24	1.00		0.04	1.00		0.72	1.00		0.29
Male	1.06	0.58–1.92		1.46	0.74–2.88		1.43	0.79–2.59		2.00	1.02–3.89		1.11	0.62–2.01		1.42	0.74–2.73	
Race																		
White	1.00		0.33	1.00		0.23	1.00		0.80	1.00		0.85	1.00		0.12	1.00		0.15
Black	1.32	0.60–2.93		1.52	0.63–3.64		1.07	0.48–2.36		1.08	0.46–2.54		0.70	0.32–1.56		0.80	0.34–1.92	
Other	0.36	0.07–1.71		0.31	0.06–1.58		0.66	0.18–2.40		0.70	0.19–2.59		0.22	0.05–1.05		0.21	0.04–1.06	
Physician-rated severity																		
Grade 1	1.00		0.22				1.00		0.24				1.00		0.30			
Grade 2	1.76	0.82–3.78					1.51	0.74–3.11					1.22	0.60–2.48				
Grade 3	2.04	0.91–4.57					1.93	0.90–4.13					1.69	0.79–3.59				
Patient-rated severity																		
GCSI ≤ 3.1	1.00		< 0.001	1.00		< 0.001	1.00		0.02	1.00		0.02	1.00		0.18			
GCSI > 3.1	2.44	1.52–3.91		2.76	1.63–4.69		1.74	1.10–2.76		1.78	1.08–2.95		1.36	0.86–2.15				
Meds																		
Antiemetic/prokinetic	2.74	1.46–5.18	0.002	2.12	1.05–4.30	0.04	1.58	0.90–2.77	0.11				1.22	0.70–2.12	0.49			
Anxiolytic	1.68	0.96–2.95	0.07				2.10	1.18–3.75	0.01	1.91	1.03–3.54	0.04	1.29	0.73–2.26	0.38			
Antidepressant	1.46	0.91–2.34	0.12				1.40	0.87–2.24	0.16				2.06	1.27–3.33	0.003	2.14	1.28–3.57	0.004
Supplemental feedings	1.28	0.68–2.43	0.44				1.16	0.62–2.19	0.65				1.67	0.87–3.21	0.12			
≥ 6 Hospitalizations in past year	1.99	1.02–3.86	0.04				1.87	0.95–3.70	0.07				2.26	1.12–4.55	0.02			
Etiology																		
Idiopathic	1.00		0.17				1.00		0.85				1.00		0.54			
Diabetic	1.41	0.86–2.28					1.05	0.65–1.70					1.16	0.72–1.88				
Gastric retention > 20% at 4 h	0.90	0.55–1.48	0.69				1.04	0.64–1.70	0.87				1.18	0.73–1.93	0.50			
Model fit				8.97		0.34				13.7		0.09				7.66		0.47

Factor	BDI $\geq$ 20				Y1 $\geq$ 46				Y2 $\geq$ 44			
	Individual ^a		Independent ^b		Individual ^a		Independent ^b		Individual ^a		Independent ^b	
	Odds ratio	95% CI	P	Odds ratio	Odds ratio	95% CI	P	Odds ratio	Odds ratio	95% CI	P	Odds ratio
Hosmer–Lemeshow χ^2 (8 d.f.)												

BDI, Beck Depression Inventory; CI, confidence interval; GCSI, Gastroparesis Cardinal Symptom Index.

^aIndividual associations were assessed using multiple logistic regression models with one model per factor without adjustments for other factors.

^bBackwards stepwise logistic regression was used to select independent factors from among the set of all candidate factors listed, controlling for age at enrollment (years), sex, and race.