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Effect of Amitriptyline and Escitalopram on Functional Dyspepsia: A Multicenter, Randomized Controlled Study

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BACKGROUND & AIMS: Antidepressants are frequently prescribed to treat functional dyspepsia (FD), a common disorder characterized by upper abdominal symptoms, including discomfort or postprandial fullness. However, there is little evidence of the efficacy of these drugs in patients with FD. We performed a randomized, double-blind, placebo-controlled trial to evaluate the effects of antidepressant therapy on symptoms, gastric emptying (GE), and meal-induced satiety in patients with FD. **METHODS:** We performed a study at 8 North American sites of patients who met the Rome II criteria for FD and did not have depression or use antidepressants. Patients (n = 292; 44 ± 15 years old, 75% were female, 70% with dysmotility-like FD, and 30% with ulcer-like FD) were randomly assigned to groups given placebo, 50 mg amitriptyline, or 10 mg escitalopram for 10 weeks. The primary end point was adequate relief of FD symptoms for ≥5 weeks of the last 10 weeks (of 12). Secondary end points included GE time, maximum tolerated volume in Nutrient Drink Test, and FD-related quality of life. **RESULTS:** An adequate relief response was reported by 39 subjects given placebo (40%), 51 given amitriptyline (53%), and 37 given escitalopram (38%) ($P = .05$, after treatment, adjusted for baseline balancing factors including all subjects). Subjects with ulcer-like FD given amitriptyline were >3-fold more likely to report adequate relief than those given placebo (odds ratio = 3.1; 95% confidence interval: 1.1−9.0). Neither amitriptyline nor escitalopram appeared to affect GE or meal-induced satiety after the 10-week period in any group. Subjects with delayed GE were less likely to report adequate relief than subjects with normal GE (odds ratio = 0.4; 95% confidence interval: 0.2−0.8). Both antidepressants improved overall quality of life. **CONCLUSIONS:** Amitriptyline, but not escitalopram, appears to benefit some patients with FD, particularly those with ulcer-like (painful) FD. Patients with delayed GE do not respond to these drugs. ClinicalTrials.gov ID: NCT00248651.

Functional dyspepsia (FD) is a common functional gastrointestinal disorder characterized by upper abdominal discomfort or pain and symptoms of meal-related fullness or satiety.[1] The condition has symptoms similar to other conditions, including gastroesophageal reflux, peptic ulcer disease, or irritable bowel syndrome (IBS). However, dyspepsia symptoms typically do not improve with proton pump inhibitor therapy and are not chronologically associated with bowel habits. The pathogenesis remains unclear, but abnormalities in gastric motor and sensory function and, more recently, low-grade duodenal inflammation, have been identified.[2,3] Research studies have shown that diagnosing FD can be difficult. Diagnostic testing usually includes upper endoscopy as well as testing for *Helicobacter pylori*. FD symptoms often interfere with school and work, and weight loss can occur due to dietary restrictions.[4–7]

FD symptom management remains challenging. Treatment can include dietary modifications, antiemetics, antispasmodics, prokinetics, and analgesics.[8] Options are quite varied and are applied based on predominant symptom. Although antidepressants, including tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs),[9] have been used for IBS, their efficacy in FD management is uncertain. Antidepressant data in FD are limited to

Abbreviations used in this paper: **CI, confidence interval; EGD, esophagogastroduodenoscopy; FD, functional dyspepsia; GE, gastric emptying; IBS, irritable bowel syndrome; MTV, maximum tolerated volume; NDI, Nepean Dyspepsia Index; OR, odds ratio; SSRIs, serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.**

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4 smaller studies utilizing amitriptyline, venlafaxine, and sertraline.[10–13] It is postulated that antidepressants might be efficacious through reduction of psychological symptoms (eg, anxiety or depression), central analgesic actions,[14] or reduction of affective arousal and sleep restoration.[15,16] Both TCAs and SSRIs have been shown to differently alter orocecal transit times and gastric accommodation.[17,18]

Despite ongoing clinical use, uncertainty remains regarding antidepressants' clinical efficacy and mechanism of treatment response in FD. The aim of this multicenter, randomized placebo-controlled trial was to assess whether 12 weeks of therapy with amitriptyline or escitalopram was more efficacious than placebo in the relief of FD symptoms and in improving quality of life. Our secondary aim was to assess whether gastric emptying (GE) and meal-induced satiety were altered by treatment with a TCA or SSRI, and whether changes in gastric physiology were associated with treatment outcome. In addition, we aimed to determine if efficacy persisted 6 months after treatment was ceased.

Methods

Study Overview

This National Institutes of Health (DK065713)–funded, multicenter, randomized double-blind parallel group trial (Clinicaltrials.gov ID: NCT00248651) comparing 12 weeks of amitriptyline, escitalopram, and matching placebo pills is summarized in Figure 1. Institutional Review Board approval was obtained at each site. Written informed consent was obtained from each subject. Mayo Clinic Rochester monitored each site, centralized data storage, and analyzed the data. Data and Safety Monitoring Board and National Institutes of Health members monitored the study bimonthly and monthly, respectively. The trial design has been reported previously.[19] Only results of the clinical primary aims will be reported. After trial commencement, to facilitate recruitment, the study was changed from 5 sites to 8 sites to facilitate recruitment. No changes in trial outcomes were made. The study ended based on funding period. All authors had access to the study data and reviewed and approved the final manuscript.

Study Participants

Enrollment was during October 2006 through October 2012. The last patient was randomized November 2012 and completed 6-month post-treatment follow-up August 2013. Inclusion criteria were age 18–75 years, Rome II criteria for FD (Table 1),[20] and a normal upper endoscopy within 5 years. FD subtype was determined from a structured interview conducted at the baseline visit, and then defined as ulcer-like or dysmotility-like. If the participant had not had an esophagogastroduodenoscopy (EGD) within 5 years, one was performed before randomization in our trial. Exclusion criteria were symptom resolution with antisecretory therapy (proton pump inhibitor use for other reasons that did not resolve FD symptoms were allowed), current antidepressant, or nonsteroidal anti-inflammatory drugs use, history of esophagitis or ulcer disease or other organic upper gastrointestinal disease, current drug or alcohol abuse, current or planned pregnancy, major abdominal surgery, or major physical illness. Individuals with a Hospital Anxiety Depression Scale score $\geq$11 on the depression scale were excluded. Patients older than age 50 years underwent an electrocardiogram. Women of childbearing years were administered a urine pregnancy test. Each site-specific investigator or coordinator recruited and enrolled participants.

Baseline Washout

Subjects had a 2- to 4-week baseline assessment period before randomization based on patient, staff, and research equipment availability for study testing. Validated symptom diaries were completed during this period.[21] Subjects were required to have at least moderate FD symptoms on the

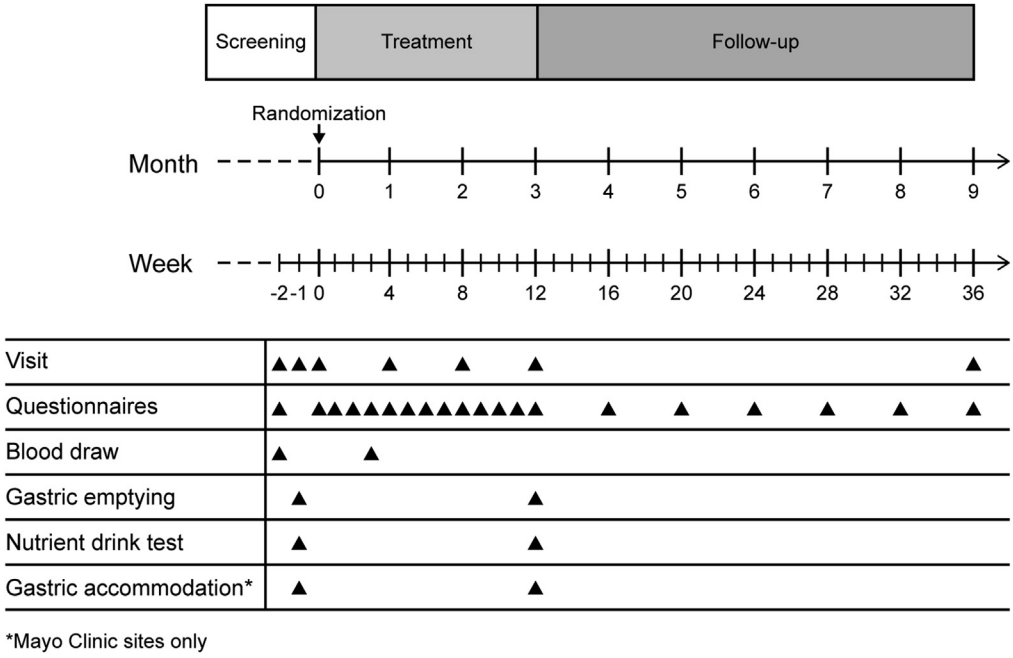

Figure 1. Study design. There was a screening period of 0–4 weeks before randomization on day 1. Two on-site visits were required before randomization, with a third visit if a gastric accommodation study was performed (Mayo Clinic sites only). Study visits were monthly during the treatment phase. Weekly assessments were performed by phone during the treatment period, and then monthly during the follow-up period.

Table 1. Rome II Diagnostic Criteria for Functional Dyspepsia[20]

Functional dyspepsia	Subtypes
At least 12 weeks, which need not be consecutive, within the preceding 12 months of: 1. Persistent or recurrent dyspepsia (pain or discomfort centered in the upper abdomen); and 2. No evidence of organic disease (including at upper endoscopy) that is likely to explain the symptoms; and 3. No evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (ie, not irritable bowel)	Ulcer-like dyspepsia Pain centered in the upper abdomen is the predominant (most bothersome) symptom. Dysmotility-like dyspepsia An unpleasant or troublesome nonpainful sensation (discomfort) centered in the upper abdomen is the predominant symptom. This sensation can be characterized by or associated with upper abdominal fullness, early satiety, bloating, or nausea.

validated Gastrointestinal Symptom Rating Scale (a score of $\geq$3) for at least 4 days during a 2-week period.

Randomization and Blinding

Dynamic allocation randomization was used whereby treatment assignment was based on the distribution across balancing factors for previous assignments. The randomization allocation schedule was created by the Division of Biomedical Statistics and Informatics at Mayo Clinic. Treatment assignment was to the smallest group with specific combinations of balancing factors. Balancing factors were sex, body mass index, race, anxiety, dyspepsia subtype, GE, meal-induced satiety, and recruitment site. Concealed allocation was assured by use of a central web-based system. A double-dummy design was implemented for subject and study personnel blinding. Blinded assessors collected outcomes data; subjects were instructed not to mention side effects to the assessor.

Treatment Arms

There were 3 treatment arms: placebo (amitriptyline placebo/escitalopram placebo), amitriptyline (50 mg amitriptyline/escitalopram placebo), or escitalopram (amitriptyline placebo/10 mg escitalopram). Pills were administered in blister packs for single nightly dosing before bed. To minimize side effects, subjects randomized to the amitriptyline arm received 25 mg (identical to the 50-mg dose) for the first 2 weeks. Amitriptyline and matching placebo were compounded by the Mayo Clinic Research Pharmacy. Escitalopram and matching placebo were provided by Forest Pharmaceuticals (New York, NY).

Study Questionnaires

Weekly global symptom assessment was measured through adequate relief of dyspepsia symptoms during the prior week.[22,23] This self-report measure is considered clinically relevant and has been tested for responsiveness in FD.[24,25] The disease-specific validated Nepean Dyspepsia Index (NDI) was used to assess FD quality of life[26] at baseline and post treatment. NDI scores are summarized into overall quality of life and 5 subscales: Interference, Knowledge/Control, Eating/Drinking, Sleep Disturbance, Work/Study (range, 0−100).[27] Validated daily symptom diaries assessing upper abdominal pain, nausea, bloating, fullness, and early satiety on a scale of 0−3 (0, nil; 1 mild; 2 moderate; 3 severe) were also collected.[21]

Gastrointestinal Physiology Tests

Scintigraphy-based solid-phase GE study was performed in all participants at baseline and treatment end. It was completed in the morning after an overnight fast using a standard meal (^{99m}Tc-labeled meal consisting of 2 scrambled eggs, 1 slice whole wheat bread, and 1 glass of skim milk) with acquisition of measurements at 0, 1, 2, and 4 hours.[28] All scans were read at one site. Delayed GE was defined as <84% emptying at 4 hours.[29] Reproducibility, performance characteristics, and coefficient of variation have been studied extensively.[30]

Nutrient Drink Test for meal-induced satiety was performed in all participants. The Nutrient Drink Test had subjects drink 120 mL Ensure (Abbott Laboratories, Chicago, IL) every 4 minutes.[31] Satiety scores were measured on a scale graded 0−5 (1, no symptoms; 5, maximum satiety). When a score of 5 was reached, the maximum tolerated volume (MTV) intake was measured. Subjects scored their symptoms (pain, fullness, bloating, nausea) using a 100-mm visual analog scale 30 minutes after completing the test, and an aggregate score was calculated as a sum of the 4 symptom scores (range, 0−400). Abnormal satiety was defined as inability to consume >800 mL Ensure.[32]

Efficacy End Points

The a priori primary end point was defined as self-report of adequate relief (yes/no) for at least 50% of weeks 3−12 of treatment (10 weeks). The first 2 weeks of treatment were excluded to allow for establishment of steady-state drug levels. Prespecified secondary end points were $t_{1/2}$ for the GE study, MTV to full satiation, satiety aggregate symptom score at 30 minutes, and NDI scores.

Compliance

Study compliance, including study medication use, was ensured by monitoring completion of questionnaires and pharmacy logs. A subset (n = 161 [55%]) had drug levels checked at week 4.

Follow-up at 6 Months

Evaluations were conducted each month for 6 months off therapy. Symptom assessment and FD medication use were measured. Relapse was defined by the answer “no” to the query regarding adequate response and/or use of an antidepressant or proton pump inhibitor or histamine-2 receptor blocker.

Statistical Analysis

An intent-to-treat analysis included all randomized subjects (97 placebo, 97 amitriptyline, 98 escitalopram). Symptom relief was evaluated for treatment effects using a logistic regression model, with adequate relief as the binary dependent variable. At least 5 weeks (of 10) of symptom relief was required to be considered a responder. The model coefficients were used to estimate the odds for adequate relief in the active treatment groups (relative to the placebo group) adjusting for randomization covariates (ie, sex, body mass index, race, anxiety, dyspepsia subtype, GE, meal-induced satiety, and recruitment site) in the multiple variable model. To ensure balance on the number of important covariates, we used a dynamic allocation randomization method. The dynamic allocation procedure works by ensuring that, as accrual proceeds, no imbalance occurs along the marginal distributions of the stratification factors across treatment arms, and the number of categories of stratification factor combinations cannot exceed one-half of the treatment group sample size (ie, n/2).[33,34] Missing data on other continuous end points was imputed using the overall mean of the corresponding nonmissing end point data. An adjustment in the error degrees of freedom in the analysis of covariance models (subtracting 1 degree of freedom for each missing value imputed) was used to obtain a more accurate estimate of the residual error variance.

To evaluate whether there were subgroups that were associated with better antidepressant response, additional a priori analyses were examined evaluating FD subtype, GE, and meal-induced satiety by incorporating specific interaction terms in separate logistic regression models. The effect of treatment on GE was assessed using an analysis of covariance model incorporating the treatment balancing factors and baseline GE summary as covariates. A similar analysis of the MTV and the aggregate symptom score in each subject was examined.

These analyses were prespecified at study design. To evaluate treatment effects on specific symptoms from the daily diary, an intent-to-treat analysis was also used based on analysis of covariance models incorporating balancing factors and the baseline (run-in period) scores. All analyses were done using SAS statistical software, version 9.3 (Cary, NC). A blinded interim analysis was done for the Data and Safety Monitoring Board (but not shared with investigators) in December 2010. A P value $<.05$ was considered statistically significant.

Sample Size

For the primary outcome of adequate relief, assuming a 20%, 25%, 30%, and 35% placebo response rate and a 20% therapeutic gain over placebo to be clinically significant, the number per group required would be 98, 107, 113, and 116, respectively, to achieve approximately 80% power at a 2-sided α level of .025 (ie, adjusting for 2 pair-wise tests, each active drug against placebo). We assumed a 25% dropout rate in each arm. The planned recruitment was for 133−134 per arm (400 total).

Using the observed variation in nonmissing GE $t_{1/2}$, a 2-sample t test at $\alpha = .025$ (ie, adjusted for 2 pair-wise comparisons) would have had approximately 80% power to detect a difference between treatment groups of 18 minutes, assuming a sample size of 98 per arm. Using the observed nonmissing data for the Nutrient Drink Test, a sample size of 98 would have provided approximately 80% power to detect a difference of 172 mL (21% relative to the overall mean) in MTV and a difference of 37 (24% relative to the overall mean) in the aggregate symptom score.

Role of the Funding Source

The National Institutes of Health was involved in study design and data interpretation. Forest Pharmaceuticals provided escitalopram and placebo only, and was not involved in the study design, data collection or interpretation, writing the report, or the decision to submit. Dr Talley had full access to the study data and has final responsibility for publication.

Results

Subjects

Overall, 399 FD patients were screened at 8 sites (Figure 2). A total of 341 individuals met eligibility criteria and 292 subjects (97 placebo, 97 amitriptyline, and 98 escitalopram) were randomized. Sample demographic and physiologic characteristics are summarized in Table 2. Mean age was 44 years, 219 (75%) were female, and 250 (86%) were Caucasian. A total of 289 (99%) had documented endoscopy data within 5 years of recruitment; 231 (80%) had an endoscopy within a year of recruitment. Median time between endoscopy and recruitment was 10 months (range, 6 days to 4.9 years). A total of 40 (of 282 tested, 14%) were serologically positive for *H pylori* antibodies. Prior cholecystectomy was uncommon (n = 26 [9%]).

Overall, 204 (70%) had dysmotility-like FD and 88 (30%) had ulcer-like FD, and 61 (21%) had delayed baseline GE and 165 (57%) had abnormal meal-induced satiety. Of those with dysmotility-like FD (n = 204), 44 (22%) had delayed GE and 116 (57%) had an abnormal satiety test; of those with ulcer-like FD (n = 88), 17 (19%) had delayed GE and 49 (57%) had an abnormal satiety test. Sixty-two (21%) also met criteria for IBS: 25 (41%) constipation-predominant IBS, 20 (33%) diarrhea-predominant IBS, 6 (10%) mixed constipation and diarrhea IBS, and 11 (18%) undifferentiated IBS. The association of FD alone vs FD−IBS overlap was not significant for age (median, 43 vs 48 years; $P = .96$), or sex (27% vs 18% female; $P = .13$).

Of the 292 subjects, 219 (75%) completed the 12-week treatment trial and 192 (65% of 292) individuals participated through the 6-month follow-up period. Among those completing treatment, the number of pills taken was similar among the 3 arms: median (range) of 168 (80−186) placebo, 168 (92−186) amitriptyline, and 168 (68−186) escitalopram of 186 maximum. Of those with drug levels checked, 58 of 81 (72%) in the amitriptyline arm and 58 of 76 (76%) in the escitalopram arm had detectable drug levels at week 4.

Adequate Relief

In the intent-to-treat analysis, the rates for adequate relief were 39 (40%) for placebo, 51 (53%) for amitriptyline, and 38 (38%) for escitalopram (Figure 3*A*), indicating a difference ($P = .05$) between the 3 treatment arms. In

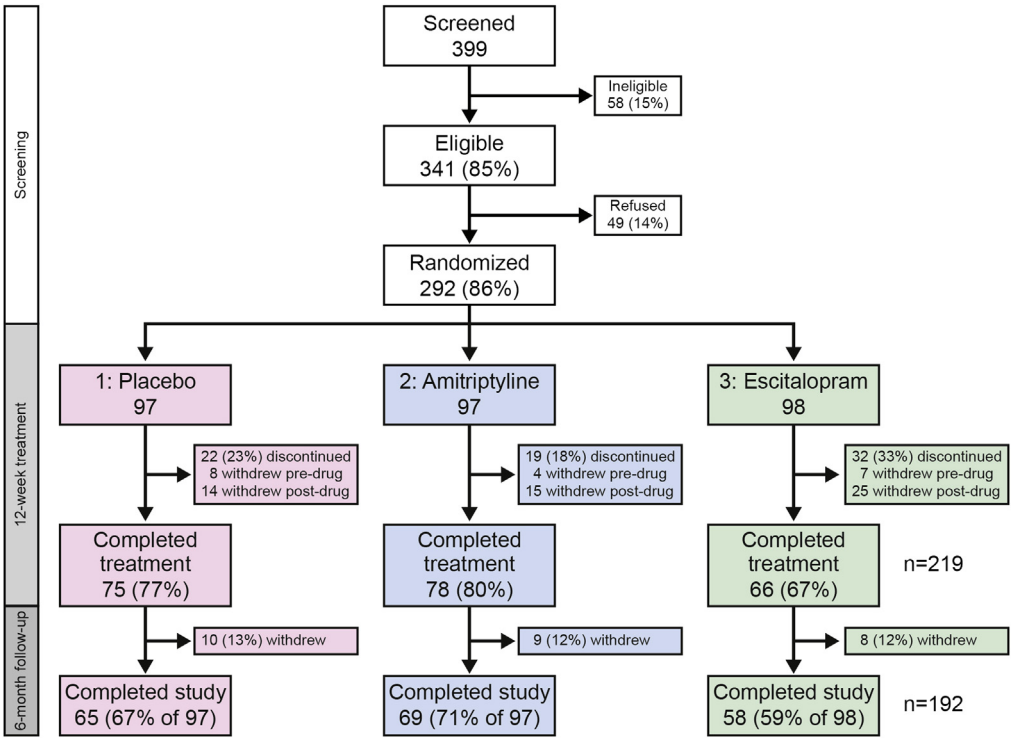

Figure 2. Screening, randomization, and follow-up. After screening the ineligible and unwilling, 292 were randomized to 1 of 3 treatment arms, with 224 (77%) completing the treatment phase. 292 were included in the intent-to-treat analysis; 205 were included in the per-protocol analysis.

treatment arm vs treatment arm comparisons, those receiving amitriptyline appeared to respond better than placebo ($P = .07$; odds ratio [OR] = 1.1; 95% confidence interval [CI]: 0.6−2.1), and escitalopram was comparable with placebo ($P = .65$). The ORs for the pair-wise comparisons are shown in Figure 4.

In ulcer-like FD, subjects receiving amitriptyline reported more adequate relief of FD symptoms than those receiving placebo or escitalopram (11 [39%] placebo vs 20 [67%] amitriptyline vs 8 [27%] escitalopram; $P = .06$ interaction term) (Figure 3*B* and *C*). Those with ulcer-like FD receiving amitriptyline had 3-fold greater odds of reporting adequate relief compared with placebo (OR = 3.1 [95% CI: 1.1−9.0]). Treatment response was otherwise similar among the 3 treatment arms in those with dysmotility-like FD (28 [41%] placebo, 31 [46%] amitriptyline, 29 [43%] escitalopram). Age, sex, body mass index, and baseline Hospital Anxiety Depression Scale scores were not associated with differential treatment response. Those with both FD and IBS were equally likely to respond to amitriptyline as those with FD alone (test for interaction $P = 1.0$). There was a borderline differential treatment effect ($P = .08$) in the small number of FD patients with a prior cholecystectomy compared with those without a prior

Table 2. Subject Characteristics (n = 292)

Characteristics	Placebo (n = 97)	Amitriptyline (n = 97)	Escitalopram (n = 98)
Age, *y*, mean (SD)	45 (16)	43 (15)	45 (15)
Female, n (%)	73 (75)	72 (74)	74 (76)
Caucasian, n (%)	83 (86)	82 (85)	85 (87)
Body mass index, mean (SD)	26.4 (5.2)	25.7 (6.0)	26.1 (5.6)
HADS score, mean (SD)			
HADS depression	3.1 (2.9)	3.1 (2.7)	3.1 (2.7)
HADS anxiety	5.0 (3.8)	5.2 (3.2)	5.4 (3.8)
Dyspepsia subtype, n (%)			
Dysmotility-like	69 (71)	67 (69)	68 (69)
Ulcer-like	28 (29)	30 (31)	30 (31)
Delayed GE, n (%)	20 (21)	20 (21)	21 (21)
Abnormal satiety, n (%)	55 (57)	55 (57)	55 (56)
Helicobacter pylori antibody−positive, n (%)	9/92 (10)	14/96 (15)	17/94 (18)
Baseline PPI use, n (%)	18 (19)	27 (28)	23 (23)

HADS, Hospital Anxiety Depression Scale; PPI, proton pump inhibitor.

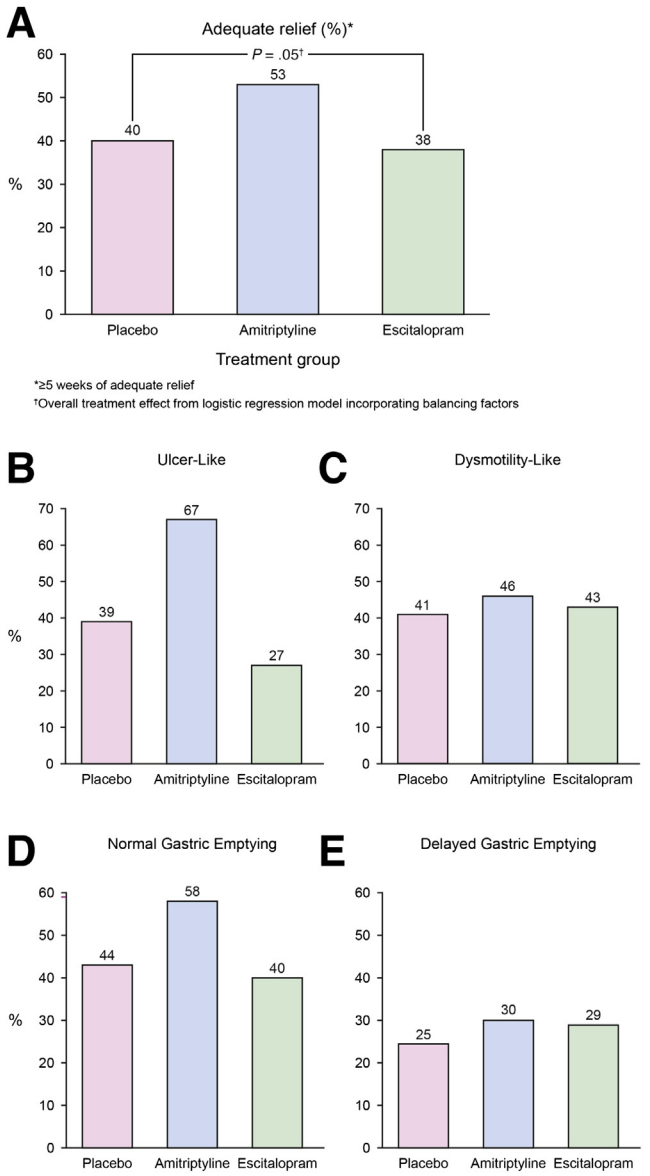

Figure 3. Primary end point: adequate relief. (*A*) Adequate relief of overall FD symptoms were reported by 39 (40%) in the placebo arm, 51 (53%) in the amitriptyline arm, and 38 (38%) in the escitalopram arm. (*B*) Patient with ulcer-like FD had higher reports of adequate relief of FD symptoms in those receiving amitriptyline. (*C*) Patients with dysmotility-like FD did not respond differently between the 3 treatment arms. (*D*) Among subjects with normal GE at baseline, adequate relief was reported by 34 (44%) in the placebo arm, 45 (58%) in the amitriptyline arm, 31 (40%) in the escitalopram arm. (*E*) Among subjects with delayed GE at baseline, adequate relief was reported by 5 (25%) in the placebo arm, 6 (30%) in the amitriptyline arm, and 6 (29%) in the escitalopram arm. Delayed GE was defined as <84% emptying at 4 hours.

cholecystectomy, with better treatment response among those with prior cholecystectomy.

In a per-protocol analysis (n = 205), response rates were highest in the amitriptyline arm: 38 (52%) for placebo, 47 (66%) for amitriptyline, and 32 (52%) for escitalopram (P = .09). Subjects receiving amitriptyline had a greater

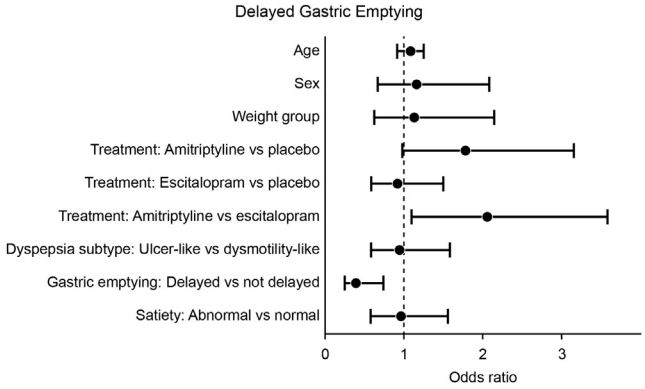

Figure 4. Odds ratios for adequate relief. By pairwise comparisons, the amitriptyline group had greater odds of adequate relief than the escitalopram group. Those with delayed GE had lower odds of adequate relief compared with those with normal GE. Age: 10-year increments. Sex: female vs male. Hospital Anxiety Depression Scale anxiety: 2 points. Weight group: obese vs nonobese. FD subtype: ulcer-like vs dysmotility-like. GE: delayed vs nondelayed. Meal-induced satiety: abnormal vs normal.

odds for adequate relief than those receiving placebo (OR = 2.1; 95% CI: 1.04−4.36; P = .04).

Gastric Emptying

The mean (SD) $t_{1/2}$ for GE at baseline was similar among the 3 groups (112 [38] placebo vs 117 [44] amitriptyline vs 120 [46] escitalopram). No differences in post-treatment $t_{1/2}$ values among the 3 treatment arms was observed (115 [40] placebo vs 117 [43] amitriptyline vs 108 [36] escitalopram) (Supplementary Figure 1). Those with delayed GE at baseline had lower odds of reporting adequate relief than subjects with normal GE (OR = 0.4; 95% CI: 0.2−0.8). The test for interaction between GE status and treatment group on response to therapy was not significant (P = .68) (Figure 3*D* and *E*).

Nutrient Drink Test

All treatment arms had similar mean (SD) baseline MTV (752 [347] placebo vs 708 [371] amitriptyline vs 755 [368] escitalopram) and baseline aggregate symptom scores (173 [84] placebo vs 196 [87] amitriptyline vs 189 [82] escitalopram). After treatment, MTV did not differ by treatment (839 [442] placebo vs 764 [319] amitriptyline vs 823 [391] escitalopram) (Supplementary Figure 2). Post-drink aggregate and individual (nausea, fullness, bloating, abdominal pain) symptom scores did not differ by treatment arm. Postprandial symptom results did not differ by FD subgroup (all interaction tests ≥0.15). Tests to evaluate whether baseline satiety predicted response to therapy were not significant. Formal tests for differential treatment effects on MTV depending on FD subtype (P = .09 for interaction effects) suggested that subjects with dysmotility-like FD had lower volumes among those treated with amitriptyline (vs placebo); while in the ulcer-like FD subgroup, lower volumes were observed in those treated with escitalopram (vs placebo).

Daily Diary Symptoms

Pretreatment, post treatment, and Δ for daily diary scores by treatment arm are summarized in Table 3. No differential treatment effects were seen for upper abdominal pain, nausea, or bloating. However, there were modest treatment effects favoring amitriptyline for fullness ($P = .03$) and early satiety ($P = .07$). FD subtype was not a predictor of symptom response for any of the 5 symptom scores.

Dyspepsia-Specific Quality of Life

Baseline NDI scores for overall quality of life and the 5 subscales were similar among treatment arms. After treatment, quality of life scores increased in all 3 arms, indicating improvement in quality of life (Table 3). Both antidepressant arms had higher post-treatment quality of life scores compared with placebo with respect to overall quality of life score ($P = .02$), as well as for Eat/Drink ($P = .06$), Interference ($P = .06$), Sleep Disturbance ($P = .01$), and

Table 3. Daily Diary Scores and Nepean Dyspepsia Index Functional Dyspepsia–Specific Quality of Life

	Baseline	Post treatment	Δ
Placebo			
Diary			
Upper abdominal pain	1.6 (1.4 to 1.8)	1.2 (1.0 to 1.4)	−0.4 (−0.6 to −0.2)
Nausea	1.2 (1.0 to 1.4)	0.8 (0.6 to 1.0)	−0.4 (−0.6 to −0.2)
Bloating	1.4 (1.2 to 1.6)	1.2 (1.0 to 1.4)	−0.3 (−0.5 to −0.2)
Fullness	1.5 (1.3 to 1.7)	1.2 (1.0 to 1.4)	−0.4 (−0.6 to −0.2)
Early satiety	1.4 (1.2 to 1.6)	1.1 (0.9 to 1.3)	−0.4 (−0.6 to −0.2)
NDI overall quality of life	63.6 (58.9 to 68.2)	73.5 (69.1 to 77.8)	9.9 (5.7 to 14.1)
Interference	68.0 (62.8 to 73.1)	76.2 (70.9 to 81.5)	8.2 (3.6 to 12.9)
Knowledge/control	62.9 (58.1 to 67.8)	72.9 (68.2 to 77.6)	10.0 (5.8 to 14.2)
Eat/drink	52.2 (45.6 to 58.9)	64.8 (59.6 to 70.1)	12.6 (6.8 to 18.4)
Sleep disturbance	67.3 (60.8 to 73.8)	76.4 (70.9 to 81.8)	9.0 (3.5 to 14.6)
Work/study	68.8 (63.0 to 74.6)	79.7 (74.5 to 84.9)	10.9 (5.3 to 16.6)
NDI mean symptom score	8.5 (8.1 to 9.0)	9.6 (9.2 to 10.0)	1.1 (0.7 to 1.4)
Abdominal pain	32.2 (29.9 to 34.4)	36.3 (34.0 to 38.6)	4.2 (2.2 to 6.2)
Postprandial distress	13.6 (12.0 to 15.3)	15.8 (14.2 to 17.4)	2.2 (1.0 to 3.3)
Amitriptyline			
Diary			
Upper abdominal pain	1.6 (1.4 to 1.8)	1.1 (0.9 to 1.3)	−0.6 (−0.8 to −0.4)
Nausea	1.1 (0.9 to 1.3)	0.7 (0.5 to 0.9)	−0.5 (−0.7 to −0.3)
Bloating	1.7 (1.5 to 1.9)	1.2 (1.0 to 1.5)	−0.4 (−0.6 to −0.2)
Fullness	1.5 (1.3 to 1.7)	0.9 (0.7 to 1.1)	−0.7 (−0.8 to −0.5)
Early satiety	1.4 (1.2 to 1.7)	0.8 (0.6 to 1.0)	−0.6 (−0.8 to −0.4)
NDI overall quality of life	63.7 (59.0 to 68.3)	80.6 (76.2 to 85.0)	16.9 (12.3 to 21.6)
Interference	69.5 (64.5 to 74.5)	83.2 (78.3 to 88.2)	13.7 (8.8 to 18.6)
Knowledge/control	62.4 (57.4 to 67.4)	78.2 (73.2 to 83.2)	15.8 (10.9 to 20.8)
Eat/drink	49.1 (43.0 to 55.2)	72.4 (66.7 to 78.0)	23.3 (16.9 to 29.7)
Sleep disturbance	67.6 (61.2 to 74.1)	86.3 (81.6 to 91.0)	18.7 (12.2 to 25.2)
Work/study	70.1 (64.6 to 75.5)	86.9 (82.6 to 91.1)	16.7 (11.9 to 21.7)
NDI mean symptom score	8.0 (7.6 to 8.5)	9.8 (9.3 to 10.2)	1.7 (1.3 to 2.1)
Abdominal pain	29.4 (27.3 to 31.6)	38.0 (35.6 to 40.4)	8.6 (5.9 to 11.3)
Postprandial distress	12.8 (11.3 to 14.4)	17.5 (16.0 to 18.9)	4.7 (3.1 to 6.2)
Escitalopram			
Diary			
Upper abdominal pain	1.7 (1.6 to 1.9)	1.4 (1.2 to 1.6)	−0.4 (−0.5 to −0.2)
Nausea	1.1 (0.8 to 1.3)	0.8 (0.6 to 1.1)	−0.2 (−0.4 to −0.0)
Bloating	1.8 (1.6 to 2.0)	1.3 (1.1 to 1.6)	−0.4 (−0.6 to −0.2)
Fullness	1.7 (1.4 to 1.9)	1.2 (1.0 to 1.5)	−0.4 (−0.6 to −0.2)
Early satiety	1.4 (1.2 to 1.7)	1.1 (0.9 to 1.3)	−0.3 (−0.5 to −0.1)
NDI overall quality of life	72.2 (67.1 to 77.3)	82.8 (78.4 to 87.1)	10.6 (5.5 to 15.6)
Interference	72.2 (67.1 to 77.3)	82.8 (78.4 to 87.1)	10.6 (5.5 to 15.6)
Knowledge/control	63.4 (58.2 to 68.6)	76.2 (71.3 to 81.1)	12.8 (7.6 to 18.0)
Eat/drink	53.3 (47.3 to 59.3)	70.6 (65.4 to 75.6)	17.3 (11.3 to 23.3)
Sleep disturbance	73.6 (67.9 to 79.2)	80.8 (75.2 to 86.3)	7.2 (1.6 to 12.8)
Work/study	75.3 (69.9 to 80.8)	87.2 (83.5 to 90.9)	11.9 (6.4 to 17.3)
NDI mean symptom score	8.4 (7.9 to 8.9)	9.7 (9.3 to 10.2)	1.3 (0.8 to 1.8)
Abdominal pain	31.6 (29.2 to 34.1)	37.1 (34.8 to 39.4)	5.5 (3.0 to 8.0)
Postprandial distress	13.1 (11.6 to 14.6)	16.7 (15.1 to 18.4)	3.6 (2.1 to 5.1)

NOTE. Values are mean (95% CI).

Work/Study ($P = .04$). Neither antidepressant fared better than placebo regarding Knowledge/Control. Greater improvements in overall and sleep-related quality of life scores were seen among those with ulcer-like FD receiving amitriptyline (test for interactions, $P = .01$ and $P = .03$, respectively). Better upper abdominal pain and postprandial distress scores were also seen in those with nondelayed GE receiving amitriptyline (test for interactions, $P = .03$ and $P = .08$, respectively).

Six-Month Follow-Up Data

Among the 123 with follow-up data in the 127 who met criteria for a responder during the active treatment phase, 90 of 123 (73%) relapsed within 6 months. By treatment group, there were 26 relapses among 38 responders in the placebo arm, 40 relapses in 51 responders in the amitriptyline arm, and 24 relapses in 34 responders in the escitalopram arm ($P = .31$).

Safety

There were 235 adverse events reported by 77 (26%) individuals: 20 (21%) on placebo, 29 (30%) on amitriptyline, and 28 (29%) on escitalopram ($P > .05$) (Supplementary Table 1). No serious adverse events were reported. Five individuals reported 5 events with a severity of 3 (of 4): very nervous at week 4 (placebo); worsening abdominal pain at week 5 not believed to be study drug-related, but resulted in study discontinuation (amitriptyline); suicidal thoughts thought to be related to drug (amitriptyline) that resulted in discontinuation of study drug and resolved after stopping; stomachache not believed to be related to study drug (escitalopram); and chest pain 2 months post treatment (escitalopram). Dizziness was more common in the antidepressant arms ($P = .01$) and drowsiness/somnolence was borderline associated with antidepressants ($P = .09$).

Discussion

Because the pathophysiology of FD remains poorly understood and a variety of treatment classes are available, health care providers do face uncertainty in selecting therapies for patients with FD. Options used in practice with limited or no data include antispasmodics, analgesics, over-the-counter remedies, as well as antidepressants to treat visceral hypersensitivity.[8] This multicenter randomized, double-blind, placebo-controlled trial comparing placebo, amitriptyline, and escitalopram in FD subjects lends support to the use of TCAs—but not SSRIs—for this common disorder. Those receiving amitriptyline had a 2-fold increased odds of reporting adequate relief than those receiving escitalopram. The improvement in FD symptoms did not directly correlate with baseline gastric physiology or changes in GE or satiation.

Amitriptyline appears to derive its benefit predominantly through improving abdominal pain. Despite the smaller number of ulcer-like FD subjects, those with ulcer-like FD receiving amitriptyline were 3-fold more likely to report symptom relief than those receiving placebo, without similar findings in those with dysmotility-like FD. This is consistent with studies showing amitriptyline is beneficial in pain syndromes, including IBS and neuropathic pain.[9,35] This differential treatment effect supports the division of FD into a pain or meal-related satiety subtype. Our findings complement the NORIG (Nortriptyline for Idiopathic Gastroparesis) trial, in which nortriptyline was not helpful in improving idiopathic gastroparesis symptoms, including nausea, meal-related satiety, fullness, anorexia, and bloating.[36] In our trial, FD patients with normal GE at baseline treated with amitriptyline reported statistically significant improvement in abdominal pain and postprandial distress.

Our study suggests that in patients with upper abdominal discomfort with a normal endoscopy, clinicians could usefully subtype the FD based on the Rome criteria. Among individuals with pain-predominant FD, a tricyclic antidepressant might be considered in the management algorithm. GE need not be performed unless nausea/vomiting are present and gastroparesis needs to be excluded. Notably FD patients with mild delay in GE or dysmotility-like FD had only a 30% and 46% response rate to amitriptyline, respectively; a tricyclic antidepressant could be considered in these subsets if depression coexists or if FD-related quality of life is poor. Although bowel irregularity was present in more than half of patients with FD, particularly dysmotility-type FD, concurrent IBS was present in only a minority. Treatment response to antidepressant therapy did not differ between patients with FD alone and FD-IBS, suggesting the presence of additional gastrointestinal symptoms does not decrease the likelihood of response to antidepressant therapy.

Although our study suggests that patients with FD are more likely to respond to tricyclic antidepressants, firm conclusions regarding the role of tricyclic antidepressants in FD management—and specifically its role in management of various FD subtypes and additional outcomes—cannot be made due to the relatively modest sample size and the resulting borderline P value of .05 with the study's a priori primary end point. The limited power was primarily due to difficulty with recruitment. Despite intensive efforts, only 292 of the planned 400 were randomized. Identifying individuals with a known diagnosis of FD (and not reflux disease), who did not meet exclusion criteria—including response to antisecretory therapy, current depression or psychiatric disease, or current antidepressant use for any reason, who were willing to participate in this intensive trial—was challenging. It is perhaps debatable whether the study outcome was truly positive. We would argue that the findings are positive in favor of amitriptyline use in FD management because the results appear to follow drug mechanisms with TCAs positively impacting those with painful FD and normal GE. In addition, the mean symptom score on the NDI improved in those who received antidepressants, as did overall FD-related quality of life and specific aspects of FD-specific quality of life improved among those receiving antidepressants. Nonetheless, although more than half of the FD patients receiving TCAs reported adequate relief of FD symptoms, clearly the remainder did not. In other words, TCAs can help FD symptoms improve, but will not resolve all symptoms in all FD patients.

Side effects were noted in a quarter of the participants, including those on placebo. Although FD patients have reported antidepressant intolerance,[37] this study found that the antidepressant side effect experience was quite heterogeneous, although gastrointestinal and neurologic symptoms were more common globally on active treatment. However, there were no common gastrointestinal symptoms among treatment groups. Only dizziness was a common neurologic symptom, particularly in the escitalopram group. This symptom heterogeneity might reflect underlying sensitivity and vigilance rather than drug-related adverse events. Although SSRIs might be perceived to be better tolerated than TCAs, we did not find this.

One potential drawback of the study design is that it includes the requirement of a normal EGD, but only within the past 5 years, raising the question that individuals with an alternative explanation for symptoms might have been included. Reassuringly, 80% of the participants had an EGD within 1 year of study recruitment. As a prior study has shown that the yield from EGD in functional dyspepsia is low in the absence of alarm features[38] and a meta-analysis in FD found that endoscopy was not superior to empiric acid suppression in terms of outcomes, the likelihood of misclassification of FD appears low.[39]

The greatest strength of this study is that although it might have been slightly underpowered to evaluate FD subgroups, it remains one of the largest and most ambitious studies of FD performed to date. Clinical trials evaluating symptom-based functional gastrointestinal disorders can be challenging when a number of end points exist (eg, adequate relief, global symptoms). This study utilized "adequate relief" as its primary outcome, which has been used and accepted in other functional gastrointestinal trials, such as IBS.[23,40] Although Rome III criteria were not applied because the study began before their publication, the current data suggest epigastric pain syndrome and ulcer-like dyspepsia cover similar domains. This study's execution and interpretation of results were regularly overseen by the National Institutes of Health and the Data and Safety Monitoring Board. Although a number of outcomes were collected in this comprehensive study, only predesignated aims and analyses are reported in this article.

In conclusion, in this large, multicenter, randomized, double-blind, placebo-controlled clinical trial, amitriptyline appeared beneficial in FD, particularly in those with ulcer-like FD. Although adverse events were common, there was no overall difference between the 3 arms (except in neurologic symptoms, with highest rates in the escitalopram arm) suggesting that with provider counseling and support, TCAs will be generally well tolerated at low doses. The results do not support the use of escitalopram in FD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.04.020.

References

1. **Tack J, Talley NJ**. Functional dyspepsia—symptoms, definitions and validity of the Rome III criteria. Nat Rev Gastroenterol Hepatol 2013;10:134–141.
2. Kindt S, Tack J. Impaired gastric accommodation and its role in dyspepsia. Gut 2006;55:1685–1691.
3. Talley NJ, Walker MM, Aro P, et al. Non-ulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. Clin Gastroenterol Hepatol 2007;5:1175–1183.
4. Camilleri M, Dubois D, Coulie B, et al. Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study. Clin Gastroenterol Hepatol 2005;3:543–552.
5. Tack J, Caenepeel P, Fischler B, et al. Symptoms associated with hypersensitivity to gastric distention in functional dyspepsia. Gastroenterology 2001;121:526–535.
6. Brook RA, Kleinman NL, Choung RS, et al. Functional dyspepsia impacts absenteeism and direct and indirect costs. Clin Gastroenterol Hepatol 2010;8:498–503.
7. Lacy BE, Weiser KT, Kennedy AT, et al. Functional dyspepsia: the economic impact to patients. Aliment Pharmacol Ther 2013;38:170–177.
8. Lacy BE, Talley NJ, Locke GR 3rd, et al. Review article: current treatment options and management of functional dyspepsia. Aliment Pharmacol Ther 2012;36:3–15.
9. Ford AC, Talley NJ, Schoenfeld PS, et al. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. Gut 2009;58:367–378.
10. Mertz H, Fass R, Kodner A, et al. Effect of amitriptyline on symptoms, sleep, and visceral perception in patients with functional dyspepsia. Am J Gastroenterol 1998;93:160–165.
11. Otaka M, Jin M, Odashima M, et al. New strategy of therapy for functional dyspepsia using famotidine, mosapride and amitriptyline. Aliment Pharmacol Ther 2005;21(Suppl 2):42–46.
12. van Kerkhoven LA, Laheij RJ, Aparicio N, et al. Effect of the antidepressant venlafaxine in functional dyspepsia: a randomized, double-blind, placebo-controlled trial. Clin Gastroenterol Hepatol 2008;6:746–752; quiz 718.
13. Tan VP, Cheung TK, Wong WM, et al. Treatment of functional dyspepsia with sertraline: a double-blind randomized placebo-controlled pilot study. World J Gastroenterol 2012;18:6127–6133.
14. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. J Psychiatry Neurosci 2001;26:30–36.
15. Clouse RE. Antidepressants for functional gastrointestinal syndromes. Dig Dis Sci 1994;39:2352–2363.
16. Clouse RE, Lustman PJ, Geisman RA, et al. Antidepressant therapy in 138 patients with irritable bowel syndrome: a five-year clinical experience. Aliment Pharmacol Ther 1994;8:409–416.
17. Gorard DA, Libby GW, Farthing MJ. Influence of antidepressants on whole gut and orocaecal transit times in

health and irritable bowel syndrome. Aliment Pharmacol Ther 1994;8:159–166.
18. Tack J, Broekaert D, Coulie B, et al. Influence of the selective serotonin re-uptake inhibitor, paroxetine, on gastric sensorimotor function in humans. Aliment Pharmacol Ther 2003;17:603–608.
19. Talley NJ, Locke GR 3rd, Herrick LM, et al. Functional Dyspepsia Treatment Trial (FDTT): a double-blind, randomized, placebo-controlled trial of antidepressants in functional dyspepsia, evaluating symptoms, psychopathology, pathophysiology and pharmacogenetics. Contemp Clin Trials 2012;33:523–533.
20. Talley NJ, Stanghellini V, Heading RC, et al. Functional gastroduodenal disorders. Gut 1999;45(Suppl 2):II37–II42.
21. Junghard O, Lauritsen K, Talley NJ, et al. Validation of seven graded diary cards for severity of dyspeptic symptoms in patients with non ulcer dyspepsia. Eur J Surg Suppl 1998:106–111.
22. Bijkerk CJ, de Wit NJ, Muris JW, et al. Outcome measures in irritable bowel syndrome: comparison of psychometric and methodological characteristics. Am J Gastroenterol 2003;98:122–127.
23. Mangel AW, Hahn BA, Heath AT, et al. Adequate relief as an endpoint in clinical trials in irritable bowel syndrome. J Int Med Res 1998;26:76–81.
24. Tack J, Delia T, Ligozio G, et al. A phase II placebo controlled randomized trial with tegaserod in functional dyspepsia patients with normal gastric emptying. Gastroenterology 2002;122:A-20.
25. Talley NJ, Van Zanten SV, Saez LR, et al. A dose-ranging, placebo-controlled, randomized trial of alosetron in patients with functional dyspepsia. Aliment Pharmacol Ther 2001;15:525–537.
26. Talley NJ, Haque M, Wyeth JW, et al. Development of a new dyspepsia impact scale: the Nepean Dyspepsia Index. Aliment Pharmacol Ther 1999;13:225–235.
27. Jones M, Talley NJ. Minimum clinically important difference for the Nepean Dyspepsia Index, a validated quality of life scale for functional dyspepsia. Am J Gastroenterol 2009;104:1483–1488.
28. Camilleri M, Zinsmeister AR, Greydanus MP, et al. Towards a less costly but accurate test of gastric emptying and small bowel transit. Dig Dis Sci 1991; 36:609–615.
29. Cremonini F, Mullan BP, Camilleri M, et al. Performance characteristics of scintigraphic transit measurements for studies of experimental therapies. Aliment Pharmacol Ther 2002;16:1781–1790.
30. Camilleri M, Iturrino J, Bharucha AE, et al. Performance characteristics of scintigraphic measurement of gastric emptying of solids in healthy participants. Neurogastroenterol Motil 2012;24:1076–e562.
31. Chial HJ, Camilleri C, Delgado-Aros S, et al. A nutrient drink test to assess maximum tolerated volume and postprandial symptoms: effects of gender, body mass index and age in health. Neurogastroenterol Motil 2002; 14:249–253.
32. Boeckxstaens GE, Hirsch DP, van den Elzen BD, et al. Impaired drinking capacity in patients with functional dyspepsia: relationship with proximal stomach function. Gastroenterology 2001;121:1054–1063.
33. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103–115.
34. Therneau TM. How many stratification factors are "too many" to use in a randomization plan? Control Clin Trials 1993;14:98–108.
35. Bryson HM, Wilde MI. Amitriptyline. A review of its pharmacological properties and therapeutic use in chronic pain states. Drugs Aging 1996;8:459–476.
36. Parkman HP, Van Natta ML, Abell TL, et al. Effect of nortriptyline on symptoms of idiopathic gastroparesis: the NORIG randomized clinical trial. JAMA 2013;310: 2640–2649.
37. Van Oudenhove L, Tack J. Is the antidepressant venlafaxine effective for the treatment of functional dyspepsia? Nat Clin Pract Gastroenterol Hepatol 2009;6:74–75.
38. Talley NJ, Vakil N. Guidelines for the management of dyspepsia. Am J Gastroenterol 2005;100:2324–2337.
39. Delaney BC, Moayyedi P, Forman D. Initial management strategies for dyspepsia. Cochrane Database Syst Rev 2003:CD001961.
40. Camilleri M. Editorial: is adequate relief fatally flawed or adequate as an end point in irritable bowel syndrome? Am J Gastroenterol 2009;104:920–922.

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Conflicts of interest
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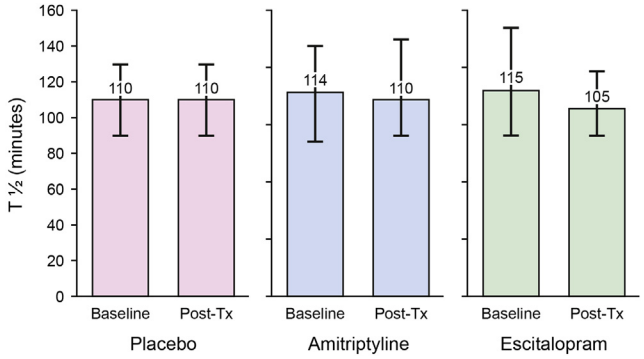
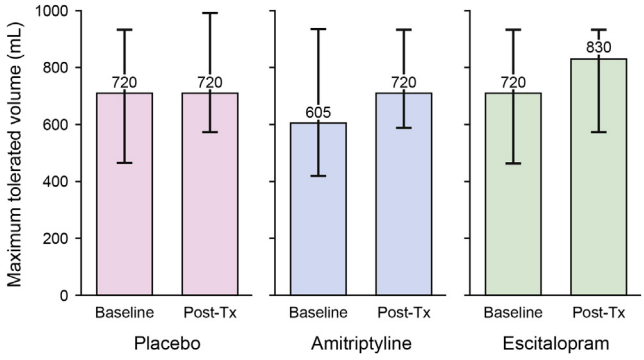


Supplementary Figure 1. GE before and after treatment (median, interquartile ranges). There were no differences in baseline solid-phase GE—$t_{1/2}$ in minutes—between treatment arms. There were also no changes in GE after treatment in all 3 treatment arms.



Supplementary Figure 2. Nutrient Drink Test (NDT) satiety test before and after treatment (median interquartile ranges). The NDT for gastric satiety showed that there were no differences in baseline meal-induced satiety—as measured by MTV of Ensure—between treatment arms. There were no changes in gastric satiety after treatment in all 3 treatment arms.

Supplementary Table 1. Adverse Events (n = 292)

Adverse event type	Total (n = 292)	Placebo (n = 97)	Amitriptyline (n = 97)	Escitalopram (n = 98)	*P* value[a]
Cardiac	4 (1.4)	2 (2.1)	0 (0)	2 (2.0)	.55
Dermatologic	11 (3.8)	8 (8.2)	0 (0)	3 (3.1)	.007
Endocrine	8 (2.7)	1 (1.0)	2 (2.1)	5 (5.1)	.29
Hematologic	1 (0.3)	1 (1.0)	0 (0)	0 (0)	.66
Abdominal pain	11 (3.8)	1 (1.0)	5 (5.2)	5 (5.1)	.24
Black stools	1 (0.3)	0 (0)	1 (1.0)	0 (0)	.66
Bloating	3 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	1.00
Clostridium difficile infection	1 (0.3)	0 (0)	1 (1.0)	0 (0)	.66
Change in appetite	2 (0.7)	0 (0)	0 (0)	2 (2.0)	.33
Constipation	8 (2.7)	1 (1.0)	5 (5.2)	2 (2.0)	.23
Diarrhea	4 (1.4)	1 (1.0)	2 (2.1)	1 (1.0)	.85
Dry mouth	2 (0.7)	0 (0)	2 (2.1)	0 (0)	.22
Heartburn	2 (0.7)	1 (1.0)	1 (1.0)	0 (0)	.55
Hemorrhoids	1 (0.3)	1 (1.0)	0 (0)	0 (0)	.66
Intestinal fluid	2 (0.7)	2 (2.1)	0 (0)	0 (0)	.22
Liver function abnormality	2 (0.7)	0 (0)	1 (1.0)	1 (1.0)	1.00
Nausea/vomiting	18 (6.2)	3 (3.1)	6 (6.2)	9 (9.2)	.22
Gastrointestinal	57 (19.5)	11 (11.3)	25 (25.8)	21 (21.4)	.03
Gynecologic	2 (0.7)	0 (0)	2 (2.1)	0 (0)	.22
Metabolic/nutritional	4 (1.4)	3 (3.1)	0 (0)	1 (1.0)	.23
Musculoskeletal/skeletal	21 (7.2)	4 (4.1)	10 (10.3)	7 (7.1)	.23
Anxiety	12 (4.1)	4 (4.1)	2 (2.1)	6 (6.1)	.41
Depression	1 (0.3)	1 (1.0)	0 (0)	0 (0)	.66
Dizziness	17 (5.8)	1 (1.0)	5 (5.2)	11 (11.2)	.009
Dream abnormalities	1 (0.3)	0 (0)	1 (1.0)	0 (0)	.66
Drowsiness or Somnolence	29 (9.9)	5 (5.2)	14 (14.4)	10 (10.2)	.09
Headache	13 (4.4)	3 (3.1)	2 (2.1)	8 (8.2)	.16
Insomnia	8 (2.7)	1 (1.0)	2 (2.1)	5 (5.1)	.29
Tingling	3 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	1.00
Neurologic	84 (28.8)	16 (16.5)	27 (27.8)	41 (41.8)	.0005
Otolaryngologic	6 (2.0)	1 (1.0)	3 (3.1)	2 (2.0)	.70
Pulmonary	9 (3.1)	1 (1.0)	6 (6.2)	2 (2.0)	.13
Psychiatric	1 (0.3)	1 (1.0)	0 (0)	0 (0)	.66
Respiratory	5 (1.7)	2 (2.1)	2 (2.1)	1 (1.0)	.75
Sensory systems	4 (1.4)	1 (1.0)	2 (2.1)	1 (1.0)	.85
Urogenital	4 (1.4)	0 (0)	4 (4.1)	0 (0)	.02

NOTE. Values are n (%).
[a]Based on Fisher's exact test.