Effect of Nortriptyline on Symptoms of Idiopathic Gastroparesis
The NORIG Randomized Clinical Trial

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IMPORTANCE Gastroparesis remains a challenging syndrome to manage, with few effective treatments and a lack of rigorously controlled trials. Tricyclic antidepressants are often used to treat refractory symptoms of nausea, vomiting, and abdominal pain. Evidence from well-designed studies for this use is lacking.

OBJECTIVE To determine whether treatment with nortriptyline results in symptomatic improvement in patients with idiopathic gastroparesis.

DESIGN, SETTING, AND PARTICIPANTS The NORIG (Nortriptyline for Idiopathic Gastroparesis) trial, a 15-week multicenter, parallel-group, placebo-controlled, double-masked, randomized clinical trial from the National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium (GpCRC), comparing nortriptyline with placebo for symptomatic relief in idiopathic gastroparesis. One hundred thirty patients with idiopathic gastroparesis were enrolled between March 2009 and June 2012 at 7 US academic medical centers. Patient follow-up was completed in October 2012. Inclusion criteria included delayed gastric emptying and moderate to severe symptom scores using the Gastroparesis Cardinal Symptom Index (GCSI).

INTERVENTIONS Nortriptyline vs placebo. Study drug dose was increased at 3-week intervals (10, 25, 50, 75 mg) up to 75 mg at 12 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome measure of symptomatic improvement was a decrease from the patient’s baseline GCSI score of at least 50% on 2 consecutive 3-week GCSI assessments during 15 weeks of treatment.

RESULTS The primary symptomatic improvement outcome did not differ between 65 patients randomized to nortriptyline vs 65 patients randomized to placebo: 15 (23% [95% CI, 14%-35%]) in the nortriptyline group vs 14 (21% [95% CI, 12%-34%]) in the placebo group (P = .86). Treatment was stopped more often in the nortriptyline group (19 [29% (95% CI, 19%-42%)]) than in the placebo group (6 [9%] (95% CI, 3%-19%)) (P = .007), but numbers of adverse events were not different (27 [95% CI, 18-39] vs 28 [95% CI, 19-40]) (P = .89).

CONCLUSIONS AND RELEVANCE Among patients with idiopathic gastroparesis, the use of nortriptyline compared with placebo for 15 weeks did not result in improvement in overall symptoms. These findings do not support the use of nortriptyline for idiopathic gastroparesis.

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Gastroparesis remains a challenging syndrome to manage, with few effective treatments and a lack of rigorously controlled trials.1 Metoclopramide, the only medication currently approved in the United States for treatment of gastroparesis, is limited by its neurologic adverse effects.2 Domperidone, a peripherally acting analog, may be safer but is not approved by the US Food and Drug Administration.3-4 Both drugs accelerate gastric emptying and have independent antinausea effects. Erythromycin, an antibiotic and motilin receptor agonist that improves gastric emptying, is limited by tachyphylaxis.5 Further, it is unclear whether a pure prokinetic drug will be an effective therapy, because there is a poor correlation between gastric emptying and symptoms.6

An alternative approach to treatment of gastroparesis is based on the hypothesis that some of the symptoms (eg, nausea, pain) arise because of neuropathic changes in enteric and sensory nerves. In clinical practice, tricyclic antidepressants (TCAs) in low doses are used as neuromodulators for treatment of nausea, vomiting, and abdominal pain in patients with gastroparesis.1,7 However, there is little evidence to support this use.1 In one retrospective analysis of open-label treatment, TCAs reduced symptoms in functional vomiting.8 In 2 studies in functional dyspepsia, low-dose TCAs decreased dyspeptic symptoms and abdominal pain.9,10 In a retrospective evaluation of patients with diabetes and nausea and vomiting, low-dose TCAs improved symptoms.10 One-third of patients had delayed gastric emptying, suggesting that this is not a contraindication for TCAs related to their anticholinergic component.

The primary aim of the NORIG (Nortriptyline for Idiopathic Gastroparesis) trial from the National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium (GpCRC) was to determine whether treatment with nortriptyline results in symptomatic improvement in patients with idiopathic gastroparesis. Nortriptyline, a secondary amine TCA, was selected because of fewer anticholinergic effects compared with the tertiary amines such as amitriptyline.10 This study used a dose-escalation strategy for nortriptyline, a practice conventionally used when treating patients with a TCA.

### Methods

This 15-week multicenter, parallel-group, placebo-controlled, double-masked, randomized clinical trial compared nortriptyline with placebo for symptomatic relief in patients with moderate to severe symptoms of idiopathic gastroparesis.

The trial was approved by the local institutional review board at each site. All enrolled patients provided written informed consent. A data and safety monitoring board met every 6 months. One planned interim analysis of the primary outcome measure occurred when approximately 50% of the patients had completed the trial using a 2-sided O’Brien-Fleming statistical stopping guideline of \( z = 2.80 \).13 Per our protocol, we present nominal \( P \) values for our primary analysis, with \( P \leq 0.05 \) considered statistically significant. The data and safety monitoring board was masked to treatment assignment during the trial.

### Study Participants

Patients aged 21 to 68 years who had experienced moderate to severe symptoms of idiopathic gastroparesis for at least 6 months were included. Inclusion criteria included delayed gastric emptying demonstrated by scintigraphy and symptom scores of 21 or greater on the 9-symptom Gastroparesis Cardinal Symptom Index (GCSI) (range of possible scores, 0-45 points).14 Patients could take prokinetic or antiemetic agents, as long as doses remained stable during the study. Patients were excluded if they had diabetic or postsurgical gastroparesis or dyspeptic symptoms with normal gastric emptying. Patients were excluded if they were currently using a TCA of any kind; using daily narcotic analgesics for abdominal pain; using anticholinergic medications, calcium channel blockers, or erythromycin; or had contraindications to nortriptyline use.

### Baseline Studies

At the initial study visit, each patient was assessed to determine study entry, provide signed informed consent, and stop disallowed medications. A history and physical examination, electrocardiogram, and screening blood tests were obtained.

In addition to a TCA adverse effects questionnaire, patients also filled out baseline symptom questionnaires to assess gastroparetic symptoms, pain, quality of life, depression, anxiety, and somatization. The Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity (PAGI-SYM) questionnaire assesses symptoms of gastroparesis, dyspepsia, and gastroesophageal reflux disease and includes abdominal pain as well as gastroparesis symptoms assessed by the GCSI. The GCSI asks about nausea, retching, vomiting, stomach fullness, inability to finish a meal, excessive fullness, loss of appetite, bloating, and abdominal distension. Severities of symptoms during the previous 2 weeks are scaled from 0 = no symptoms to 5 = very severe. The Gastrointestinal Symptom Rating Scale (GSRS) assesses gastrointestinal symptoms seen in irritable bowel syndrome and peptic ulcer disease. The Brief Pain Inventory specifically assesses pain. The Medical Outcomes Study 36-Item Short-Form Health Survey version 2 was used to assess the patients’ views of overall physical and mental health. Psychological functioning was assessed using the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI). The Patient Health Questionnaire (PHQ-15) is a measure of somatization. Patients answered questions regarding symptoms that could be attributed to adverse effects of nortriptyline. A Global Overall Relief of Symptoms question asked “During the past 7 days, have you had adequate relief of your stomach symptoms?” A Clinical Global Patient Impression (CGPI) question quantified overall relief of symptoms. This question asked, “Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during the past...
week?” with responses scaled from −3 = very considerably worse to 3 = completely better.

Patients had to have a negative upper endoscopy result and evidence of delayed gastric emptying on scintigraphy (gastric retention >60% at 2 hours, >10% at 4 hours, or both) using a low-fat, egg-white meal with imaging at 0, 1, 2, and 4 hours.24,25

Electrogastrography (EGG) recorded electrical activity of gastric smooth muscle using cutaneous abdominal electrodes.26 The frequency and amplitude of the EGG signal was assessed; power is the strength (amplitude) of a specific frequency of the recorded EGG signal according to fast Fourier analysis.26 A satiety test with EGG26,27 was also performed. After a 30-minute fasting baseline EGG recording was obtained, patients drank a nutritional supplement beverage (Ensure; Abbott Nutrition) (1.1 kcal/mL) every 5 minutes until they felt completely full, at which time another 30-minute EGG recording was obtained.

Treatment
The centrally administered randomization scheme assigned eligible patients in randomly permuted blocks of treatment group assignments stratified by clinical center. Randomized patients were seen at 3-week intervals for a total of 15 weeks during treatment and at 3 weeks after treatment to assess symptom improvement and adverse effects.

The dosing of the study medications was escalated identically in both treatment groups: one 10-mg capsule orally at bedtime for 3 weeks, then one 25-mg capsule for another 3 weeks, then two 25-mg capsules (50 mg) for 3 weeks, then three 25-mg capsules (75 mg) for the final two 3-week periods of treatment.

If a common, nonserious adverse effect to the study drug developed, investigators followed a standardized management plan. If the adverse effect became bothersome, the study drug dosage was reduced to the last dose tolerated. If patients developed intolerable or serious adverse effects, the drug was stopped for 1 week. If the adverse effects disappeared, an attempt was made to reintroduce the study drug after 1 week at the previous lower tolerated dose. If the dose was well tolerated, the patient continued to receive this dose for the remainder of the study. If the symptoms reappeared, the study drug was stopped and the patient completed follow-up without medication. Adverse effects listed in the consent statement included dry mouth, drowsiness, sedation, fatigue, dizziness, seizures, palpitations, blurred vision, constipation, and rash and, in severely depressed patients, an increased risk of suicide.

Rescue medications (promethazine, ondansetron, or both) were allowed as needed for nausea and vomiting. For pain, patients could take their usual analgesic medications, generally tramadol, proproxephene, or both, on an intermittent basis.

At the follow-up visits (every 3 weeks), symptom questionnaires were completed, including PAGI-SYM, BDI, Global Overall Relief of Symptoms, CGPI, and a TCA adverse effects questionnaire. Capsule counts were performed to quantify adherence to treatment. At the week-9 visit, an electrocardiogram was performed prior to increasing the study drug dose to 75 mg for the remaining 6 weeks of treatment. At the week-12 visit (75 mg of study drug per protocol), an EGG with satiety test and electrocardiogram were performed. Following the end of the trial at 15 weeks, the study medication dose was tapered to zero over a 2-week period, with a final assessment at 18 weeks.
Outcome Measures
The primary outcome measure of symptomatic improvement was a decrease from the patient’s baseline GCSI score of at least 50% on 2 consecutive 3-week GCSI assessments over 15 weeks of treatment.

Per-protocol prespecified secondary outcome measures included specific symptoms (individual symptom sub-scores from the GCSI), individual symptom scores, Global Overall Relief of Symptoms questionnaire, CGPI, physiologic measures (volume of nutritional beverage consumed during satiety testing), adverse event rates, and counts of adverse effects requiring stopping medication.

Statistical Analysis
The primary analysis included all patients on an intention-to-treat basis in which the proportion of patients with sympto-
matic improvement were compared between the groups randomized to nortriptyline vs placebo. Patients without at least 2 follow-up GCSI scores were imputed as nonresponders (2 patients in each group). Comparisons were made with the use of the Mantel-Haenszel χ² test stratified by clinic. Secondary outcome measures were analyzed with χ² test for binary outcomes or analysis of covariance regression models for continuous outcomes relating the change in the continuous outcome from baseline to follow-up to treatment group and baseline value of the outcome. Analyses of the patterns of response by time in GCSI scores and other measures at 3-week intervals through the end of treatment were shown graphically. Statistical significance of differences in patterns between groups used longitudinal repeated-measures multiple linear regression models of each measure related to treatment group, baseline value of the measure, and indicator variables for each time interval. Treatment × time interactions were tested first; none of the interactions for any measure were significant (P < .05 for all).

The planned sample size was 130 patients with equal assignment to 2 groups (65 per group). The study had 90% power to detect a 2-fold increase in the overall symptomatic improvement rate assuming 10% loss to follow-up, 30% symptomatic improvement rate in the placebo group, and a 2-sided type I error of 5%.

Sensitivity analyses included logistic regression of the primary outcome on treatment group using 100 multiple imputation data sets for observations missing the primary outcome, using treatment group and GCSI score at baseline as predictors for the logistic imputation model. Statistical analyses were generated using SAS version 9.3 (SAS Institute Inc) and Stata release 12 (StataCorp).

Results

Patient Characteristics

Study patients were enrolled between March 2009 and June 2012 (Figure 1). Patient follow-up was completed in October 2012. Of the 130 study patients who underwent randomization, 65 were assigned to receive nortriptyline and 65 to receive placebo. The 2 groups were similar with respect to demographic characteristics, clinical and laboratory data, and gastroparesis symptoms (Table 1, Table 2, and eTable 1 in Supplement). Overall at baseline, the study population was 89% women, 83% white, had a mean age of 41 years, and had a mean body mass index of 27 (calculated as weight in kilograms divided by height in meters squared). The mean severity of symptoms quantitated by GCSI score was 3.8 for nausea, 3.9 for early satiety, 3.7 for bloating, and 30.6

Table 2. Baseline Gastric Diagnostic Test Results by Treatment Group

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean (SD)</th>
<th>Nortriptyline (n = 65)</th>
<th>Placebo (n = 65)</th>
<th>Total, Mean (SD) (N = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric emptying scintigraphy</td>
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<tr>
<td>1 h</td>
<td></td>
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<tr>
<td>No. of evaluable patients</td>
<td>63</td>
<td>62</td>
<td></td>
<td>80 (13)</td>
</tr>
<tr>
<td>Gastric retention, %</td>
<td>80 (14)</td>
<td>80 (12)</td>
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<td></td>
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<tr>
<td>2 h</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of evaluable patients</td>
<td>58</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric retention, %</td>
<td>61 (17)</td>
<td>59 (17)</td>
<td>60 (17)</td>
<td></td>
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<tr>
<td>4 h</td>
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<tr>
<td>No. of evaluable patients</td>
<td>56</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric retention, %</td>
<td>26 (16)</td>
<td>25 (17)</td>
<td>26 (16)</td>
<td></td>
</tr>
<tr>
<td>Satiety test, volume consumed, median (IQR), mL</td>
<td>269 (225-424)</td>
<td>240 (177-382)</td>
<td>240 (207-400)</td>
<td></td>
</tr>
<tr>
<td>Electrogastrography, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of evaluable patients</td>
<td>54</td>
<td>50</td>
<td>104</td>
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</tr>
<tr>
<td>Average power in bradygastria region (1.0–2.5 cpm)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>50 (20)</td>
<td>43 (18)</td>
<td>46 (19)</td>
<td></td>
</tr>
<tr>
<td>0-30–min post satiety test</td>
<td>40 (13)</td>
<td>41 (15)</td>
<td>41 (14)</td>
<td></td>
</tr>
<tr>
<td>Average power in normal region (2.5–3.7 cpm)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20 (15)</td>
<td>19 (10)</td>
<td>20 (13)</td>
<td></td>
</tr>
<tr>
<td>0-30–min post satiety test</td>
<td>24 (14)</td>
<td>23 (11)</td>
<td>23 (13)</td>
<td></td>
</tr>
<tr>
<td>Average power in tachygastria region (3.7–10.0 cpm)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>21 (10)</td>
<td>26 (10)</td>
<td>23 (10)</td>
<td></td>
</tr>
<tr>
<td>0-30–min post satiety test</td>
<td>27 (7)</td>
<td>28 (10)</td>
<td>27 (8)</td>
<td></td>
</tr>
<tr>
<td>Average power in duodenal region (10.0–15.0 cpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10 (13)</td>
<td>12 (10)</td>
<td>11 (10)</td>
<td></td>
</tr>
<tr>
<td>0-30–min post satiety test</td>
<td>9 (8)</td>
<td>8 (7)</td>
<td>9 (7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: cpm, cycles per minute; IQR, interquartile range.
Table 3. Comparison of Primary and Secondary Outcomes by Treatment Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nortriptyline</th>
<th>Placebo</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients randomized</td>
<td>65</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>≥2 consecutive visits with GCSI score ≤50% of baseline, No. (%)</td>
<td>15 (23.1) [13.5 to 35.2]</td>
<td>14 (21.5) [12.3 to 33.5]</td>
<td>.86</td>
</tr>
<tr>
<td><strong>Secondary outcomes assessed after 15 wk of treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of evaluable patients</td>
<td>56</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Patient assessment of upper gastrointestinal symptom severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total GCSI score</td>
<td>−8.8 (−11.7 to −5.9)</td>
<td>−7.2 (−9.6 to −4.9)</td>
<td>.47</td>
</tr>
<tr>
<td>Nausea subscore</td>
<td>−2.5 (−3.6 to −1.4)</td>
<td>−2.7 (−3.7 to −1.8)</td>
<td>.67</td>
</tr>
<tr>
<td>Fullness or early satiety subscore</td>
<td>−5.0 (−6.5 to −3.5)</td>
<td>−3.3 (−4.6 to −2.1)</td>
<td>.11</td>
</tr>
<tr>
<td>Bloating, subscore</td>
<td>−1.3 (−2.1 to −0.5)</td>
<td>−1.2 (−1.9 to −0.4)</td>
<td>.86</td>
</tr>
<tr>
<td>Upper abdominal pain score</td>
<td>−1.7 (−2.6 to −0.7)</td>
<td>−1.7 (−2.5 to −1.0)</td>
<td>.85</td>
</tr>
<tr>
<td>Lower abdominal pain score</td>
<td>−0.9 (−1.7 to 0.0)</td>
<td>−0.3 (−1.0 to 0.4)</td>
<td>.26</td>
</tr>
<tr>
<td>GERD subscore</td>
<td>−4.3 (−6.8 to −1.9)</td>
<td>−5.6 (−7.7 to −3.5)</td>
<td>.85</td>
</tr>
<tr>
<td>Constipation score</td>
<td>−0.2 (−0.7 to 0.2)</td>
<td>−0.4 (−0.8 to −0.1)</td>
<td>.20</td>
</tr>
<tr>
<td>Diarrhea score</td>
<td>−0.4 (−0.8 to 0.1)</td>
<td>−0.7 (−1.0 to −0.3)</td>
<td>.65</td>
</tr>
<tr>
<td><strong>Gastroparesis symptoms inventory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Global Patient Impression score</td>
<td>1.3 (1.0 to 1.6)</td>
<td>0.9 (0.5 to 1.3)</td>
<td>.17</td>
</tr>
<tr>
<td>Gastrointestinal symptom rating scale, mean score</td>
<td>−0.5 (−0.8 to −0.3)</td>
<td>−0.5 (−0.8 to −0.3)</td>
<td>.77</td>
</tr>
<tr>
<td>SF-36 Quality of Life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component summary</td>
<td>3.8 (1.3 to 6.4)</td>
<td>1.7 (−0.2 to 3.6)</td>
<td>.20</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>1.8 (−1.4 to 5.1)</td>
<td>0.9 (−1.3 to 3.1)</td>
<td>.47</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>−2.6 (−5.0 to −0.2)</td>
<td>−3.1 (−4.9 to −1.3)</td>
<td>.89</td>
</tr>
<tr>
<td>Brief Pain Inventory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity score</td>
<td>−1.1 (−1.9 to −0.4)</td>
<td>−0.5 (−1.1 to 0.1)</td>
<td>.10</td>
</tr>
<tr>
<td>Interference score</td>
<td>−1.1 (−1.8 to −0.4)</td>
<td>−0.2 (−0.9 to 0.6)</td>
<td>.06</td>
</tr>
<tr>
<td>State-Trait Anxiety Inventory</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>State anxiety</td>
<td>0.4 (−2.9 to 3.7)</td>
<td>−0.1 (−2.6 to 2.4)</td>
<td>.78</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>−0.3 (−3.0 to 2.5)</td>
<td>−1.7 (−3.5 to 0.1)</td>
<td>.43</td>
</tr>
<tr>
<td>PHQ-15 score</td>
<td>−2.4 (−3.6 to −1.2)</td>
<td>−1.5 (−2.5 to −0.5)</td>
<td>.17</td>
</tr>
<tr>
<td><strong>Secondary outcomes assessed after 12 wk of treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>n = 55c</td>
<td>n = 59c</td>
<td></td>
</tr>
<tr>
<td>Value</td>
<td>0.5 (0.1 to 0.8)</td>
<td>0.0 (−0.3 to 0.3)</td>
<td>.06</td>
</tr>
<tr>
<td>Satiety test</td>
<td>n = 49c</td>
<td>n = 55c</td>
<td></td>
</tr>
<tr>
<td>Volume consumed, mL</td>
<td>7 (−24 to 39)</td>
<td>1 (−35 to 36)</td>
<td>.71</td>
</tr>
<tr>
<td>Electrogastroscopy, %</td>
<td>n = 39c</td>
<td>n = 33c</td>
<td></td>
</tr>
<tr>
<td>Average power in bradygastric region (1.0−2.5 cpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>−1 (−10 to 7)</td>
<td>6 (−1 to 13)</td>
<td>.59</td>
</tr>
<tr>
<td>0–30-min post satiety test</td>
<td>−2 (−7 to 4)</td>
<td>−1 (−7 to 4)</td>
<td>.54</td>
</tr>
<tr>
<td>Average power in normal region (2.5−3.7 cpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, %</td>
<td>0 (−5 to 6)</td>
<td>−2 (−7 to 2)</td>
<td>.42</td>
</tr>
<tr>
<td>0–30-min post satiety test, %</td>
<td>−1 (−5 to 3)</td>
<td>1 (−4 to 6)</td>
<td>.73</td>
</tr>
<tr>
<td>Average power in tachygastric region (3.7−10.0 cpm)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline, %</td>
<td>2 (−3 to 6)</td>
<td>−4 (−8 to 0)</td>
<td>.70</td>
</tr>
<tr>
<td>0–30-min post satiety test, %</td>
<td>2 (−2 to 5)</td>
<td>0 (−3 to 3)</td>
<td>.50</td>
</tr>
<tr>
<td>Average power in duodenal region (10.0−15.0 cpm)</td>
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<td></td>
</tr>
<tr>
<td>Baseline, %</td>
<td>−1 (−6 to 4)</td>
<td>0 (−3 to 4)</td>
<td>.56</td>
</tr>
<tr>
<td>0–30-min post satiety test, %</td>
<td>1 (−3 to 6)</td>
<td>1 (−1 to 3)</td>
<td>.65</td>
</tr>
</tbody>
</table>

*Abbreviations: cpm, cycles per minute; GCSI, Gastroparesis Cardinal Symptom Index; GERD, gastroesophageal reflux; PHQ-15, 15-item Patient Health Questionnaire.

a P values derived from Mantel-Haenszel test stratified by clinic for binary outcome or analysis of covariance model regressing change from baseline on treatment group and baseline value of the outcome for continuous outcomes.

b Using logistic regression, the relative risk of the primary outcome comparing nortriptyline with placebo is 1.06 (95% CI, 0.65 to 2.00).

c No. of evaluable patients.
for total GCSI. Retention at 4 hours for scintigraphic gastric emptying averaged 26% (moderate retention).

Follow-up and Treatment
Patients completed 94% of the study visits; 91% in the nortriptyline group and 96% in the placebo group (P = .24). Thirty of 65 patients (46%) in the nortriptyline group and 45 of 65 (69%) in the placebo group were successful with both the dose and the timing of the dose-escalation protocol (P = .01). In the nortriptyline group, 42 patients (65%) achieved a maximum dose of 75 mg, 7 (11%) achieved 50 mg, 7 (11%) achieved 25 mg, and 9 (14%) achieved 10 mg.

Primary Outcome
Overall symptomatic improvement by primary outcome did not differ between the treatment groups: 15 (23% [95% CI, 14%–35%]) in the nortriptyline group vs 14 (21% [95% CI, 12%–34%]) in the placebo group (relative risk of improvement, 1.06 [95% CI, 0.56–2.00]; P = .86) (Table 3).

Secondary Outcomes
The treatment group comparisons of changes from baseline to 12 or 15 weeks for secondary outcomes are shown in Table 3 and eTable 3 in Supplement. There were no treatment group differences in overall GCSI subscores for nausea, fullness or early satiety, and bloating. However, there was a greater decrease in the loss-of-appetite component score in the nortriptyline group (−1.6 [95% CI, −2.1 to −1.1]) vs the placebo group (−0.9 [95% CI, −1.4 to −0.5]) (P = .03). There were no treatment group differences in the GSRS, CGPI, Global Overall Relief of Symptoms questionnaire, BDI, Brief Pain Inventory, STAI, PHQ-15 score, or 36-Item Short-Form Health Survey quality-of-life measures.

At 12 weeks, there were no treatment group differences in change in the amount of nutritional beverage consumed in the satiety test or in the electrogastrography results.

Alternate Definitions of Primary Outcome Measure
There were no treatment group differences when varying the definition of the primary outcome to at least 1 visit with a 50% decrease in GCSI (43% for nortriptyline vs 32% for placebo; P = .20) or at least 1 visit with a 25% decrease in GCSI (66% for nortriptyline vs 69% for placebo; P = .70) or a 25% decrease in GCSI for at least 2 consecutive visits (49% for nortriptyline vs 54% for placebo; P = .61) (eTable 2 in Supplement).

Treatment-group comparisons of patterns of change over 3-week intervals are shown for GCSI subscores and total score (Figure 2), GSRS scores (Figure 3), GCSI component scores (eFigure 1 in Supplement), PAGI-SYM upper abdominal pain scores, (eFigure 2 in Supplement), and CGPI scores (eFigure 2 in Supplement). The nortriptyline group had a sustained greater decrease in GSRS abdominal pain score (P = .04) and GCSI inability to finish a meal component (P = .05) and a sustained greater increase in CGPI scores (P = .02). There were no significant treatment effects in other secondary outcomes.

Components comprising subscores are scaled from 0 (no symptoms) to 5 (very severe). GCSI total score and subscores for nausea, fullness or early satiety, and bloating are sums of 9, 3, and 2 components, respectively. There were no differences in changes during the trial in the 3 GCSI subscores (nausea, fullness or early satiety, bloating) and total GCSI score between the nortriptyline group compared with the placebo group.
Nortriptyline and Idiopathic Gastroparesis

Figure 3. Changes From Baseline in Gastrointestinal Symptom Rating Scale (GSRS) Scores by Treatment Group

Adverse Events and Effects

A similar number of adverse events were recorded in the 2 groups: 27 (95% CI, 18 to 39) adverse events in the nortriptyline group vs 28 (95% CI, 19 to 40) in the placebo group (P = .89) (eTable 3 in Supplement). There were 5 serious adverse events (1 allergic reaction, 2 vomiting, 1 gastrointestinal tract-related, and 1 cardiac event) in the nortriptyline group vs 1 (abdominal pain) in the placebo group. Treatment was stopped more often with nortriptyline (19 [29% (95% CI, 19% to 42%)] vs 6 [9% (95% CI, 3% to 19%)]) (P = .007), with the primary reason being adverse effects (n = 10 vs 3). In the nortriptyline group, of the 19 patients who stopped treatment early, 9 stopped after taking 10 mg/d, 3 after taking 25 mg/d, 4 after 50 mg/d, and 3 after 75 mg/d. At 15 weeks there was greater severity of dry mouth and urinary retention in the nortriptyline group than in the placebo group (eTable 3 in Supplement).

Discussion

In this, to our knowledge the first adequately powered randomized clinical trial of a neuromodulator in idiopathic gastroparesis, nortriptyline did not improve overall symptoms in idiopathic gastroparesis over a 15-week period. Our primary outcome assessed overall gastroparetic symptoms using a cumulative score of 9 symptoms contained in the GCSI, with a decrease in symptom score of at least 50% for 2 consecutive 3-week periods required to show improvement. Our results suggest that TCAs may not be effective in the treatment of overall symptoms in patients with idiopathic gastroparesis.

Although the primary outcome parameter for this study was not achieved, there are several caveats. First, it is possible that poor tolerance of the nortriptyline (nearly one-third of the patients did not complete treatment, and nearly half could not adhere to the dose-escalation schedule) may have been a factor. However, there was no suggestion of improvement even in a per-protocol analysis. Second, our placebo response rate was unexpectedly low (30% planned vs 22% observed), suggesting that our primary outcome may have been overly stringent, compared with other trials for gastroparesis in which a prominent placebo effect has been observed using different criteria for improvement. The power of the study decreases from 90% to 70% if a 22% improvement even in a per-protocol analysis. Second, our placebo response rate was unexpectedly low (30% planned vs 22% observed), suggesting that our primary outcome may have been overly stringent, compared with other trials for gastroparesis in which a prominent placebo effect has been observed using different criteria for improvement.28 The power of the study decreases from 90% to 70% if a 22% rate in the placebo group is assumed. Last, these results cannot be generalized to patients with diabetic gastroparesis, who may have more autonomic neuropathy than patients with idiopathic disease.29 Our findings do not support the use of nortriptyline as adjunct or secondary therapy for idiopathic gastroparesis. It should, however, be noted that a recent study showed positive results using amitriptyline (a precursor of nortriptyline) for the treatment of functional dyspepsia, a closely related condition.30
Our patients had idiopathic gastroparesis with delayed gastric emptying. The effect of nortriptyline on gastric emptying is not known. Although some TCAs delay gastric emptying, nortriptyline has fewer anticholinergic adverse effects and is the least likely of the TCAs to affect gastric emptying. The planned gastric emptying breath test to be performed during screening and treatment was removed early in the study at the suggestion of the US Food and Drug Administration.

The frequency of adverse effects was similar in the nortriptyline and placebo groups, although there were 5 serious adverse events in the nortriptyline group vs 1 in the placebo group. Patients in the nortriptyline group had slightly increased dry mouth and urinary retention, both expected adverse effects of TCAs. Treatment was stopped because of adverse effects more often with nortriptyline than with placebo.

**Conclusions**

This study shows that among patients with idiopathic gastroparesis, the use of nortriptyline compared with placebo for 15 weeks did not result in improvement in overall symptoms. Our results raise general doubts about the utility of tricyclic antidepressants in low doses as a strategy for the treatment of idiopathic gastroparesis.

**ARTICLE INFORMATION**

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**Author Contributions:** Drs Parkman and Van Natta had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Parkman, Abell, Nguyen, Snape, Koch, Hasler, Farrugia, Lee, Unalp-Arida, Tonascia, Hamilton, Pasricha. Acquisition of data: Parkman, Van Natta, Abell, McCallum, Sarosiek, Nguyen, Snape, Koch, Hasler, Pasricha. Analysis and interpretation of data: Van Natta, Abell, McCallum, Sarosiek, Nguyen, Snape, Koch, Hasler, Farrugia, Lee, Unalp-Arida, Tonascia, Pasricha. Drafting of the manuscript: Parkman, Van Natta, Abell, McCallum, Snape, Koch, Hasler, Farrugia, Unalp-Arida, Tonascia, Pasricha. Critical revision of the manuscript for important intellectual content: Van Natta, Abell, McCallum, Sarosiek, Nguyen, Snape, Koch, Hasler, Farrugia, Lee, Unalp-Arida, Tonascia, Hamilton, Pasricha. Statistical analysis: Van Natta, Abell, Tonascia. Obtained funding: McCallum, Snape, Koch, Hasler, Farrugia, Unalp-Arida, Hamilton, Pasricha. Administrative, technical, or material support: Sarosiek, Snape, Koch, Lee, Unalp-Arida, Tonascia, Pasricha. Study supervision: Parkman, Abell, McCallum, Nguyen, Hasler, Unalp-Arida, Tonascia.

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