Selective effects of serotonergic psychoactive agents on gastrointestinal functions in health

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Chial, Heather J., Michael Camilleri, Duane Burton, George Thomforde, Kevin W. Olden, and Debra Stephens. Selective effects of serotonergic psychoactive agents on gastrointestinal functions in health. Am J Physiol Gastrointest Liver Physiol 284: G130–G137, 2003; 10.1152/ajpgi.00266.2002.—This study evaluated the effects of serotonergic psychoactive agents on gastrointestinal functions in healthy human subjects. Participants received one of four regimens in a randomized, double-blind manner: buspirone, a 5-HT1A receptor agonist (10 mg twice daily); paroxetine, a selective serotonin reuptake inhibitor (20 mg daily); venlafaxine-XR, a selective serotonin and norepinephrine reuptake inhibitor (75 mg daily); or placebo for 11 days. Physiological testing performed on days 8–11 included scintigraphic assessment of gastrointestinal and colonic transit, the nutrient drink test, and assessment of the postprandial change in gastric volume. Fifty-one healthy adults (40 females, 11 males) participated in this study. No effects on gastric emptying or colonic transit were identified with any agent. Small bowel transit of a solid meal was accelerated by paroxetine. Buspirone decreased postprandial aggregate symptom and nausea scores. Venlafaxine-XR increased the postprandial change in gastric volume. Buspirone, paroxetine, and venlafaxine-XR affect upper gastrointestinal functions in healthy humans. These data support the need for clinical and physiological studies of these agents in functional gastrointestinal disorders.

Antidepressant; motility; paroxetine; buspirone; venlafaxine

Serotonin is an important neurotransmitter in both the brain and the gastrointestinal tract, where it plays a key role in the regulation of sensory and motor functions (14). Many patients with functional gastrointestinal disorders have comorbid psychiatric diagnoses including anxiety, mood, and somatoform disorders (9). Although psychoactive agents (e.g., antidepressants and anxiolytics) with serotonergic activity have been widely used in the treatment of patients with functional gastrointestinal disorders, including irritable bowel syndrome and nonulcer dyspepsia, it is unclear if these medications improve symptoms through central or peripheral mechanisms (7, 11, 14). Preliminary data suggest these medications affect gastrointestinal physiology (10, 11, 20, 28). We chose to evaluate three commonly prescribed psychoactive serotonergic agents: buspirone, paroxetine, and venlafaxine-XR. We excluded tricyclic agents from this study because these medications have been evaluated in previous mechanistic studies (12, 22).

Buspirone, a serotonin 1A (5-HT1A) receptor agonist, is used to treat anxiety and depression. A preliminary report of a crossover study of buspirone in patients with functional dyspepsia showed a reduction in symptoms and enhanced gastric accommodation to a meal (28). In animal models, buspirone abolished the stimulatory effects of mental stress and corticotropin releasing factor on cecal motility through 5-HT1A receptors (20). The active metabolite of buspirone, 1-pyrimidinylpiperazine, has α2-adrenoceptor antagonist properties, which might be expected to cause fundic contraction, given the gastric relaxation demonstrated with the α2-adrenoceptor agonist clonidine (30).

Paroxetine is a potent selective serotonin reuptake inhibitor that has been shown to enhance motor activity in the small intestine. It increased migrating motor complex frequency (10), increased the propagation velocity of phase III contractions in the small intestine (10), and accelerated orocecal transit (11). Effects on gastric emptying and colonic transit were not evaluated.

Venlafaxine is an antidepressant that inhibits the reuptake of both serotonin and (at higher doses) norepinephrine (23). Adverse event reports suggest it may have gastrointestinal effects, because nausea and vomiting occur in 10–43 and 6–10% of patients, respectively (21). Effects of venlafaxine on gastrointestinal functions are unknown.

Our long-term goal is to develop therapeutic approaches that target specific physiological abnormalities and related symptoms in patients with functional gastrointestinal disorders. The aim of our study was to compare the effects of buspirone, paroxetine, and venlafaxine-XR vs. placebo on 1) gastrointestinal and colonic transit, 2) the maximum tolerated volume of a meal.

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nutrient drink, 3) postprandial symptoms, and 4) changes in gastric volume after a standardized meal in healthy adults. Validated noninvasive techniques have been developed in our laboratory to measure these functions (4–6, 16).

MATERIALS AND METHODS

Experimental Design and Participants

This randomized, double-blind, placebo-controlled, parallel-group, single-center study was conducted in healthy adults between the ages of 18 and 65 yr recruited from the local community by public advertisement. All candidates who met the eligibility criteria for the study underwent a complete history and physical examination, including an electrocardiogram, before enrollment. Volunteers were screened by means of an abridged bowel disease questionnaire (29) to ensure they had no current or chronic gastrointestinal symptoms. The Hospital Anxiety and Depression Questionnaire was used to screen all volunteers for psychiatric dysfunction. Exclusion criteria were 1) abdominal surgery other than appendectomy, cesarean section, or tubal ligation, 2) a history of chronic gastrointestinal or systemic illnesses that could affect gastrointestinal motility, 3) use of medications that may alter motility or interact with the study medications, 4) use of any of the study medications within the last 30 days, 5) pregnancy, and 6) psychiatric or psychological dysfunction. All participants gave written, informed consent. Blood tests for pregnancy were performed in all women of child-bearing potential before starting the study medication and within 48 h of undergoing any of the tests that incorporated radioisotopes. The study was approved by the Mayo Institutional Review Board and was conducted in the General Clinical Research Center at the Mayo Clinic in Rochester, MN.

Study volunteers took the assigned medication twice daily for 11 days as shown in Fig. 1. On days 8–10, gastrointestinal and colonic transit were measured by scintigraphy (4, 5). Evaluation of the maximum tolerated volume and postprandial symptoms using the nutrient drink test (6) and gastric emptying of the nutrient liquid by scintigraphy was completed on day 10. Change in gastric volume after a standardized meal was assessed by single-photon emission-computed tomography (SPECT) on day 11 (16).

Study Medications

After the initial screening, subjects were randomized to receive one of four regimens of two tablets daily for 11 days: 10 mg buspirone by mouth twice daily; 20 mg paroxetine by mouth each morning, and placebo by mouth each evening; 75 mg venlafaxine-XR by mouth each morning and placebo by mouth each evening; or placebo by mouth twice daily. On days 8–11, the study volunteers took the morning dose of the assigned study medication 1 h before physiological testing was performed. The duration of treatment was selected after consideration of the pharmacokinetics of all test medications and the need to ensure study blinding.

Buspirone has a half-life of 2–3 h after single oral doses of 10–40 mg, and peak plasma levels occur 40–90 min after a single oral dose of 20 mg (18, 22a). The half-life of paroxetine is 10–24 h, and the minimum time to steady-state blood levels is 5 days (19, 26). Venlafaxine-XR has a half-life of 5–11 h and a minimum time to achieve steady-state blood levels of 3 days (19, 26). Thus we determined that a treatment period of 7 days would ensure steady-state blood levels of all three study medications on days 8–11 when the physiological measurements were performed in this study. Selected doses of buspirone, paroxetine, and venlafaxine-XR were consistent with standard starting doses of these medications when used to treat patients with depression and/or anxiety. These doses were selected to minimize the risk of adverse side effects reported in the literature with higher doses of these medications. Although the serotonergic effects of venlafaxine-XR predominate at lower doses of the medication, we would expect some noradrenergic activity at the dose (75 mg daily) used in this study (23).

Study medications were prepared and dispensed by the Research Pharmacy of the Mayo General Clinical Research Center in a randomized order; all of the study medications were identical in appearance. Volunteers who withdrew from the study were replaced in accordance with the randomization schedule maintained by the research pharmacist. The clinical investigators, study personnel, and volunteers were blinded to the treatment assignments until after the data analysis was complete.

Scintigraphic Transit

Scintigraphic transit studies were used to evaluate gastric emptying, small bowel transit, and colonic transit. Our laboratory has validated, reliable methods to noninvasively and accurately assess these functions in healthy volunteers and in patients with known motility and functional gastrointestinal disorders (4, 5, 34, 35). A delayed-release capsule containing 111In-labeled charcoal was used to evaluate colonic transit. After an overnight fast, the capsule was administered with a glass of water on day 8. A 99mTc-labeled sulfur colloid-labeled egg meal was used to assess gastric emptying and small bowel transit. The 99mTc-labeled breakfast meal was administered after the 111In-labeled capsule had emptied from the stomach on the basis of scintigraphic imaging. The eggs were served with one slice of buttered bread and an 8-oz glass of 1% milk (total calories: 296 kcal, 32% protein, 35% fat, 33% carbohydrate). Standardized meals were given 4 h (chicken, potato, and pudding; total calories: 478 kcal, 18% protein, 35% fat, and 46% carbohydrate) and 8 h (roast beef sandwich, cookie, 2% milk; total calories: 548 kcal, 21% protein, 33% fat, 46% carbohydrate) after ingestion of the radiolabeled breakfast meal. After the meal at 8 h, other meals were ingested ad libitum.

Anterior and posterior gamma camera images were obtained 0, 1, 2, 3, 4, and 6 h after the test meal ingestion to assess gastric emptying. The proportion of 99mTc reaching the colon at 6 h was used as a measure of small bowel transit. Gamma camera images were obtained at 4, 6, 8, 24, 32, and 48 h to assess colonic transit of the 111In-labeled charcoal.
Nutrient Drink Test and Gastric Emptying of Liquids

An adaptation of the method of Tack et al. (27) was used to measure the maximum tolerated volume. Subjects ingested 30 ml of a nutrient drink (1 kcal/ml Ensure) per minute. The cup containing the nutrient drink was filled using a constant-rate perfusion pump, and participants were required to maintain intake at the filling rate until the maximum tolerated volume was reached. Participants scored their satiation (feeling of fullness) at 5-min intervals using a graphic rating scale that combined verbal descriptors on a scale graded 0–5 (0 = no symptoms, 5 = maximum satiation). Participants stopped meal intake when a score of 5 was reached. The first glass of the nutrient drink was radiolabeled with 0.05 mCi of $^{111}$In-labeled diethyleneetriamine penta-acetic acid to facilitate the measurement of gastric emptying of liquid; scintigraphic scans were performed at 0, 10, 30, 60, 90, 120, 150, and 180 min after beginning ingestion of the nutrient drink. Emptying of the nutrient drink was summarized by the percent emptied at 30 min and the time to 50% emptying ($T_{50}$).

Thirty minutes after reaching the maximum tolerated volume, participants scored their symptoms of bloating, fullness, nausea, and pain using 100-mm visual analog scales anchored with the words “unnoticeable” and “unbearable” at the left and right ends (i.e., maximum score 100 for each symptom). The aggregate symptom score was defined as the sum of the visual analog scale scores for each symptom (i.e., maximum score 400). The timing of symptom assessment was intended to be consistent with previous studies by Tossetti et al. (33) in the literature.

We have reported normal values for the nutrient drink test in adolescents and adults (6) and have demonstrated responsiveness of the aggregate symptom score in a previous study of alosetron in healthy volunteers (17).

Assessment of Fasting and Postprandial Gastric Volumes

Gastric accommodation is a robust, vagally mediated reflex in health that results in reduced gastric tone, increased compliance, and increased gastric volume. Accommodation allows the ingestion of large volumes of solids or liquids without inducing postprandial symptoms. An abnormally low postprandial gastric volume may contribute to the development of symptoms in patients with functional dyspepsia, postvagotomy surgery, postfundoplication dyspepsia, rumination syndrome, and diabetic vagal neuropathy (24, 25, 27, 31, 32).

A noninvasive method has been developed (16) and validated (3) in our laboratory to measure fasting and postprandial gastric volumes using an intravenous injection of $^{99m}$Tc-pertechnetate ($^{99m}$TcO$_4^{-}$) and imaging with SPECT. Tomographic images were acquired on a large field-of-view dual-headed gamma camera system (SMV SPECT System; SMV America, Twinsburg, OH). Gastric volumes were measured using the SPECT-ANALYZE PC 2.5 (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN) software system (16). There is a high degree of correlation between volumes measured by SPECT and barostat balloon in response to distension and to a meal (3).

Gastric mucosa is able to take up intravenously administered $^{99m}$TcO$_4^{-}$ from the circulating blood pool. Starting 10 min after the intravenous injection of 10 mCi $^{99m}$TcO$_4^{-}$, imaging was performed during fasting and for a total of 32 min after ingestion of a 300-ml nutrient drink (1 kcal/ml Ensure) through a straw. Gastric volumes were assessed during two postprandial periods: 0–10 and 10–20 min after the meal. Transaxial images of the stomach were rendered with ANALYZE to reconstruct three-dimensional images and to measure gastric volumes during the fasting and postprandial periods. Volume changes and ratios between the fasting and postprandial periods were calculated.

Data Analysis

Transit data. The geometric mean of counts in the anterior and posterior gastric regions of interest was used to estimate the proportion of $^{99m}$Tc emptied at 2 and 4 h (gastric emptying of solids). The proportion of $^{99m}$Tc reaching the colon at 6 h was estimated. This measure of orocecal transit serves as a surrogate marker for small bowel transit when gastric emptying is assessed simultaneously (5). The colonic geometric center at 4, 24, 32, and 48 h was estimated using the geometric mean of counts in the ascending, transverse, descending and rectosigmoid colon, and stool, weighted by factors of 1–5, respectively. The primary variable of interest was the colonic geometric center at 24 h.

Nutrient drink test. The maximum tolerated volume of nutrient drink ingested was recorded. Individual symptom scores (maximum score 100) for bloating, fullness, nausea, and pain and the aggregate symptom score, the sum of the individual symptom scores (maximum score 400), were documented. Data for liquid gastric emptying were recorded as the percent emptied at 30 min (at which time all participants had ingested the same volume of nutrient liquid) and $T_{50}$.

Fasting and postprandial gastric volumes. Fasting and postprandial gastric volumes were measured by ANALYZE reconstructed, three-dimensional images of the stomach. Two time periods, 0–10 and 10–20 min after the meal, were assessed, and the average of these two postprandial gastric volume estimates constituted the primary endpoint for estimating postprandial volume changes: 1) the difference in gastric volume between the postprandial and fasting periods and 2) the ratio of the postprandial to fasting gastric volumes.

Statistical Methods

Endpoints. The primary endpoints selected for analysis were 1) gastric emptying of solids at 2 h, 2) $t_{1/2}$ of gastric emptying of nutrient drink (liquid gastric emptying), 3) the colonic geometric center at 24 h, 4) the maximum volume of Ensure ingested, 5) the aggregate symptom score, and 6) the postprandial change in gastric volume. Secondary endpoints were 1) percentage of nutrient drink emptied at 30 min, 2) colonic filling of solids at 6 h (a measure of small bowel transit), 3) the individual symptom scores for bloating, fullness, nausea, and pain 30 min after reaching the maximum tolerated volume, 4) percentage of nutrient drink emptied at 30 min, and 5) the postprandial-to-fasting gastric volume ratio.

Sample size estimates. The sample size (13 per group) was based on a two-sample t-test for a two-sided $\alpha = 0.05$ and $\beta = 0.20$ (80% power) using data from previous studies conducted in healthy volunteers in our laboratory. Because this was an exploratory study to assess whether these agents have effects of potential clinical significance, the study was powered to demonstrate the following effect sizes for the endpoints of greatest interest: gastric emptying of solids at 2 h, 35%; colonic geometric center at 24 h, 45%; maximum tolerated volume, 25%; aggregate symptom score, 49%; and the postprandial change in gastric volume, 23%. We considered these effect sizes to be clinically significant.

Analysis. ANOVA was used for comparison of baseline characteristics (age, gender, height, weight, and body mass index) among the four groups. We used the nonparametric
Kruskal-Wallis test to assess overall treatment effects. When the overall effect was significant ($P < 0.05$) or showed a trend ($P \leq 0.1$), we used the Mann-Whitney U-test for pairwise comparisons of the effect of each medication vs. placebo. Data are displayed as median (interquartile range); $P < 0.05$ was considered significant. The $P$ value was unadjusted for comparisons of drug vs. placebo when the overall drug effect (on the Kruskal-Wallis test) was $\leq 0.1$.

**RESULTS**

**Participant Characteristics**

Fifty-nine volunteers were screened and all were eligible for participation and were enrolled in the study. Of the 59 volunteers enrolled, 51 completed the study. Three volunteers were noncompliant and did not present for scheduled testing. One volunteer who received buspirone withdrew due to nausea and vomiting. Two volunteers who received paroxetine withdrew: one for dizziness and insomnia and one for dizziness, nausea, and headache. Two volunteers who received venlafaxine-XR withdrew: one due to nausea and one due to insomnia and difficulty concentrating. All of the five volunteers who withdrew from the study due to side effects from the medications did so within 24–72 h of starting the study medication. These individuals did not undergo any subsequent testing and could not be included in the final analysis. Of the volunteers who completed the study, 11 received buspirone; 12, paroxetine; 15, venlafaxine-XR; and 13, placebo.

Patient demographics are displayed in Table 1. No significant differences in age, gender, height, weight, or body mass index were detected among groups.

**Effects on Gastrointestinal and Colonic Transit**

The overall effect on gastric emptying of solids at 2 h ($P = 0.3$) was not statistically significant among treatment groups (Fig. 2). On the other hand, overall colonic filling at 6 h, a surrogate measure of orocecal transit, was borderline statistically significant among treatment groups (Kruskal-Wallis test, $P = 0.09$). Moreover, paroxetine significantly accelerated colonic filling at 6 h compared with placebo [82% (41.3% to 99%) vs. 47% (24.5% to 59.5%), Mann-Whitney test, $P < 0.05$]; buspirone and venlafaxine-XR did not significantly alter colonic filling at 6 h relative to placebo (Fig. 2). Because paroxetine did not significantly alter gastric emptying, the increased colonic filling at 6 h suggests that paroxetine accelerated small bowel transit. Colonic transit at 24 h ($P = 0.7$) was not statistically significant among treatment groups (Table 2).

The overall effect on gastric emptying of liquids estimated as percent emptied at 30 min (at which time all participants had ingested the same volume, 900 ml) and the $T_{50}$ were not statistically significant among treatment groups ($P = 0.4$ and $P = 0.6$, respectively) (Table 2).

**Nutrient Drink Test: Maximum Tolerated Volume and Effects on Postprandial Symptoms**

The overall effect of the study medications on the maximum tolerated volume of nutrient drink was not statistically significant among treatment groups ($P = 0.90$) (Table 3). On the other hand, the overall aggregate symptom scores were significantly different among treatment groups ($P = 0.007$). Buspirone was associated with significantly lower aggregate symptom scores compared with placebo [median (interquartile range): 126 (94–170) vs. 253 (182–301), $P = 0.007$] (Fig. 3A). A trend toward reduced aggregate symptom scores was also observed for paroxetine compared with placebo [187 (148–241) vs. 253 (182–301), $P = 0.09$]. With regard to the individual symptom scores, overall treatment differences were borderline statistically significant for nausea ($P = 0.08$), fullness ($P = 0.1$), and pain ($P = 0.1$) (Fig. 3B). Buspirone was associated with

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Buspirone</th>
<th>Paroxetine</th>
<th>Venlafaxine-XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>13</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Age, range in years</td>
<td>29.3 ± 2.4 (22–49)</td>
<td>31.8 ± 2.4 (22–46)</td>
<td>30.7 ± 2.2 (20–45)</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>12/3</td>
<td>8/3</td>
<td>8/3</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.7 ± 0.03</td>
<td>1.7 ± 0.02</td>
<td>1.7 ± 0.02</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77 ± 5</td>
<td>79 ± 5</td>
<td>79 ± 5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6 ± 1.2</td>
<td>27.2 ± 1.7</td>
<td>27.5 ± 1.6</td>
</tr>
</tbody>
</table>

Data are means ± SE. F, female; M, male.
lower nausea scores compared with placebo [17 (0–27) vs. 75 (13–91), P = 0.05]. A trend toward reduced pain scores was also observed for buspirone compared with placebo [6 (0–9) vs. 42 (3–57), P = 0.09]. Paroxetine and venlafaxine-XR did not alter the individual symptom scores for bloating, fullness, nausea, or pain compared with placebo (Fig. 3B).

Effects on Fasting and Postprandial Gastric Volume

Fasting gastric volumes did not differ among treatment groups (P = 0.8) (Table 4). Overall treatment differences were borderline statistically significant for the postprandial change in total gastric volume (P = 0.1). Venlafaxine-XR increased the postprandial change in total gastric volume compared with placebo [522 (418–602) vs. 414 (365–470) ml, P < 0.05] (Table 4 and Fig. 4). Overall treatment differences were not significant for the postprandial-to-fasting gastric volume ratio (P = 0.2). However, the postprandial-to-fasting gastric volume ratio was enhanced by venlafaxine-XR compared with placebo [3.9 (3.2–4.3) vs. 2.9 (2.6–3.1)]. Buspirone and paroxetine did not significantly affect the postprandial change in gastric volume or the gastric volume ratio compared with placebo (Table 4).

DISCUSSION

This study preliminarily explored the effects of buspirone, paroxetine, and venlafaxine-XR (prototype serotonergic psychoactive agents) on gastrointestinal and colonic transit, the maximum tolerated volume of a nutrient drink, postprandial symptoms, and the change in gastric volume after a standardized meal in healthy adults. Data showed several significant results despite our expectation that we would only be able to identify large effects with the sample size used.

The 5-HT1A receptor agonist buspirone reduced postprandial aggregate symptom and nausea scores, but did not increase the total volume of nutrient drink ingested or the postprandial change in gastric volume relative to placebo. It is worth noting that the postprandial symptoms were measured 30 min after completion of the fully satiating liquid meal, not at the time when the maximum tolerated volumes of the nutrient drink or gastric volumes by SPECT were measured.

Our data suggest that the reduced postprandial symptoms recorded with buspirone may not be related to a change in gastric volume. On the other hand, enhanced gastric accommodation and reduced meal-related symptoms were demonstrated in a previous study of buspirone by Tack et al. (28). Nonetheless, it has not been proven that reduced sensation results from pharmacologically increased gastric accommodation. In a recent report by Boeckxstaens et al., (2) the drinking capacity did not predict impaired gastric accommodation or visceral hypersensitivity measured by barostatic balloon in patients with dyspeptic symptoms. More work is necessary to understand the relationship among gastric accommodation, gastric emptying, satiation, and postprandial symptoms.

Table 3. Nutrient drink test results

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum Tolerated Volume, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1,284 (957–1,554)</td>
</tr>
<tr>
<td>Buspirone</td>
<td>1,164 (1,017–1,411)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1,229 (932–1,422)</td>
</tr>
<tr>
<td>Venlafaxine-XR</td>
<td>1,257 (975–1,475)</td>
</tr>
</tbody>
</table>

Data are medians; numbers in parentheses are interquartile range.
Similarities and differences between our study and the study by Tack et al. (28) are worthy of further analysis. First, two different study populations were assessed; our study was performed in healthy male and female volunteers, whereas the study by Tack et al. (28) was performed in 14 female patients with functional dyspepsia. Second, the dose of buspirone differed between the two studies; we used 10 mg twice daily (to reflect the more commonly performed dosing in clinical practice and to enhance study blinding with other medications in this protocol), whereas Tack et al. (28) used 10 mg three times daily. Third, different techniques were used to assess gastric accommodation; we used SPECT imaging of the stomach to assess the postprandial change in volume of the whole stomach, whereas Tack et al. (27) used the gastric barostat technique, which assesses only the proximal stomach. However, we cannot exclude the possibility of type II error in our assessment of effects of buspirone on gastric accommodation.

The selective serotonin reuptake inhibitor paroxetine accelerated small bowel transit without affecting gastric emptying or colonic transit. Stimulation of small bowel motility by paroxetine has been demonstrated using gastroduodenal manometry (10) and the lactulose hydrogen breath test (11). Paroxetine did not influence postprandial symptoms or change the postprandial gastric volume response relative to placebo. The serotonin and norepinephrine reuptake inhibitor venlafaxine-XR enhanced the postprandial increase in total gastric volume. Fasting gastric volumes did not differ between individuals who received venlafaxine-XR and those who received placebo. Therefore, the differences detected in the postprandial-to-fasting gastric volume ratio and in the postprandial change in gastric volume reflect true effects of venlafaxine-XR on the postprandial gastric volume response. The fact that no effects on fasting gastric volume were observed suggests that venlafaxine-XR modulated the reflex response of the stomach to meal ingestion. This response is influenced by vagal and adrenergic input. In addition, serotonergic receptors (5-HT1A and 5-HT3) are known to influence vagal afferent pathways and can, therefore, alter the reflex accommodation response to feeding (8).

Although the effects of venlafaxine-XR on postprandial gastric volume may be related to serotonergic and/or noradrenergic effects of the medication, it has been suggested that noradrenergic effects are less prominent than serotonergic effects at the dose administered in this study (75 mg daily) (13). Interestingly, a similar increase in postprandial gastric volume relative to placebo was observed in healthy volunteers with the α-adrenergic agonist clonidine in our laboratory (30). It is possible that the stomach is more sensitive to noradrenergic effects of venlafaxine than other organs, e.g., the brain or blood vessels.

Venlafaxine-XR enhanced the postprandial volume response without influencing the maximum tolerated volume of nutrient drink or postprandial symptoms. At first glance, this may seem paradoxical. However, as discussed previously, more work is necessary to understand the relationship among gastric accommodation, gastric emptying, satiation, and postprandial symptoms (2).

We cannot exclude the possibility that buspirone, paroxetine, and venlafaxine-XR have important effects of a smaller magnitude that were not detected in our study due to type II error. For example, a few trends were observed that did not reach statistical significance: paroxetine reduced aggregate symptom scores

### Table 4. Gastric Volumes Measures with SPECT

<table>
<thead>
<tr>
<th>Volume (ml)</th>
<th>Placebo</th>
<th>Buspirone</th>
<th>Paroxetine</th>
<th>Venlafaxine-XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postprandial</td>
<td>622(582–646)</td>
<td>684(613–741)</td>
<td>670(539–752)</td>
<td>667(622–789)</td>
</tr>
<tr>
<td>Volume change</td>
<td>414(365–470)</td>
<td>474(377–563)</td>
<td>434(360–496)</td>
<td>522*(418–602)</td>
</tr>
<tr>
<td>Ratio</td>
<td>2.9(2.6–3.1)</td>
<td>3.1(2.2–5.1)</td>
<td>2.9(2.6–3.5)</td>
<td>3.9(3.2–4.3)</td>
</tr>
</tbody>
</table>

Data are medians; numbers in parentheses are interquartile range. *P < 0.05 vs. placebo.

**Fig. 4.** SPECT images demonstrating the postprandial change in gastric volume (venlafaxine-XR vs. placebo). The images are from two individual volunteers: one received venlafaxine-XR and the other received placebo.
by a median of 66 points (change from placebo of 26%, \( P = 0.09 \)), and buspirone reduced pain scores by a median of 36 points (an 86% change from placebo, \( P = 0.09 \)). The lack of effect of buspirone, paroxetine, and venlafaxine-XR on gastric emptying and colonic transit does not appear to reflect a type II error, because the median and interquartile ranges are similar to those with placebo. However, we cannot exclude the possibility that other doses may have changed transit results relative to placebo.

Our assessment of liquid gastric emptying was somewhat suboptimal considering that it was combined with the nutrient drink test and the final volume ingested was different in each participant. Nevertheless, the percentage of nutrient drink emptied at 30 min was standardized as all participants had consumed identical volumes of nutrient drink (i.e., 900 ml) at this time point and no differences were observed between the drugs and placebo.

In summary, our study provides convincing data that buspirone, paroxetine, and venlafaxine-XR affect upper gastrointestinal functions in healthy adults. Before proposing that specific agents be targeted to treatment of specific physiological abnormalities identified on formal testing and before dismissing any of these medications as potential therapies for functional gastrointestinal disorders, more in-depth physiological and clinical studies are required in patients. Nevertheless, our current data are encouraging and document several therapeutic opportunities with serotonergic psychoactive agents in functional gastrointestinal disorders.

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