Original Article

Clinical Trial: Efficacy of Mosapride Controlled-release and Nortriptyline in Patients With Functional Dyspepsia: A Multicenter, Double-placebo, Double-blinded, Randomized Controlled, Parallel Clinical Study

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Background/Aims
Prokinetic agents and neuromodulators are among the treatment options for functional dyspepsia (FD), but their comparative efficacy is unclear. We aimed to compare the efficacy of mosapride controlled-release (CR) and nortriptyline in patients with FD after 4 weeks of treatment.

Methods
Participants with FD were randomly assigned (1:1) to receive mosapride CR (mosapride CR 15 mg and nortriptyline placebo) or nortriptyline (mosapride CR placebo and nortriptyline 10 mg) in double-placebo, double-blinded, randomized controlled, parallel clinical study. The primary endpoint was defined as the proportion of patients with overall dyspepsia improvement after 4 weeks treatment. The secondary endpoints were changes in individual symptom scores, anxiety, depression, and quality of life.

Results
One hundred nine participants were recruited and assessed for eligibility, and 54 in the mosapride CR group and 50 in the nortriptyline group were included in the modified intention-to-treat protocol. The rate of overall dyspepsia improvement was similar between groups (53.7% vs 54.0%, $P = 0.976$). There was no difference in the efficacy of mosapride CR and nortriptyline in a subgroup analysis by FD subtype (59.3% vs 52.5% in postprandial distress syndrome, $P = 0.615$; 44.4% vs 40.0% in epigastric pain syndrome, $P = > 0.999$; 50.0% vs 59.1% in overlap, $P = 0.565$; respectively). Both treatments significantly improved anxiety, depression, and quality of life from baseline.

Conclusion
Mosapride CR and nortriptyline showed similar efficacy in patients with FD regardless of the subtype. Both treatments could be equally helpful for improving quality of life and psychological well-being while also relieving dyspepsia.
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Key Words
Depression; Dyspepsia; Mosapride; Nortriptyline; Prokinetics

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Introduction

Functional dyspepsia (FD) is defined as troublesome postprandial fullness, early satiation, epigastric pain, or burning in the absence of any organic gut disease.[1] Several studies have shown a significant overlap in symptoms and pathophysiology, such as delayed gastric emptying, impaired accommodation, visceral hypersensitivity, and *Helicobacter pylori* infection.[2-6] Therefore, various treatment options, such as proton pump inhibitors (PPIs), histamine 2 receptor antagonists, prokinetics, or neuromodulators, are considered to improve the symptoms of FD. Nevertheless, these treatments sometimes lead to unsatisfactory symptomatic improvement.[7] PPIs are recommended as the first-line treatment for FD in both Western and Asian countries.[8-11]

Views differ regarding whether prokinetics or neuromodulators should be the next step in cases that are refractory to PPIs.[8-11] These differences of opinion are related to geographic differences in the epidemiology and clinical patterns of FD subgroups.[12] In the Western countries, epigastric pain syndrome (EPS) accounts for a greater proportion than postprandial distress syndrome (PDS). Neuromodulators such as antidepressants, antipsychotics, and other central nervous system-targeted medications are widely used in patients with EPS.[13-16] The most widely accepted mechanism of neuromodulation is based on the deficiency of 1 or more monoamines, such as serotonin (5-HT), noradrenaline, and dopamine, in patients with FD.[16,17] However, PDS predominates among FD patients in Asia. Prokinetics are widely used as the second-line treatment option following PPIs in Korea, Japan, and other Asian countries.[8-10,18] Prokinetics act through various receptors to exert a stimulatory effect on gastric motility.[19] Unfortunately, studies of prokinetics have been unsuccessful in providing convincing evidence of symptomatic improvement in patients with FD.[20,21] In addition, quite a few prokinetics have limited use or have been withdrawn from the market

due to adverse effects.[20,22,23] Among prokinetics, mosapride has been proven to be relatively safe owing to its low affinity for 5-HT1, 5-HT2, α1, α2, and D2 receptors, binding to which causes side effects such as arrhythmia, extrapyramidal symptoms, and hyperprolactinemia in the gastrointestinal tract.[24]

Clinical trials comparing the efficacy of prokinetics and neuromodulators in FD could help clinicians avoid the confusion arising when they encounter markedly different guidelines from Asian and Western guidelines for FD. To the best of our knowledge, no trials have compared the efficacy of prokinetics and neuromodulators in patients with FD. Therefore, our first aim is to investigate the efficacy of prokinetics and neuromodulators in FD patients. Second, we aim to compare changes in total symptoms, individual symptom relief, anxiety, depression, and the quality of life (QoL) in FD patients in response to prokinetics or neuromodulators.

Materials and Methods

Study Design Overview

This multicenter, double placebo, double-blinded, randomized controlled, parallel clinical study was conducted at 15 hospitals in Korea. Ethical approval for the scientific and ethical aspects of the study was obtained before the initiation of the study from each ethics committee at the participating sites. (Daegu Catholic University Medical Center [CR-19-094-L], Eunpyeong St. Mary's Hospital [PC19MEDV0053], Gangneung Asan Hospital [GNAH 2019-06-022], Dankook University Hospital [DKUH 2019-07-004], Konyang University Hospital [KYUH 2019-07-006], Keimyung University Hospital [DSMC 2019-07-022], Ewha Womans University Seoul Hospital [SEUMC 2019-06-019], Seoul National University Bundang Hospital [B-1908/558-007], Inje University Ilsan Paik Hospital [ISPAIK 2019-07-002], Gangnam Severance Hospital [3-2019-0177], Incheon St. Mary's Hospital [OC-

19MEDV0100], Gyeongsang National University Changwon Hospital [GNUCH 2019-06-035], Bucheon St. Mary's Hospital [HC20MIDV0068]) Written informed consent was obtained from every patient. All study procedures followed the Helsinki Declaration to protect human participants and complied with the Good Clinical Practice Guidelines. This study was registered under the identifier No. KCT0004340 at the Korea Clinical Research Information Service (http://cris.nih.go.kr) on October 8, 2019. All authors had access to the study data and reviewed and approved the final manuscript.

Patients

The study participants were patients ≥ 19 years of age diagnosed with FD according to the Rome IV criteria.[25] These symptoms are severe enough to interfere with usual activities and have occurred at least 3 days per week over the last 3 months with an onset of at least 6 months in advance, without an identifiable structural or biochemical abnormality.[25] No structural lesions of upper gastrointestinal tract were detected endoscopically 12 weeks prior to enrollment. Potential participants were excluded if they had hypersensitivity or allergy to the trial drugs, took other medications that may alter gastric motility, had undergone previous abdominal surgery that may alter gastric motility (except for appendectomy and hysterectomy), or had peptic ulcers, gastric cancer, esophageal cancer, acute or chronic pancreatitis, pancreatic cancer, inflammatory bowel disease, biliary tract disease (except for asymptomatic cholelithiasis), diabetes gastroparesis, predominant symptoms of gastroesophageal reflux, or irritable bowel disease rather than dyspepsia. Recent history of taking medication affecting the gastrointestinal system: prokinetics, erythromycin, acid release inhibitors (histamine 2 receptor antagonists, PPIs, or potassium-competitive acid blockers), gastric mucosa protectors, anticholinergics, antispasmodics, antidepressants (tricyclic antidepressants and selective 5-HT reuptake inhibitors), systemic nonsteroidal anti-inflammatory drugs, and systemic glucocorticosteroids. Patients treated with any of the listed drugs who wished to participate in this study were eligible for enrollment after a wash-out period of 1 week.

Study Design

Participants were randomly assigned in a ratio of 1:1 to the mosapride controlled-release (CR) mosapride group or nortriptyline group using the block randomization method. Patients were assigned to treatment according to a sequentially numbered randomization list in the order the calls were received. Study staff, the participants, and the data analysts were masked to the allocation until study completion. The hospital pharmacists packed the medication into identical containers according to the randomization code.

In the mosapride CR group, both mosapride CR (15 mg) before breakfast (Gastiin CR, Korea United Pharm, Inc, Seoul, Korea), which provides immediately sustained drug release and allows once-daily administration, and nortriptyline placebo without active ingredients before going to bed, with an appearance, packaging, storage method, and dosing identical to those of nortriptyline (10 mg) were administered for 4 weeks. In the nortriptyline group, mosapride CR placebo without active ingredients before breakfast and nortriptyline (10 mg; Sensival tab, Ilsung Pharm Co, Seoul, Korea) before going to bed were administered for 4 weeks. Up to 3 doses of 250 mg a day of magnesium oxide acting for 8 hours as a rescue drug was allowed during the treatment period, and the amount of the rescue drug taken was documented.

A blood analysis (including a complete blood count, electrolyte, liver function test, blood urea nitrogen, creatinine, hemoglobin A1c, and *H. pylori* immunoglobulin G), urinalysis (including human chorionic gonadotropin), and electrocardiography were performed before the trial and in the 4 weeks of the trial.

Outcome Measurements

The primary endpoint was defined as the proportion of patients with overall dyspepsia improvement. This was evaluated using a 7-point Likert scale (markedly deteriorated, deteriorated, slightly deteriorated, no change, slightly improved, much improved, or very much improved) at 4 weeks of treatment. Overall dyspepsia improvement was defined as a response of "much improved" or "very much improved" after 4 weeks of drug administration.

The secondary endpoints were (1) the change in frequency and severity of gastrointestinal symptoms, determined using the Self Evaluation Questionnaire for Dyspepsia (SEQ-DYSPEPSIA); (2) the change in anxiety and depression, determined using the Hospital Anxiety and Depression Scale (HADS); and (3) the change in QoL, determined using the Nepean Dyspepsia Index-Korean version (NDI-K) questionnaire at 4 weeks from baseline. In addition, the number of rescue medications and adverse events was calculated.

The SEQ-DYSPEPSIA, which includes major FD symptoms (epigastric pain, epigastric soreness, postprandial fullness, and early satiety) and minor symptoms (bloating, belching, and nausea), is composed of 11 items on a 5-point Likert scale.[26] It was reported to have good internal consistency (alpha = 0.770-0.905) and an acceptable test-retest reliability (intraclass correlation coefficient = 0.733-0.859).[26] The HADS is a frequently used tool to

assess psychological distress, which consists of 7 items for anxiety and 7 items for depression subscales.[27] The internal consistency, measured by Cronbach's alpha, of the HADS Korean version was reported to be 0.89 for anxiety and 0.86 for depression.[28] The NDI-K consists of 25 questions on 5 QoL areas: stress/sleep, disturbance of daily life, eating/drinking, knowledge and control, and work/study. The questions are scored on a range of 1-5 points, with a higher score indicating better QoL.[29]

Adverse events were defined as any undesirable medical symptoms or conditions that emerged in participants during test drug administration (including changes in laboratory values), regardless of an apparent causal relationship. The amount of magnesium oxide used as a rescue drug was calculated during the treatment period.

Sample Size

Sample size estimation was based on detecting the proportion of patients with overall dyspepsia improvement after the trial. Prior studies reported rates of 56.9% for mosapride CR and 53.6% for nortriptyline.[30,31] The sample estimate used an error of 2.3% to estimate the true value of the proportion of overall dyspepsia responders in the population as about 4.5%. Assuming an alpha value of 0.05, a desired power of 80%, and a dropout rate of 20%, a minimum of 108 participants, consisting of 54 in each group, needed to be recruited.

Statistical Methods

The baseline characteristics of participants between the mosapride CR and nortriptyline groups were compared using Pearson's chi-square test or Fisher's exact test for categorical variables and the unpaired Student's t test for continuous variables. The proportion of patients with overall dyspepsia improvement was compared between the 2 groups and according to the FD subtypes of the 2 groups in modified intention-to-treat (MITT) and per-protocol (PP) analysis sets. Changes in the frequency and severity of gastrointestinal symptoms, anxiety and depression, and QoL at 4 weeks from baseline were compared using the 2-sample test or the Mann–Whitney U test. The frequency of adverse events and the number of rescue medications used in the mosapride CR and nortriptyline groups were compared using the Student's t test. Statistical analyses were performed using SPSS version 21 for Windows (IBM Corp, Armonk, NY, USA). The data were expressed as means $\pm$ SD. Two-sided P-values of < 0.05 were considered statistically significant.

Results

Study Participants

The flow of screening and recruitment of study participants is
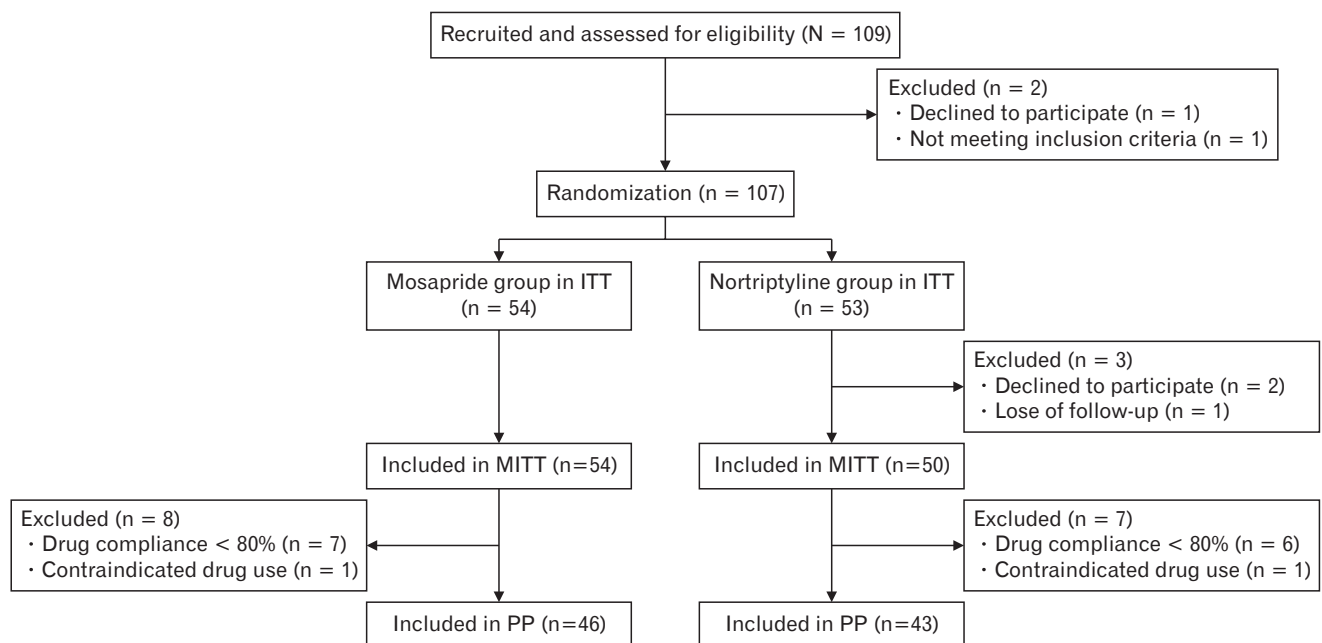

Figure 1. Schematic diagram of the study flow. ITT, intention-to-treat; MITT, modified intention-to-treat; PP, per-protocol.

demonstrated in Figure 1. Between August 2019 and June 2021, 109 potential participants were recruited and assessed for eligibility, and 107 participants were randomly assigned to the mosapride CR (n = 54) and nortriptyline group (n = 53). Three participants in the nortriptyline group were excluded because they declined to participate (n = 2) or were lost to follow-up (n = 1). Fifty-four participants in the mosapride CR group and 50 participants in the nortriptyline group were included in the MITT analysis. Fifteen participants (8 in the mosapride CR group and 7 in the nortrip-

tyline group) failed to take at least 80% of the trial drugs or took contraindicated drugs but completed the outcome measurements using a questionnaire. These participants were excluded from the PP analysis but included in the MITT analysis. There was no significant difference in baseline clinical characteristics in both groups (Table 1).

Primary Endpoint

The primary endpoint of this trial was the proportion of patients

Table 1. Baseline Clinical Characteristics of the Study Subjects

Modified intention-to-treat analysis	Mosapride CR (n = 54)	Nortriptyline (n = 50)	Total (N = 104)	P-value
Age (yr)	52.1 ± 14.0	47.4 ± 13.0	49.8 ± 13.7	0.083
Sex				0.715
Male	18 (33.3)	15 (30.0)	33 (31.7)	
Female	36 (66.7)	35 (70.0)	71 (68.3)	
Height (cm)	161.6 ± 8.2	161.4 ± 7.5	161.5 ± 7.8	0.870
Weight (kg)	61.6 ± 10.8	60.7 ± 10.2	61.2 ± 10.5	0.997
Alcohol use				0.876
Never-drinker	26 (48.1)	22 (44.0)	48 (46.2)	
Former-drinker	9 (16.7)	8 (16.0)	17 (16.3)	
Current drinker	19 (35.2)	20 (40.0)	39 (37.5)	
Smoking status				0.065
Never-smoker	42 (77.8)	41 (82.0)	83 (79.8)	
Former-smoker	10 (18.5)	3 (6.0)	13 (12.5)	
Current smoker	2 (3.7)	6 (12.0)	8 (7.7)	
FD subtypes				0.425
PDS	27 (50)	23 (46.0)	50 (48.1)	
EPS	9 (16.7)	5 (10.0)	14 (6.5)	
Overlap	18 (33.3)	22 (44.0)	40 (38.4)	
Helicobacter pylori infection	11 (20.4)	16 (32.0)	37 (35.6)	0.388

CR, controlled-release; FD, functional dyspepsia; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome.
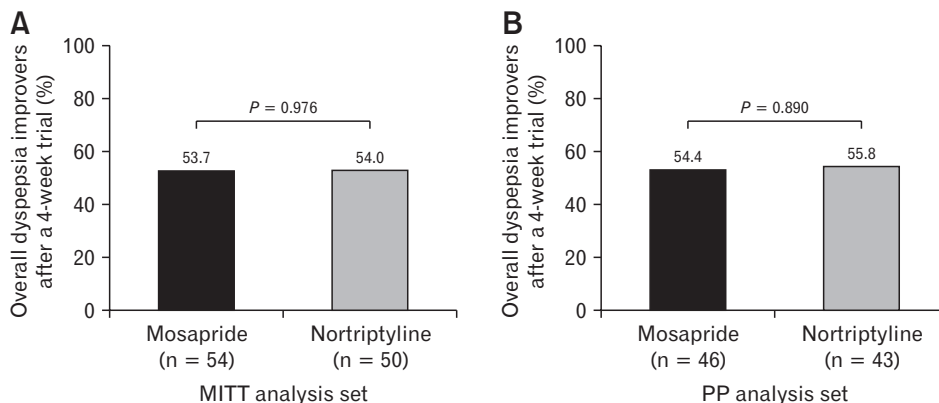Data are presented as mean ± SD or n (%).

Figure 2. The proportion of patients with overall dyspepsia improvement after a 4-week trial. (A) Modified intention-to-treat (MITT) analysis set. (B) Per-protocol (PP) analysis set.
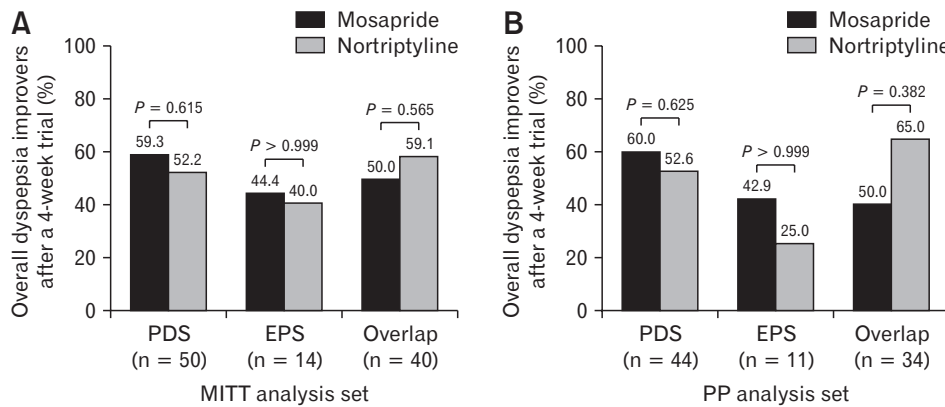
Figure 3. The proportion of patients with overall dyspepsia improvement after a 4-week trial according to the functional dyspepsia subtype. (A) Modified intention-to-treat MITT analysis set. (B) Per-protocol (PP) analysis set. PDS, postprandial distress syndrome; EPS, epigastric pain syndrome.

Table 2. Change in Total Symptom and Individual Symptom Relief Score of a 4-Week Drug Administration

Modified intention-to-treat analysis	Change in frequency			Change in severity		
	Mosapride CR (n = 54)	Nortriptyline (n = 50)	P-value	Mosapride CR (n = 54)	Nortriptyline (n = 50)	P-value
Total symptom score change	−7.4 ± 7.1	−8.9 ± 7.1	0.149	−7.6 ± 7.0	8.1 ± 7.2	0.787
P-value	< 0.001	< 0.001		< 0.001	< 0.001	
Dyspepsia symptoms						
Early satiety	−0.6 ± 1.3	−0.9 ± 1.4	0.249	−0.7 ± 1.2	−0.8 ± 1.3	0.530
P-value	< 0.001	< 0.001		< 0.001	< 0.001	
Postprandial fullness or discomfort	−1.0 ± 1.2	−1.3 ± 1.4	0.350	−1.0 ± 1.1	−1.3 ± 1.2	0.289
P-value	< 0.001	< 0.001		< 0.001	< 0.001	
Epigastric bloating	−1.1 ± 1.3	−1.2 ± 1.4	> 0.999	−1.0 ± 1.0	−0.9 ± 1.2	0.656
P-value	< 0.001	< 0.001		< 0.001	< 0.001	
Epigastric pain or soreness	−0.8 ± 1.2	−0.9 ± 1.2	0.773	−0.8 ± 1.1	−0.7 ± 1.0	0.588
P-value	< 0.001	< 0.001		< 0.001	< 0.001	
Nausea	−0.4 ± 0.7	−0.5 ± 0.8	0.822	−0.5 ± 1.0	−0.6 ± 1.0	0.977
P-value	< 0.001	< 0.001		< 0.001	< 0.001	
Vomiting	−0.2 ± 0.6	−0.1 ± 0.3	0.828	0.2 ± 0.7	−0.1 ± 0.5	0.797
P-value	0.140	0.030		0.120	0.190	
Belching	−0.7 ± 1.3	−1.0 ± 1.5	0.159	−0.7 ± 1.0	−0.9 ± 1.1	0.142
P-value	< 0.001	< 0.001		< 0.001	< 0.001	
Gastroesophageal reflux disease symptoms						
Heartburn	−0.9 ± 1.0	−0.9 ± 1.2	0.921	−1.0 ± 1.1	−1.0 ± 1.3	0.898
P-value	< 0.001	< 0.001		< 0.001	< 0.001	
Retrosternal chest pain or discomfort	−0.8 ± 1.1	−0.8 ± 1.2	0.787	−0.8 ± 1.2	−0.7 ± 1.1	0.540
P-value	< 0.001	< 0.001		< 0.001	< 0.001	
Acid reflux	−0.5 ± 1.0	−0.5 ± 0.9	0.819	−0.5 ± 1.0	−0.5 ± 0.8	0.883
P-value	< 0.001	< 0.001		< 0.001	< 0.001	
Regurgitation	−0.4 ± 0.9	−0.7 ± 1.1	0.154	−0.4 ± 1.0	−0.5 ± 1.1	0.820
P-value	0.003	< 0.001		0.003	0.001	

CR, controlled-release.
Data are presented as mean ± SD.

with overall dyspepsia improvement, defined as participants who answered "much improved" or "very much improved" for overall dyspepsia after a 4-week trial. The proportion of overall responders at a 4-week drug administration was 53.7% (29/54 patients) for the mosapride CR group and 54.0% (27/50 patients) for the nortriptyline group ($P = 0.976$) (MITT analysis set). In the PP analysis set, there was no difference in the proportion of patients with overall dyspepsia improvement between the mosapride CR group (54.4%) and the nortriptyline group (55.8%) ($P = 0.890$) (Fig. 2). In addition, the proportion of patients with overall dyspepsia improvement after 4 weeks of drug administration according to the FD subtypes was comparable regardless of the specific treatment group such as mosapride CR or nortriptyline in both MITT and PP analysis sets (Fig. 3).

Secondary Efficacy Endpoints

Change in total symptoms of functional dyspepsia

Regarding the change in frequency and severity of total symptoms after 4 weeks of drug administration, significant symptom improvement was demonstrated in both the mosapride CR and nortriptyline groups. In addition, there was no difference in the degree of improvement between the mosapride CR group and the nortriptyline group. In subgroup analyses of individual symptom relief scores after 4 weeks of drug administration, all symptoms showed improvement, except for vomiting in both the mosapride CR and nortriptyline group in the MITT (Table 2) and PP (Supplementary Table 1) analysis sets.

Anxiety, depression, and quality of life

After 4 weeks of drug administration, both anxiety and depression improved in both groups. These differences in the degree of improvement were not significantly different between the mosapride CR and nortriptyline groups in MITT (Table 3) and PP (Supplementary Table 2) analysis sets.

Regarding the QoL after 4 weeks of drug administration, significant improvement was shown in both the mosapride CR and nortriptyline groups. This improvement in QoL was larger in the nortriptyline group than in the mosapride CR group (17.2 ± 19.2 in the mosapride CR group vs 24.9 ± 22.8 in the nortriptyline group, $P = 0.023$).

Rescue medication use and safety

There was no difference in the mean number of rescue medication tablets used in both groups (0.5 ± 1.1 in the mosapride CR group vs 1.0 ± 2.1 in the nortriptyline group, $P = 0.380$). There were also no severe adverse events. As shown in Table 4, mild adverse events were reported in 14.3% (8/54) of patients in the mosapride CR group versus 12.0% (6/50) in the nortriptyline group. All adverse events disappeared after cessation of treatment. However, 7 participants (12.3%) in the mosapride CR group and 6 participants (14.0%) in the nortriptyline group discontinued the drugs due to adverse events ($P = 0.881$).

Discussion

This multicenter, double-placebo, double-blinded, randomized controlled, parallel clinical trial was conducted to assess the efficacy of mosapride CR and nortriptyline in patients with FD. Our findings show noteworthy conclusions contrary to previous findings to date.

Table 3. Changes in Anxiety, Depression, and Quality of Life After a 4-Week Drug Administration

Modified intention-to-treat analysis	Mosapride CR (n = 54)	Nortriptyline (n = 50)	P-value
Anxiety	−2.1 ± 4.5	−2.1 ± 2.3	0.622
P-value	0.001	< 0.001	
Depression	−1.4 ± 4.7	−1.6 ± 3.3	0.784
P-value	0.030	0.001	
Quality of life	17.2 ± 19.2	24.9 ± 22.8	0.023
P-value	< 0.001	< 0.001	

CR, controlled-release.
Data are presented as mean ± SD.

Table 4. Adverse Events

	Mosapride CR (n = 54)	Nortriptyline (n = 50)
Subjects of adverse events	8 (14.8)	6 (12.0)
Kind of adverse events[a]		
Headache, dizziness, and sleepiness	2 (3.7)	3 (6.0)
Palpitation	0 (0)	1 (2.0)
Gastrointestinal dysfunction	4 (7.4)	3 (6.0)
Insomnia	1 (1.8)	2 (4.0)
Dysuria	1 (1.8)	0 (0)
Fatigue	1 (1.8)	0 (0)
Pruritus, sweat	2 (3.7)	0 (0)
Oropharyngeal pain, cough	1 (1.8)	1 (2.0)

[a]The types of adverse reactions included all of the subjects' various adverse events.
CR, controlled-release.
Data are presented as n (%).

First, mosapride CR and nortriptyline demonstrated comparable efficacy in the treatment of FD patients. These results are contrary to the treatment algorithm used when selecting therapeutic agents in both Western and Asian guidelines. Specifically, Western guidelines have recommended neuromodulators (specifically, tricyclic antidepressants) rather than prokinetics after PPIs.[11] However, Asian guidelines, including those from Korea and Japan, have recommended prokinetics after PPIs, because the effect of nortriptyline on FD was not superior to placebo in the management of Asian patients with FD.[10,31,32] However, our results could support the hypothesis that both mosapride CR and nortriptyline have similar efficacy for FD, at least in East Asians. The relative risk reduction of FD symptoms (33% [95% CI, 0.18-0.45 vs control] and 26% [95% CI, 0.61-0.91 vs control]) and number-to-treat number (7 vs 6) in both prokinetics and neuromodulators, respectively, were found to be similar, which could be supportive evidence for our results.[20,33] Additionally, combined administration of prokinetics and neuromodulators is prescribed for FD patients who do not respond to medications. However, it is not clear whether this combination is effective as there are few research results. As a representative study, there was a study conducted in Japan that confirmed the effect of combination therapy of acotiamide and esomeprazole in FD refractory to PPI monotherapy, but the sample size was small and there was no control group.[34] Therefore, future research on the effects of this combination will be needed.

Second, we found comparable efficacy of mosapride CR and nortriptyline when the FD patients were divided into 3 groups (PDS, EPS, and overlap). In other words, when the degree of relief of individual symptoms corresponding to PDS and EPS was quantified and calculated, all symptoms corresponding to PDS and EPS improved and there was no difference in symptom improvement between the 2 groups. These results are also inconsistent with previous diagnoses as well as treatment algorithms. The PDS and EPS subtypes were identified based on symptoms in the Rome III and Rome IV criteria.[5] In the management of FD, prokinetics have been recommended as a first-line treatment in people with PDS,[10,35] whereas neuromodulators were predicted to be more effective in the EPS subtype.[36] The rationale for this classification is based on the expectation that the underlying pathophysiological mechanisms of each subtype differ, and an appropriate therapeutic agent can be selected based on the corresponding subtype.[37] It would be ideal to select an appropriate therapeutic agent for FD based on the underlying pathophysiological mechanisms. However, our results suggest that dyspepsia symptoms are not specific to any particular pathophysiological mechanism or pathogenic agent. Our findings support the possibility that each etiology can affect the overall functioning of the gastroduodenal region and lead to various types of sensorimotor dysfunction that can be associated with several dyspepsia symptoms, including PDS and EPS symptoms.[37] It is more likely that multiple dysfunctions, rather than a single dysfunction, are involved in the development of dyspepsia symptoms.[37] Therefore, considering the pathophysiology of FD, it seems that both prokinetics and neuromodulators had an effect, regardless of the subtype.

Third, we confirmed improvements in QoL and psychological well-being after either prokinetic or neuromodulator treatment. Population-based studies have shown that compared to healthy controls, patients with FD are more likely to have higher levels of depression before diagnosis and are more likely to have comorbid anxiety, and this is known to be associated with a reduced QoL.[38,39] This study confirmed that QoL and psychological well-being improved through the control of dyspepsia symptoms. In addition, these positive effects on QoL and psychological well-being had comparable efficacy in mosapride CR and nortriptyline. These results are contrary to those of a previous meta-analysis demonstrating no benefit in improving QoL with prokinetics.[20]

Finally, no serious adverse events were observed for either drug. Nortriptyline has a black box warning for an increased risk of suicide, major depression, and urinary retention.[33] There may have been no difference in the incidence of side effects in this study because it did not include many elderly patients. Furthermore, we used mosapride CR as a safer option than dopamine receptor 2 antagonists such as metoclopramide, levosulpiride, and domperidone, which cause extrapyramidal symptoms. These results can serve as important criteria for the selection of drug treatments for FD.

Our study had some limitations. First, this study was approved by the Korea Food and Drug Administration as a parallel clinical study where mosapride CR and nortriptyline groups of treatment were given without a control group because neuromodulators, including nortriptyline, have not yet been approved for the treatment of FD in Korea. Due to the limitations of the study protocol mentioned above, there were no data on how effect for placebo drug is present, which may overlook the natural improvement in dyspeptic symptoms. Further studies are required to evaluate the efficacy of neuromodulators in Asian patients with FD. Second, unlike in Western countries, there were more patients with the PDS subtype than with the EPS subtype, so the distribution of FD subtypes assigned to each study group was inevitably uneven.[40]

In conclusion, this is the first report to demonstrate a comparable efficacy of mosapride CR and nortriptyline in patients with FD, regardless of the FD subtype. Both mosapride CR and nortripty-

line could be equally helpful to achieve improvements in QoL and psychological well-being, as well as in FD symptoms. We believe that these results will help set the standard for actual drug treatment of FD among Koreans and other Asians.

Supplementary Materials

Note: To access the supplementary tables mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm23147.

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Author contributions: Original data were collected from all participating centers in a central database. Chung Hyun Tae, Jung-Hwan Oh, and Joong Goo Kwon: planning and conducting the study, collecting, and analyzing data, interpreting the results, and approval of the final draft; Chung Hyun Tae and Ra Ri Cha: drafting the manuscript; Jong Kyu Park, Ki Bae Bang, Kyung Ho Song, Ju Yup Lee, and Cheol Min Shin: planning and conducting the study, collecting data, and approval of the final draft; and Ra Ri Cha, Jong Wook Kim, Young Hoon Youn, Cheal Wung Huh, and Tae-Guen Gweon: conducting the study, collecting data, and approval of the final draft. All authors had access to the study data and reviewed and approved the final manuscript.

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