Efficacy of the 5-HT1A Agonist Tandospirone Citrate in Improving Symptoms of Patients With Functional Dyspepsia: A Randomized Controlled Trial

Hiroto Miwa, MD, PhD[1], A. Nagahara, MD, PhD[2], K. Tominaga, MD, PhD[3], T. Yokoyama, MD, PhD[4], Y. Sawada, MD, PhD[5], K. Inoue, MD, PhD[6], Kiyoshi Ashida, MD, PhD[7], T. Fukuchi, MD[7], M. Hojo, MD, PhD[2], H. Yamashita, MD[7], T. Tomita, MD, PhD[1], K. Hori, MD, PhD[1] and T. Oshima, MD, PhD[1]

OBJECTIVES: **Functional dyspepsia (FD) is a common condition in the general population; however, its treatment remains a challenge. The aim of this study was to examine the efficacy of tandospirone citrate, a new partial agonist of the 5-hydroxytryptamine 1A (5-HT1A) receptor, in improving the symptoms of patients with FD.**

METHODS: **In this double-blind, placebo-controlled, multicenter study, FD patients were randomized to treatment with 10 mg t.i.d. tandospirone citrate or to placebo for 4 weeks. The primary end point was change in abdominal symptom scores. The difference in the proportion of responders (a total abdominal symptom score of 0 or 1) was also assessed. The quality-of-life questionnaire, the SF-8, and a psychological test questionnaire, the State-Trait Anxiety Inventory (STAI), were completed at baseline and at weekly intervals.**

RESULTS: **Data were available for 144 patients: 73 for tandospirone and 71 for placebo. Improvements in total abdominal scores were significantly larger with tandospirone than placebo at weeks 1, 2, and 4. Significantly greater improvements in the tandospirone group were observed in upper abdominal pain ($P=0.02$) and discomfort ($P=0.002$) at week 4. The proportion of responders was significantly greater in the active treatment arm at weeks 3 ($P=0.017$) and 4 ($P=0.0016$). Significant improvements in STAI ($P<0.0001$) were reported in both arms, as well as in the majority of questions in the SF-8 ($P=0.04$). No serious adverse events were reported, with similar rates in both study arms.**

CONCLUSIONS: **Despite a considerable placebo effect, the benefits of tandospirone were shown in terms of improvement in abdominal symptom scores.**

Am J Gastroenterol advance online publication, 28 July 2009; doi:10.1038/ajg.2009.427

INTRODUCTION

Functional dyspepsia (FD) is a common condition in the general population and is defined as persistent or recurrent pain, or discomfort in the upper abdomen without organic disease (1). The reported prevalence of the condition in Japan is 13% (2) and a rate of 28% (3) has been shown in an international surveillance study. Although there has been a marked reduction in the recurrence rate of peptic ulcers since the introduction of therapies to cure infections of *Helicobacter pylori* (4–7), treatment of FD remains a challenge. The pathophysiology of the condition has not been fully elucidated and it is considered to be multifactorial with psychological factors having an important function. The recommended first-line treatment of patients with ulcer-like dyspepsia is the use of an antisecretory agent and for those with dysmotility-like dyspepsia, prokinetic agents are recommended (8).

[1]Division of Upper Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan; [2]Department of Gastroenterology, Juntendo University, School of Medicine, Tokyo, Japan; [3]Department of Gastroenterology, Osaka City University Graduate School of Medicine, Osaka, Japan; [4]Department of Technology Assessment and Biostatistics, National Institute of Public Health, Saitama, Japan; [5]Department of Gastroenterology, Takarazuka Municipal Hospital, Hyogo, Japan; [6]Department of Internal Medicine, Matsue Red Cross Hospital, Shimane, Japan; [7]Department of Gastroenterology, Saiseikai Nakatsu Hospital, Osaka, Japan. **Correspondence:** Hiroto Miwa, MD, PhD, Division of Upper Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya-city, Hyogo, 663-8501, Japan. E-mail: miwahgi@hyo-med.ac.jp
Received 25 February 2009; accepted 22 June 2009

Serotonin (5-hydroxytryptamine, 5-HT) has been implicated in the control of gastrointestinal motility, sensitivity, and secretion, and as a consequence, serotonergic agents have been explored as potential therapeutic agents for gastrointestinal disorders (9). The clinical use of these agents has focused on selective serotonin reuptake inhibitors as well as 5-HT receptor antagonists and agonists. Fourteen types of serotonin receptors are currently known. Among them, 5-HT1A agonist, 5-HT1B/D agonist, 5-HT2A antagonist, 5-HT3 antagonist, and 5-HT4 agonists are used clinically for various diseases. Regarding 5-HT1A agonist, buspirone inhibits tone of the proximal stomach and delays gastric emptying rate in a dose-dependent manner (10), and R-137696, another 5-HT1A agonist, also induces a relaxation of the proximal stomach (11). However, a 4-week, placebo-controlled trial of R-137696 in patients with FD failed to show any beneficial effect (12). Tandospirone is a new partial agonist of the 5-HT1A receptor that has anxiolytic effects. It belongs to the same class of drugs as buspirone, namely the azapirones. It has none of the non-anxiolytic effects associated with benzodiazepine agents, i.e., muscle relaxant, anticonvulsant, and sedative effects. In this study, we investigated whether this drug improves the symptoms of FD and whether such improvements were accompanied by changes in psychometric parameters and quality of life.

METHODS

Design and participants

The study was a double-blind, placebo-controlled, multicenter study of patients with FD conducted at six hospitals (three university hospitals and three very large general hospitals). Patients meeting the Rome II FD criteria (13) were eligible for enrollment. The inclusion criteria applied were: existence of moderate or severe (not mild) degree of the following symptoms the week before trial commencement: epigastric pain; epigastric discomfort; bloating; postprandial fullness; early satiety; nausea or vomiting; appetite loss; and belching. Patients were required to have undergone an upper gastrointestinal endoscopy within 6 months of enrollment showing no organic lesions, such as malignant tumors, peptic ulcers, and reflux esophagitis, which would explain their symptoms. This was confirmed during their enrollment in the study. Patients were also required to be aged 20 years and over, and be an outpatient at the relevant center.

Patients excluded from the study were those who had apparent non-organic causes for dyspepsia, such as overeating, overdrinking, a particular stressful event, and non-steroidal anti-inflammatory drug intake; those with a primary complaint of heartburn; patients with irritable bowel syndrome or suspected irritable bowel syndrome; with a history of upper GI surgery; with severe panic or anxiety disorder, psychological diseases, or suspected psychological diseases; or with severe hepatic or renal dysfunction. Furthermore, patients who had been administered the following drugs within 1 week of the study drug dosing were excluded: prokinetics; acid suppression drug (proton pump inhibitor, H2 receptor antagonist); prostaglandins; and non-steroidal anti-inflammatory drugs. Patients who had taken anti-anxiety or tranquilizers within 4 weeks before the study drug dosing were also excluded.

Finally, any patients who were pregnant, lactating, and/or who were attempting to conceive were excluded, as well as patients who were regarded as not being suitable participants by the study investigators. All patients gave their written informed consent for participating in the study. The study protocol was approved by the internal review board of each center.

Randomization and treatment

Randomization was done using a computerized random number table with the key cord securely stored. Patients were randomized to one of two study arms. The treatment arm involved 10 mg t.i.d. tandospirone citrate (Sediel, Dainippon Sumitomo Pharmaceutical, Osaka, Japan) for 4 weeks. The placebo arm involved an identical placebo tablet (Seiko Eiyo Yakuhin, Osaka, Japan) t.i.d. for 4 weeks.

The following concomitant medications were prohibited: prokinetics; acid suppression drugs (proton pump inhibitor, H2 receptor antagonist); prostaglandins; and non-steroidal anti-inflammatory drugs. Permitted concomitant medications included those that had been prescribed for treatment and/or prevention of complications before obtaining informed consent whether they were not one of the prohibited drugs. These drugs were continued during the study period without changing dosage and dosage timing.

Symptom assessment

Patients were questioned about the following eight abdominal symptoms: epigastric pain; epigastric discomfort; upper abdominal distention; bloating (feeling of food staying longer in the stomach); early satiety; nausea and vomiting; appetite loss; and belching. The severity of each symptom was rated as: 0: no symptom; 1: mild; 2: moderate; and 3: severe, and the patients were also allowed to use the rating 0.5 (between 0 and 1), 1.5 (between 1 and 2), and 2.5, (between 2 and 3). The maximum total score was 24. This questionnaire was basically made by modifying Gastrointestinal Symptom rating Scale (GSRS), and we previously used this scale in other clinical trials (13,14).

A quality-of-life questionnaire, the SF-8, and a psychological test questionnaire, the State-Trait Anxiety Inventory (STAI), were completed by the patient at baseline and at weekly intervals , during the study. The SF-8 was converted into the scoring system standardized for the Japanese population in 2002 (15), with point 50 indicating the mean score of the Japanese population. The STAI questionnaire consisted of 40 questions (20 questions for state and 20 questions for trait anxiety). The STAI was also converted to the scoring system standardized for the Japanese population (16). Adverse events were also recorded during the study.

Study end points

The primary efficacy outcome for the study was the change in total abdominal symptom score from baseline to week 4. The

statistical significance was assessed based on the mean difference in the change of scores between treatment groups. As the mean score was not easily interpreted for clinical relevance, the difference in proportion of responders between groups was also estimated, in which the responders were defined as those having a total abdominal symptom score of 0 or 1. To express supportive evidence for the primary outcome, the following secondary outcomes were assessed: (1) change in each abdominal symptom; (2) change in STAI score; and (3) change in SF-8 score.

Statistics

To have an 80% chance of detecting as significant ($P<0.05$, two-sided) a two-point difference in change of total symptom score between treatment and placebo arms, with an assumed s.d. of 5.5 and a loss to follow-up of 10%, 75 patients were required for each arm. The primary and secondary end points were analyzed according to the intention-to-treat principle. The last-observation carry-forward method was used to impute missing data. For patients without data throughout weeks 1 to 4, the mean value for both arms combined was imputed so as to make the difference between the two arms conservative. Data were summarized as percentage, mean, and s.d., or as median and 25th and 75th percentiles. The primary efficacy outcome was statistically tested by analysis of covariance, in which the dependent variable was the difference in change of total abdominal symptom score from baseline to week 4, and the covariate was the total abdominal symptom score at baseline. The difference in proportions of responders between treatment and placebo groups was calculated with a 95% confidence interval, and statically tested by Cochran–Mantel–Haenszel test adjusted for the quartile categories of baseline total score. For the analysis of secondary outcomes, the difference in change of each abdominal symptom score or SF-8 quality-of-life score from baseline to week 4 was compared between treatment and placebo groups by van Elteren test (stratified Mann–Whitney *U*-test), adjusted for the baseline score. The difference in change of STAI from baseline to week 4 was compared between treatment and placebo groups by analysis of covariance adjusted for the baseline value.

RESULTS

A total of 150 patients were enrolled in the study with randomization of 75 patients each to tandospirone and placebo. Data on 144 patients, 73 for tandospirone and 71 for placebo, were available. In the other six patients, there were no data available at week 1 and later (**Figure 1**). To carry out an intention-to-treat analysis, the mean value for both arms combined was imputed for such patients so as to make the difference between the two arms conservative. The baseline patient characteristics are shown in **Table 1**. Both treatment arms were well balanced for gender, age, height, body weight, BMI, disease suffering period, *H. pylori* status as well as smoking and alcohol use. The change in total abdominal symptom scores is shown in **Table 2**. Statistically significant

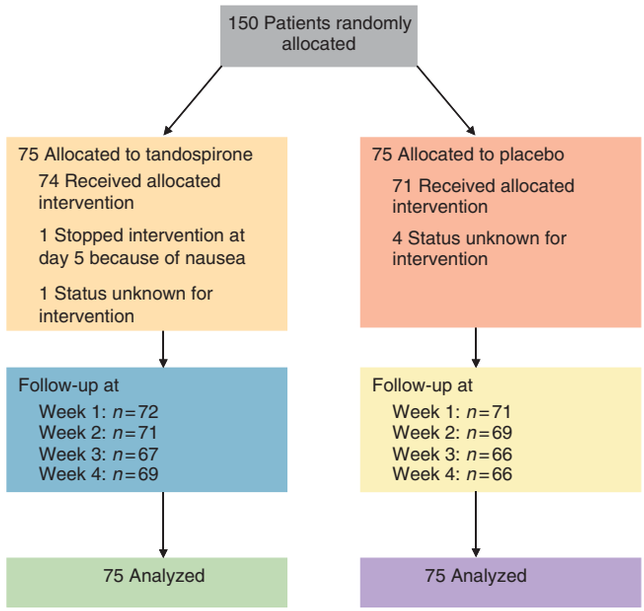

Figure 1. Flow diagram of a multicenter trial comparing symptoms of functional dyspepsia between patients treated by tandospirone citrate and by a placebo.

Table 1. Patient background characteristics at randomization

	Tandospirone (*n*=75)	Placebo (*n*=75)	*P*[a]
Sex (% of males)	24.0%	29.7%	0.464
Age (years)	46.2±16.8	46.5±17.6	0.904
Body height (cm)	158.4±7.6	160.1±8.4	0.222
Body weight (kg)	51.7±9.4	53.3±9.5	0.318
Body mass index (kg/m^2)	20.5±2.6	20.7±2.8	0.621
Disease suffering period (months)	12 (3, 36)	12 (3, 36)	0.628
Helicobacter pylori status			
Positive	20.0%	21.6%	0.339
Negative	25.3%	35.1%	
Unknown	54.7%	43.2%	
Smoking status			
Yes	10.7%	10.7%	1.000
No	88.0%	86.7%	
Unknown	1.3%	2.7%	
Alcohol consumption			
Yes	34.7%	32.0%	0.896
No	64.0%	65.3%	
Unknown	1.3%	2.7%	

Values are expressed as percentage, mean±s.d., or median (25th and 75th percentiles).

[a]Fisher's exact test, Student's *t*-test, and Mann–Whitney *U*-test for comparing percentage, mean, and median values, respectively.

Table 2. Improvement of abdominal symptoms in patients treated by tandospirone and placebo

	Tandospirone	Placebo	Change from baseline				
			Tandospirone		Placebo		*P* for difference in change[b]
	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	*P*[a]	Mean ± s.d.	*P*[a]	
Total score							
Baseline	8.66 ± 3.77	8.22 ± 3.68					
At week 1	6.65 ± 3.54	7.45 ± 4.25	−2.00 ± 2.30	<0.0001	−0.77 ± 2.25	0.0095	0.0016
At week 2	5.45 ± 3.67	6.51 ± 4.33	−3.21 ± 3.03	<0.0001	−1.71 ± 2.83	<0.0001	0.0028
At week 3	4.96 ± 3.87	5.47 ± 3.67	−3.69 ± 3.29	<0.0001	−2.74 ± 2.87	<0.0001	0.086
At week 4	4.10 ± 4.02	4.89 ± 3.41	−4.56 ± 3.34	<0.0001	−3.33 ± 3.47	<0.0001	0.036
Upper abdominal pain							
Baseline	1.21 ± 1.05	1.12 ± 0.94					
At week 4	0.58 ± 0.78	0.73 ± 0.73	−0.63 ± 0.90	<0.0001	−0.40 ± 0.83	<0.0001	0.021
Discomfort							
Baseline	1.55 ± 0.96	1.54 ± 0.84					
At week 4	0.64 ± 0.80	1.00 ± 0.81	−0.92 ± 0.95	<0.0001	−0.53 ± 0.91	<0.0001	0.002
Bloating							
Baseline	0.99 ± 1.00	1.03 ± 1.03					
At week 4	0.50 ± 0.80	0.67 ± 0.89	−0.49 ± 0.84	<0.0001	−0.36 ± 0.86	0.0003	0.310
Early satiety							
Baseline	1.16 ± 0.94	1.17 ± 1.00					
At week 4	0.50 ± 0.68	0.62 ± 0.81	−0.66 ± 0.85	<0.0001	−0.55 ± 0.76	<0.0001	0.364
Nausea							
Baseline	1.21 ± 1.06	1.14 ± 1.06					
At week 4	0.72 ± 0.96	0.61 ± 0.81	−0.49 ± 0.92	<0.0001	−0.53 ± 0.88	<0.0001	0.815
Vomiting							
Baseline	0.85 ± 1.01	0.87 ± 0.95					
At week 4	0.34 ± 0.69	0.39 ± 0.63	−0.51 ± 0.79	<0.0001	−0.47 ± 0.90	<0.0001	0.658
Anorexia							
Baseline	0.64 ± 0.93	0.63 ± 0.89					
At week 4	0.37 ± 0.71	0.34 ± 0.63	−0.27 ± 0.69	0.0004	−0.29 ± 0.71	0.0004	0.723
Belching							
Baseline	1.04 ± 1.14	0.73 ± 0.87					
At week 4	0.45 ± 0.67	0.53 ± 0.78	−0.59 ± 0.91	<0.0001	−0.20 ± 0.77	0.035	0.228

The primary end point was the total score at week 4. The lower the score, the better the symptoms. The last-observation carry-forward method was applied to impute missing values. For patients with no data throughout weeks 1–4 ($n=2$ and 4 for tandospirone and placebo arms, respectively), the mean value for both groups combined was imputed so as to make the difference between the two arms conservative.

[a]*P* value for change from baseline calculated by paired *t*-test (total score) or Wilcoxon signed rank test (individual score). [b]*P* value for difference in change between the tandospirone and placebo groups calculated by analysis of covariance including the baseline value as a covariate (total score) or by van Elteren test adjusted for the baseline value (individual score).

improvements in scores were observed from week 1 onwards and this was maintained through to 4 weeks in both tandospirone and placebo group. Improvement of the total symptom scores was significantly larger in tandospirone arm than in placebo arm at week 4; and a significant difference was also seen at week 1 and 2. The histograms for the distribution of the total symptom scores before and after treatment, in both arms are shown in **Figure 2**. The proportion of patients responding to treatment

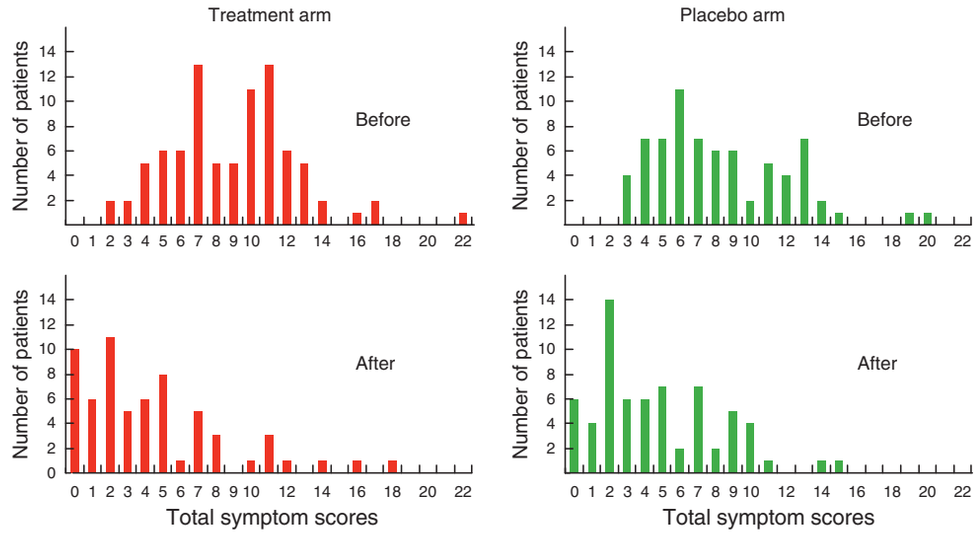

Figure 2. The histograms for the distribution of the total symptom scores before and after treatment of patients using tandospirone citrate or placebo. The responder was defined as a patient whose total symptom scores became 0 or 1 at week 4.

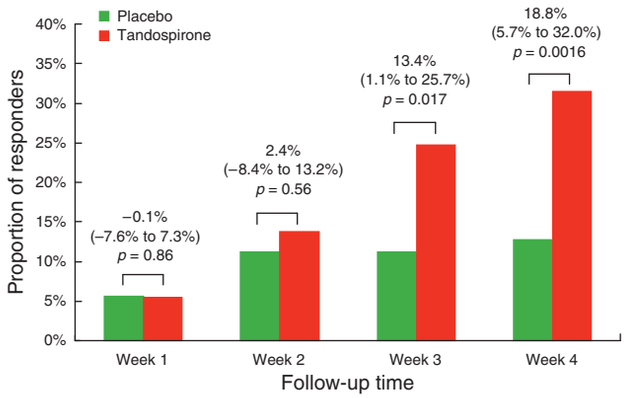

Figure 3. Proportion of responders in patients treated with trandospirone citrate or placebo. The primary end point was assessed at week 4. The difference of proportions (95% confidence interval) and *P* value are shown on top of the bars. *P* values were calculated by Cochran–Mantel–Haenszel test adjusted for the quartile categories of baseline total score. Two patients in tandospirone arm and four patients in the placebo arm, with no data throughout weeks 1–4, were excluded. On assuming these six patients as responders, so as to make the difference between the two arms conservative, *P* values were found to be 0.090 and 0.014 at weeks 3 and 4, respectively.

increased with time in the tandospirone group from 5.5%, at week 1, to 31.5%, at week 4 (**Figure 3**), whereas response rates for placebo were less than 15% throughout the study. The proportion in the active treatment arm and the placebo arm was significantly different at week 4 (by 18.8% (95% confidence interval = 5.7%–32.0%), $P = 0.0014$); and a significant difference was also seen at week 3.

The changes in scores for individual abdominal symptoms are also shown in **Table 2**. Significant improvements were observed for each item for both tandospirone and placebo. However, significantly greater improvements were observed in upper abdominal pain and discomfort at week 4 in the tandospirone group compared with placebo. Changes in individual STAI scores of state and trait, as well as overall score at week 4 are shown in **Table 3**. Significant improvements were reported in both arms of the study. However, there was no significant difference in change of STAI score between the two arms. An analysis of STAI in patients who responded to treatment and those who did not, indicates that both state and trait anxiety scores were improved to a significantly higher degree in responders treated with tandospirone, whereas improvement of these scores were not significantly different between responders and non-responders in placebo arm (data not shown).

Significant improvements over baseline were reported in each of the eight questions of the SF-8 for both arms of the study at 4 weeks with the exception of Q2 in the tandospirone arm (**Table 4**). A comparison of the difference in change between the two groups revealed no significant differences in any items. Difference in change between non-responders and responders was not statistically different between tandospirone and placebo arms. However, SF-8 scores were significantly improved only in responders of tandospirone group in Q1, Q3, and Q8 (in Q7, the scores were significantly improved in both groups) (Data not shown).

Data on 144 patients were available for the safety analysis. The adverse events recorded during the study are shown in **Table 5**. No serious adverse events were reported and the incidence of individual events was similar in the two treatment arms.

DISCUSSION

There is evidence for the association of stress and dyspeptic symptoms (17,18) and patients in a depressive or anxiety state are more likely to seek medical care for the dyspepsia symptoms (19). Such patients also complain that their symptoms

Table 3. Improvement of STAI in patients treated with trandospirone or placebo

	Tandospirone	Placebo	Change from baseline				
			Tandospirone		Placebo		*P* for difference in change[b]
	Mean±s.d.	Mean±s.d.	Mean±s.d.	*P*[a]	Mean±s.d.	*P*[a]	
State anxiety							
Baseline	48.3±9.1	48.9±8.0					
At week 4	43.2±9.2	44.5±7.8	−5.1±8.9	<0.0001	−4.4±8.6	<0.0001	0.411
Trait anxiety							
Baseline	50.5±10.1	50.4±9.8					
At week 4	46.9±9.5	47.3±9.1	−3.6±5.9	<0.0001	−3.1±7.4	0.0005	0.658
Overall							
Baseline	98.8±17.1	99.3±15.8					
At week 4	90.2±16.7	91.8±14.7	−8.7±13.1	<0.0001	−7.5±14.1	<0.0001	0.493

STAI, State-Trait Anxiety Index.

The lower the score, the less the anxiety. For subjects with no data for STAI (n=4 and 6 for tandospirone and placebo arms, respectively), the mean value for both groups combined was imputed so as to make the difference between the two arms conservative.

[a]*P* value for change from baseline calculated by paired *t*-test. [b]*P* value for difference in change between the tandospirone and placebo groups by analysis of covariance including the baseline value as a covariate.

are more severe than other patients with the condition (20). A meta-analysis published in 2000 of 11 randomized clinical trials of antidrepressants in patients with functional gastrointestinal disorders, including non-ulcer dyspepsia has been conducted (21). Results from the studies suggest that antidepressants were an effective form of treatment and that the benefit was clinically significant. The review suggested that because subtherapeutic doses of antidepressants were tested, the benefits shown were not due entirely to the antidepressant properties of these drugs. The meta-analysis also showed that most studies in this area involved relatively few patients (7 to 32 patients in the case of non-ulcer dyspepsia). We reported a subsequent review of studies conducted after 2000 (22) and indicated that of the 13 studies reviewed, dyspeptic symptoms improved significantly with antidepressant treatment in 11 studies.

Tandospirone, a 5-HT1A agonist, selectively binds to the 5-HT1A receptor (23). It has primarily been investigated in the treatment of anxiety (24), but has also been studied in eating disorders (25) and gastrointestinal diseases (26). It has been approved in Japan for the treatment of anxiety disorders and psychosomatic disorders (especially autonomic imbalance, essential hypertension, and peptic ulcer). However, to date, there are limited data on the effectiveness of tandospirone in treating FD (26,27). A small-scale study of 79 patients compared the efficacy of famotidine, mosapride, and tandospirone in controlling dyspeptic symptoms over a 4-week period (26). Symptomatic relief was reported in four of the 15 (26.7%) patients treated with tandospirone compared with nine of 22 (40.9%) and 15 of 23 (65.2%) patients treated with mosapride and famotidine, respectively. Another study involving the same drug comparator groups and 64 patients with FD (27), showed no significant improvement in symptoms with tandospirone treatment. These reports suggest that tandospirone was not likely to be efficacious in the treatment of FD patients. Nevertheless, the results might be biased, as it is known that placebo response rate is particularly high in patients with FD. In addition, the dropout rate for the tandospirone-treated patients was very high, suggesting the presence of study bias. Theoretically tandospirone could be effective in improving dyspeptic symptoms not only through its anxiolytic action but also through improving gastric accommodation. 5-HT1A receptors are known to be presynaptically located on cholinergic nerve endings and neuromuscular junction, and their activation causes smooth muscle relaxation (28). It has been reported that the 5-HT1A receptor agonists, buspirone and R137696, affect stomach tone (10,29). With these observations, tandospirone may have a relaxing property of the proximal stomach, though such data are not yet available.

This study is the first randomized, placebo-controlled, multicenter study on tandospirone in patients with FD, who met Rome II criteria. With regard to the primary efficacy end point of the study, a statistically significant difference in the total abdominal symptom score at 4 weeks was identified between the tandospirone and placebo arms. A comparison of the difference between the two groups showed significant better efficacy in tandospirone over placebo at week 1, 2, and 4. In looking at the change of symptom score of each item, significant improvements were reported for all items in both treatment arms. For upper abdominal pain and discomfort, these improvements were significantly greater with tandospirone than with the placebo. No difference between groups was noted for improvement in early satiety, suggesting that the predominant mechanism of this 5-HT1A agonist in symptom improvement may be mediated by an anti-anxiety effect, not by improving gastric accommodation. The strengths of the study are its randomized

Table 4. Improvement of SF-8 in patients treated with tandospirone or placebo

	Tandospirone	Placebo	Change from baseline				
			Tandospirone		Placebo		*P* for difference in change[b]
	Mean±s.d.	Mean±s.d.	Mean±s.d.	*P*[a]	Mean±s.d.	*P*[a]	
Q1							
Baseline	40.8±6.0	41.0±5.4					
At week 4	46.9±7.4	46.5±6.8	6.1±8.5	<0.0001	5.5±7.5	<0.0001	0.608
Q2							
Baseline	47.7±7.4	46.5±7.6					
At week 4	48.9±7.5	49.4±4.6	1.2±8.0	0.1031	2.8±8.6	0.006	0.557
Q3							
Baseline	46.5±7.2	45.6±8.2					
At week 4	48.5±6.8	48.7±5.8	2.0±6.0	0.0168	3.1±9.2	0.0067	0.828
Q4							
Baseline	45.1±7.3	43.7±8.6					
At week 4	48.2±7.3	48.2±7.4	3.1±8.4	0.0095	4.5±7.9	<0.0001	0.507
Q5							
Baseline	44.9±7.5	44.8±6.1					
At week 4	48.4±6.0	48.1±5.8	3.5±7.8	0.0003	3.3±8.1	0.0001	0.836
Q6							
Baseline	44.6±8.1	44.0±9.4					
At week 4	47.7±7.5	47.5±7.7	3.1±8.3	0.0036	3.5±9.6	0.0034	0.708
Q7							
Baseline	44.0±6.1	42.6±6.5					
At week 4	47.6±6.2	48.0±5.9	3.6±6.8	<0.0001	5.4±6.7	<0.0001	0.296
Q8							
Baseline	46.9±6.6	45.8±7.5					
At week 4	48.6±6.7	49.4±4.6	1.7±6.3	0.0511	3.6±8.9	<0.0001	0.574

The lower the score, the worse the quality of life. For patients with no data for quality of life (n=13 and 14 for tandospirone and placebo arms, respectively), the mean value for both groups combined was imputed so as to make the difference between the two arms conservative.

[a]*P* value for change from baseline calculated by Wilcoxon signed rank test. [b]*P* value for difference in change between the tandospirone and placebo groups calculated by van Elteren test adjusted for the baseline value. Q1: Overall, how would you rate your health during the past 4 weeks? Q2: During the past 4 weeks, how much did physical health problems limit your usual physical activities (such as walking or climbing stairs)? Q3: During the past 4 weeks, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health? Q4: How much bodily pain have you had during the past 4 weeks? Q5: During the past 4 weeks, how much energy did you have? Q6: During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends? Q7: During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed, or irritable)? Q8: During the past 4 weeks, how much did personal or emotional problems keep you from doing your usual work, school, or other daily activities?

placebo controlled design, the evaluation of anxiety in conjunction with dyspeptic symptoms and the striking change in symptoms, which is rarely seen in FD studies.

Regarding the ratio of the responders, significantly more patients responded to treatment with tandospirone than to placebo at both weeks 3 and 4. The proportion of responders in patients treated with tandospirone increased steadily after week 4 of the study to achieve a rate of 31.5% at the end of the study, whereas that in placebo patients was <15% throughout the study period. These results are in line with the fact that that the drug is known to work gradually (30,31). A longer period study might show an increase in the proportion of responders, considering this property of the drug. The placebo response rate of 15% was relatively low compared with the 35% rate usually observed in these patient groups (32). This might be due to the rather strict definition of responder applied. In this study, the symptom scale, although not validated in Japanese population, uses a stringent end point of none/minimal symptoms. In addition, this might

Table 5. Incidence of adverse events among patients treated with tandospirone or placebo

Adverse event	Tandospirone citrate	Placebo
	n (%)	*n* (%)
Faintness	1 (1.3%)	0
Malaise	0	1 (1.3%)
Abdominal asthenia	0	1 (1.3%)
Dizziness	5 (6.7%)	2 (2.7%)
Nightmares	0	1 (1.3%)
Sleepiness	2 (2.7%)	7 (9.3%)
Insomnia	0	1 (1.3%)
Headache	1 (1.3%)	0
Heartburn	0	1 (1.3%)
Nausea	0	2 (2.7%)
Diarrhea	1 (1.3%)	1 (1.3%)
Constipation	0	1 (1.3%)

Subjects without information on adverse events ($n=2$ and 4 for tandospirone and placebo arms, respectively) were excluded.

also be due to the fact that the study was done mainly in the university hospital or in very large general hospitals, in which the patients had already been treated by primary-care physicians and, therefore, potentially had a reduced placebo response. This study is small, and the duration of follow-up is short, but the observed changes are large. Nearly one-third of the patients were cured by this drug eloquently that shows the usefulness of this drug, and these results encourage longer-term studies.

No significant differences were observed between the total scores for the STAI and SF-8 for the two treatment arms. However, further analysis of the STAI scores in the tandospirone group showed that the improvement in trait anxiety score was higher in patients classified as responders compared with non-responders. This result would suggest that anxiety status has a function in the pathogenesis of FD in certain patient populations. Regarding the individual questions of the SF-8, questions 1, 3, 7, and 8 significantly improved in responders although the difference of change between responders and non-responders did not reach a statistically significant score. With regard to the equivalent results for the placebo group, there was no correlation between STAI and SF-8 scores, and response to treatment, with the exception of SF-8 question 7. Overall, these findings would confirm that the symptomatic response to treatment is not a placebo effect and that it translates into benefits in quality of life and anxiety state. Together with the finding that only the specific symptoms of discomfort and pain were significantly improved to a greater degree in the tandospirone group, it can be speculated that tandospirone might act in the central nervous system, resulting in the improvement of symptoms in patients with FD.

It is a noteworthy that tandospirone did not increase the risk of side effects compared with placebo and can be considered a safe medication. The fact that widespread use of another 5-HT1A agonist, buspirone, in the treatment of dyspeptic patients was hampered due to side effects, such as somnolence and dizziness (33), this can be considered as a strength of tandospirone. In terms of abuse potential with this agent, studies suggest that this is lower than those for the benzodiazepines and barbiturates (25). The results obtained in this study should be further confirmed in a more generalized population. Positioning of tandospirone for treatment of FD should be further discussed as it has the potential for reduced abuse potential compared with the benzodiazepines.

ACKNOWLEDGMENTS

This trial is registered with UMIN Clinical Trials Registry, number C000000326.We greatly appreciate Satomi Nakano for her dedicated secretarial assistance. We thank Professor Nimish Vakil for fruitful scientific discussion about this study.

CONFLICT OF INTEREST

Guarantor of the article: Hiroto Miwa, MD, PhD.
Specific author contributions: Design of the study, writing the protocol, correcting patients, and writing the paper: H. Miwa; carrying out statistical analyses and writing the paper: T. Yokoyama; enrolling patients and carrying out the study: H. Miwa, A. Nagahara, K. Tominaga, T. Yokoyama, Y. Sawada, K. Inoue, K. Ashida, T. Fukuchi, M. Hojo, H. Yamashita, T. Tomita, K. Hori, and T. Oshima; review and approval of the paper: H. Miwa, A. Nagahara, K. Tominaga, T. Yokoyama, Y. Sawada, K. Inoue, K. Ashida, T. Fukuchi, M. Hojo, H. Yamashita, T. Tomita, K. Hori, and T. Oshima.
Financial support: This study was financially supported by the grant provided by the Waksman Foundation of Japan (06–9).
Potential competing interests: Hiroto Miwa is a consultant to AstraZeneca (Japan) Dainippon-Sumitomo, Takeda Pharmaceutical, Tsumura, and Eisai. Kiyoshi Ashida is a consultant to Eisai and Takeda Pharmaceutical.

Study Highlight

WHAT IS CURRENT KNOWLEDGE

- ✓ Functional dyspepsia (FD) is a common condition in the general population; however, its treatment remains a challenge.
- ✓ Tandospirone citrate is a 5-hydroxytryptamine 1A (5HT1A) agonist, which has not only an anxiolytic effect but also a relaxing property of the proximal stomach.
- ✓ Whether tandospirone citrate is useful for the treatment of patients with FD remains unknown.

WHAT IS NEW HERE

- ✓ This is the first randomized controlled trial of 5HT1A agonist tandospirone citrate in patients with FD.
- ✓ The proportion of responders was significantly greater in the treatment arm (tandospirone citrate) at weeks 3 ($P=0.017$) and 4 ($P=0.0016$).
- ✓ State-Trait Anxiety Inventory and SF-8 scores improved in cured patients in the tandospirone arm.
- ✓ No serious adverse events were reported, with similar rates in tandospirone and placebo arms.

REFERENCES

1. Talley NJ, Stanghellini V, Heading RC *et al.* Functional gastroduodenal disorders. Gut 1999;45:S1137–42.
2. Kawamura A, Adachi K, Takashima T *et al.* Prevalence of functional dyspepsia and its relationship with *Helicobacter pylori* infection in a Japanese population. J Gastroenterol Hepatol 2001;16:384–8.
3. Stanghellini V. Three-month prevalence rates of gastrointestinal symptoms and the influence of demographic factors: results from the Domestic/International Gastroenterology Surveillance Study (DIGEST). Scand J Gastroenterol 1999;231:S20–8.
4. Sung JJ, Chung SC, Ling TK *et al.* Antibacterial treatment of gastric ulcers associated with *Helicobacter pylori*. N Engl J Med 1995;332:139–42.
5. Hentschel E, Brandstätter G, Dragosics B *et al.* Effect of ranitidine and amoxicillin plus metronidazole on the eradication of *Helicobacter pylori* and the recurrence of duodenal ulcer. N Engl J Med 1993;328:308–12.
6. NIH Consensus Conference. *Helicobacter pylori* in peptic ulcer disease. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. JAMA 1994;272:65–9.
7. European *Helicobacter Pylori* Study Group. Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report. Gut 1997;41:8–13.
8. Fisher RS, Parkman HP. Management of nonulcer dyspepsia. N Engl J Med 1998;339:1376–81.
9. Gershon MD, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology 2007;132:397–414.
10. Coulie B, Tack J, Janssens J. Influence of buspirone-induced fundus relaxation on the perception of gastric distension in man. Gastroenterology 1997;110:A767 abstract.
11. Talley NJ, Vakil N. Practice parameters committee of the American college of gastroenterology. Guidelines for the management of dyspepsia. Am J Gastroenterol 2005;100:2324–37.
12. Tack J, Van Elzen B, Tytgat G *et al.* A placebo controlled trial of the 5-HT1A aginist R137696 on symptoms, visceral hypersensitivity and impaired fundic accommodation in functional dyspepsia. Gastroenterology 2004;126:A70 abstract.
13. Miwa H, Hirai S, Nagahara A *et al.* Cure of *Helicobacter pylori* infection does not improve symptoms in non-ulcer dyspepsia patients—a double-blind placebo-controlled study. Aliment Pharmacol Ther 2000;14:317–24.
14. Miwa H, Osada T, Nagahara A *et al.* Effect of a gastro-protective agent, rebamipide, on symptom improvement in patients with functional dyspepsia - A double blind placebo controlled study in Japan. J Gastroenterol Hepatol 2006;21:1826–31.
15. Fukuhara S, Suzukamo Y. Instruments for measuring Health-related Quality of Life-SF8 and SF36. J Clin Exp Med [Igaku no Ayumi] 2005;213:133–6 (in Japanese).
16. Nakazato K, Mizuguchi T. Development and validation of Japanese version of State-Trait anxiety inventory —a study with female subjects. Jpn J Psychosom Med [AShinshin-Igaku] 1982;22:107–12 (in Japanese).
17. Erckenbrecht JF, Schafer R, Kohler G *et al.* Dyspeptic symptoms in healthy volunteers with stress are related to stress-induced increase of anxiety—results of prospective study with a longterm "physiological" stress model. J Gastrointest Motil 1993;5:189–94.
18. Barry S, Dinan TG. Functional dyspepsia: are psychosocial factors of relevance? World J Gastroenterol 2006;12:2701–7.
19. Talley NJ, Zinsmeister AR, Schleck CD *et al.* Dyspepsia and dyspepsia subgroups: a population-based study. Gastroenterology 1992;102:1259–68.
20. Kroenke K, Jackson JL, Chamberlin J. Depressive and anxiety disorders in patients presenting with physical complaints: clinical predictors and outcome. Am J Med 1997;103:339–47.
21. Jackson JL, O'Malley PG, Tomkins G *et al.* Treatment of functional gastrointestinal disorders with antidepressant medications: a meta-analysis. Am J Med 2000;108:65–72.
22. Hojo M, Miwa H, Yokoyama T *et al.* Treatment of functional dyspepsia with antianxiety or antidepressive agents: systematic review. J Gastroenterol 2005;40:1036–42.
23. Hamik A, Oksenberg D, Fischette C *et al.* Analysis of tandospirone (SM-3997) interactions with neurotransmitter receptor binding sites. Biol Psychiatry 1990;28:99–109.
24. Murasaki M, Mori A, Endo S *et al.* Late phase II study of a new anxiolytic, SM 3997 (tandospirone) on neurosis. Rinsho Hyoka 1992;20:259–93.
25. Tamai H, Komaki G, Kubota S *et al.* The clinical efficacy of a 5-HT1A agonist, SM-3997, in the treatment of bulimia. Int J Obes 1990;14:289–92.
26. Kinoshita Y, Hashimoto T, Kawamura A *et al.* Effects of famotidine, mosapride and tandospirone for treatment of functional dyspepsia. Aliment Pharmacol Ther 2005;21:S37–41.
27. Seno H, Nakase H, Chiba T. Usefulness of famotidine in functional dyspepsia patient treatment: comparison among prokinetic, acid suppression and antianxiety therapies. Aliment Pharmacol Ther 2005;21:S32–6.
28. Kindt S, Tack J. Impaired gastric accommodation and its role in dyspepsia. Gut 2006;55:1685–91.
29. Boeckxstaens G, Tytgut G, Wajs E *et al.* The influence of the novel 5-HT1A agonist R137696 on the proximal stomach function in healthy volunteers. Neurogastroenterol Motil 2006;18:919–26.
30. Barradell LB, Fitton A. Tandospirone. CNS Drugs 1996;5:147–53.
31. Murasaki M, Mori A, Endo S *et al.* Late Phase II study of a new anxiolytic, SM-3997 (tandospirone), on various neurosis. Rinsho Hyoka 1992;20:259–93 (in Japanese).
32. Musial F, Klosterhalfen S, Enck P. Placebo responses in patients with gastrointestinal disorders. World J Gastroenterol 2007;13:3425–9.
33. Kindt S, Tack J. Mechanisms of serotonergic agents for treatment of gastrointestinal motility and functional bowel disorders. Neurogastroenterol Motil 2007;19:S32–9.