# A Double-Blind, Randomized, Placebo-Controlled Trial of Paroxetine Controlled-Release in Irritable Bowel Syndrome

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**Background:** *Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disease that causes significant impairment in quality of life and accounts for $8 billion per year to the healthcare system and loss of productivity in the workplace.* **Objective:** *The authors examined the efficacy and safety of paroxetine controlled-release (paroxetine-CR) in patients with IBS.* **Method:** *Seventy-two patients with IBS participated in a 12-week, double-blind, randomized, placebo-controlled study of paroxetine-CR (12.5 mg–50 mg/day). Efficacy was measured by Composite Pain Scores (primary outcome) and the Clinical Global Impression–Improvement (CGI–I) and Severity (CGI–S) ratings.* **Results:** *In intent-to-treat analyses, there were no significant differences between paroxetine-CR (N = 36) and placebo (N = 36) on reduction in Composite Pain Scores, although the proportion of responders on CGI–I was significantly higher in the paroxetine-CR group. The treatment was well tolerated.* **Conclusion:** *The study did not demonstrate a statistically significant benefit for paroxetine-CR over placebo on the primary outcome measure, although there was improvement in secondary outcome measures. Overall, paroxetine-CR seems to have potential benefit in IBS. Studies with adequate samples may clarify the role of paroxetine-CR in IBS.*
(Psychosomatics 2009; 50:78–86)

Irritable bowel syndrome (IBS) is classified as a functional gastrointestinal (GI) disease characterized by chronic abdominal discomfort with associated changes in bowel-movement frequency, consistency, and passage.[1,2] Additional symptoms may include pain relieved by defecation, looser stools at onset of pain, abdominal distension, mucus per rectum, and sensation of incomplete evacuation.[1] The prevalence of IBS is approximately 10% to 15% of the United States population, with a slight predominance of women.[3] IBS results in significant morbidity, with patients reporting three times as many absences from school and work as those without the disorder.[4] The average number of days away from work per year is estimated to be between 8.5 and 21.6 days, and there are considerable medical costs.[5] Also, the illness can impair quality of life and lead to increased medical help-seeking, since IBS accounts for 12% of all visits to primary-care physicians and 28% of all visits to gastroenterologists, with an estimated annual cost of $8 billion to the healthcare system.[6,7]

Bidirectional comorbidities between psychiatric illness and IBS are common. Several studies have shown that

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up to 70%-to-90% of patients with IBS who seek treatment have psychiatric comorbidity, most notably, mood and anxiety disorders.[2] Recent studies have also shown a high prevalence of IBS in psychiatric patients who seek treatment, with a prevalence of 19% in schizophrenia, 59% in dysthymia, 29% in major depressive disorder, 35% in obsessive-compulsive disorder, and 46% in panic disorder.[8–16]

Although the etiology of IBS is unclear, there is considerable evidence that brain–gut interactions are a major pathophysiological factor in the development of IBS.[6] A number of findings indicate that psychological stress aggravates GI homeostasis, leading to abnormal motility and visceral hypersensitivity.[17] Patients with IBS are particularly vulnerable to stress. They have more negative life events than patients with other GI disorders, and a correlation between severity of IBS symptoms and stress perception has been found.[18,19] Serotonin (5-HT), norepinephrine, and substance P have been the primary neurotransmitters implicated in IBS.[6] Altered firing of the locus ceruleus has been related to abnormal GI motility,[20] and 5-HT, which is abundant in gut enterochromaffin cells and myenteric interneurons, has mainly been implicated.[21] In particular, 5-HT3 and 5-HT4 receptors have been considered the most important in gut reflex and GI motility, and are located in vagal afferent neurons and presynaptic nerve terminals, respectively.[22,23]

Traditional pharmacological treatment options for IBS include antispasmodic agents, antidiarrheal agents such as loperamide, bulk laxatives, anticholinergics, 5-HT3 receptor agonists, 5-HT4 receptor agonists, and antidepressants such as tricyclic antidepressants (TCAs). In a number of randomized, placebo-controlled trials, the efficacy of TCAs in patients with IBS has been reported.[24–27] Because of the side effects of TCAs, selective serotonin reuptake inhibitors (SSRIs) may be useful for the treatment of IBS. Recently, it was also demonstrated that SSRIs can alter bowel physiology; for example, paroxetine can accelerate small-bowel transit without affecting gastric emptying or colonic transit.[28] However, there are only case reports and open-label studies, and there are few double blind, placebo-controlled studies with SSRIs in the treatment of IBS.[13,29–35]

It has been shown that SSRIs provide some benefit in chronic-pain patients[36] and can also affect gut-transit time and GI motility,[37] justifying their potential usefulness in the treatment of IBS. In particular, paroxetine, having proven efficacy for major depressive disorder and anxiety disorders, which are common in patients with IBS, is a popular SSRI, given its pharmacological and safety profile. Our preliminary findings indicated that paroxetine immediate-release (paroxetine-IR) and citalopram were beneficial and well-tolerated in patients with IBS.[13,30] The controlled-release formulation of paroxetine (paroxetine-CR) is probably associated with improved medication compliance and better tolerability, although this needs to be confirmed in prospective, head-to-head, controlled trials.[38–40] Hence, we designed this double blind, placebo-controlled study to evaluate whether paroxetine-CR would be efficacious and safe in the treatment of IBS patients.

## METHOD

This was a 12-week, double blind, randomized, flexible-dose, parallel-group, placebo-controlled study. The primary and secondary objectives were to compare the efficacy and safety of paroxetine-CR with placebo in patients with IBS.

### Subjects

After prescreening 527 subjects by telephone, 92 subjects came in for a formal screening, and 72 subjects were finally randomized, as shown in Figure 1.

Subjects were men and women age 18–75 years who had a confirmed diagnosis of IBS by use of Rome II diagnostic criteria (Table 1).[17,41]

The additional criteria for eligibility were the following: 1) Patients had ≥1 year of symptoms; 2) Patients able to maintain their usual diet; 3) Patients had had a documented full colonoscopy/flexible sigmoidoscopy in the past to rule out structural disorders; and 4) Patients able to comply with the study procedures.

Exclusion criteria were the following: 1) severe concurrent medical disease such as heart disease, cardiac arrhythmia, and glaucoma; 2) current psychotic, depressive, or anxiety disorders, bipolar disorder, substance dependence/abuse, or anorexia nervosa or bulimia, on the basis of an interview with the Mini-International Neuropsychiatric Interview (MINI);[42] 3) significantly abnormal blood test results (complete blood cell count; blood chemistry, anemia test, and erythrocyte sedimentation rate); 4) anatomical lesions of the colon in investigations done before the study; 5) history of lactose intolerance; 6) antidepressant treatment in the previous 6 weeks; 7) medication or surgery interfering with the assessment of IBS or with putative effect on transit; 8) participation in an investigational drug study within 30 days; and 9) pregnancy or lactation (female patients).

### Efficacy and Safety Measures

The primary efficacy measure, a priori, was a change in Composite Pain scores (frequency × duration) recorded on the Interactive Voice Response System (IVRS)[43] from Week 1 to the end of treatment (Week 12). The severity of abdominal pain/discomfort and other IBS symptoms (constipation, diarrhea, incomplete emptying, and bloating/abdominal distension) were all monitored by IVRS, using an ordinal scale rated from 1 to 9, with 1 being mild pain/discomfort and 9 being very severe pain/discomfort.

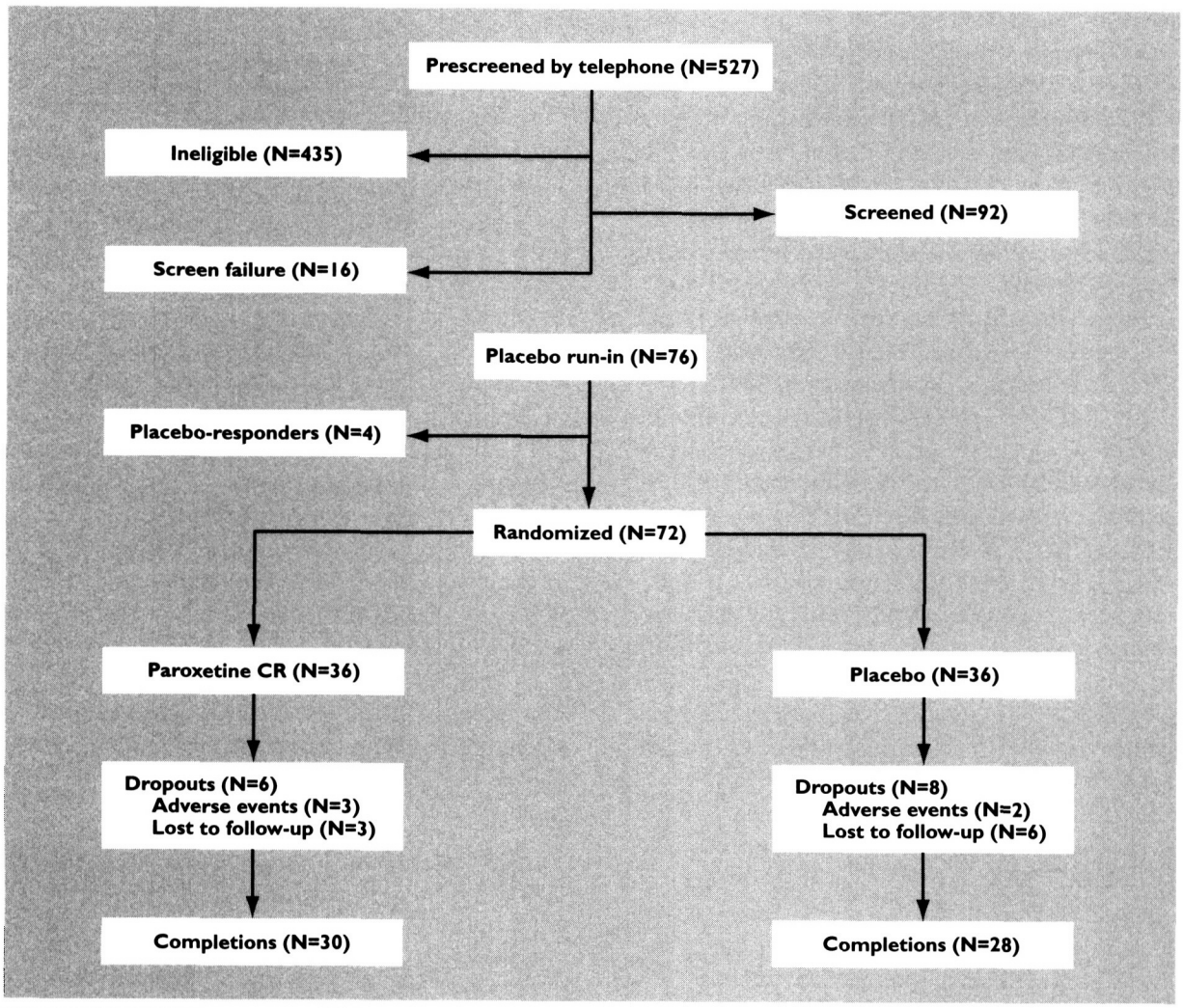
Secondary efficacy measures included the Clinical Global Impression–Improvement (CGI–I) and Severity (CGI–S) scores.[44] The Responders were defined as subjects having CGI–I scores of 1 or 2 at the end of treatment or achieving a ≥1-point decrease in CGI–S scores from baseline to the end of treatment. Adverse effects were determined by the Systematic Assessment For Treatment-Emergent Events (SAFTEE).[45]

### Procedures

The study was conducted at two sites, Duke University Medical Center and Thomas Jefferson University. The study protocol was approved by the Institutional Review Board of each participating institution. Written informed consent was obtained from all subjects before we performed any study procedures.

Screening procedures included a review of clinical history, establishing any comorbid psychiatric disorders indicated by the structured MINI interview, a physical examination, urine drug and pregnancy screening, and

**FIGURE 1. Subject Disposition for the Study**



routine laboratory tests including complete blood count, liver and renal functioning, thyroid status, and electrolytes. After screening, 72 eligible subjects were randomly assigned to receive either paroxetine-CR (N = 36) or placebo (N = 36). Based on tolerability and response, paroxetine-CR was started at 12.5 mg/day and increased biweekly in 12.5-mg/day increments, the maximum dose being 50 mg/day. If the patient could not tolerate higher doses, the dose was reduced, and the patient was maintained at the maximum tolerated dose. At the end of the 12 weeks, the medication was tapered over 2 weeks. No other psychotropic medications were permitted during the study except for medications to alleviate treatment-emergent adverse effects. Placebo was administered in an identical manner. Participants were monitored biweekly (every other week) from Week 0 to Week 12. Vital signs and weight were also taken at each visit. Compliance was assessed at each visit by pill count.

The telephone-based IVRS was used as a monitoring tool for self-rated improvement during the entire study period. All subjects were required to complete daily diary entries of their GI symptoms from Week 1 to Week 12. Subjects were instructed to call daily before bedtime, using a toll-free number. They entered a password and identification number and then recorded their diary entries in response to previously recorded questions (e.g., "Did you experience abdominal pain or discomfort today? If Yes, press 1; if No, press 2."). The psychometric validity of IVRS in administering diagnostic and symptom-rating scales by telephone has been evaluated in several studies.[43]

### Data Analysis

The group differences on outcome variables were compared by intent-to-treat (ITT) analysis, with the last observation carried forward (LOCF), to account for dropouts and missing data (at least one post-baseline visit). The categorical and continuous clinical variables were compared between the two treatment groups by chi-square analyses, analysis of variance (ANOVA), and *t*-tests, where appropriate. ANOVA examined the difference in the mean score of the Pain Composite Score on IVRS. Respondent outcome between the two treatment groups was compared by chi-square analysis.

## RESULTS

### Baseline Characteristics

The mean age of the subjects was 49.0 years; 63 (87.5%) were women (N = 31 in the paroxetine-CR and N = 32 in the placebo group), and 54 (75.0%) were Caucasian. Fifty-eight subjects (80.6%) completed the study: 30 (83.3%) in the paroxetine-CR group and 28 (77.8%) in the placebo group. The mean dose of paroxetine-CR was 30.0 mg/day.

### Primary Outcome

There were no significant differences in reduction of IVRS Composite Pain Scores between the paroxetine-CR (–2.8) and placebo (–1.9) groups ($F = 0.09$, $p = 0.82$; Figure 2).

Also, there were no differences in reduction in IVRS Composite Pain Scores (at ≥25%) between the paroxetine-CR group (52.0%) and the placebo group (39.0%) at the end of treatment. All other IBS symptom subanalyses on constipation, bloating, diarrhea, and distress found no significant differences between the two treatment groups.

### Secondary Outcome

Twenty-five of 36 subjects (69.4%) in the paroxetine-CR group showed CGI–I scores of 1 or 2 at the end of treatment, versus 6 of 36 (16.7%) in the placebo group (Fisher's exact test = 18.2; $p < 0.01$). Twenty-one of 36 subjects (58.3%) in the paroxetine-CR group had a ≥1-point reduction in CGI–S scores from baseline to end of treatment, versus 10 out of 36 (27.8%) in the placebo group (Fisher's exact test = 6.85; $p < 0.01$).

### Safety

There were 14 dropouts (19.4%) in the entire sample (paroxetine-CR: N = 6; placebo: N = 8), with dropouts due

**TABLE 1. Rome II Diagnostic Criteria for Irritable Bowel Syndrome (IBS)[a]**

At least 12 weeks, which need not be consecutive, in the preceding 12 months, of abdominal discomfort or pain that has 2 of 3 features:
1. Relieved with defecation; and/or
2. Onset associated with a change in frequency of stool; and/or
3. Onset associated with a change in form (appearance) of stool

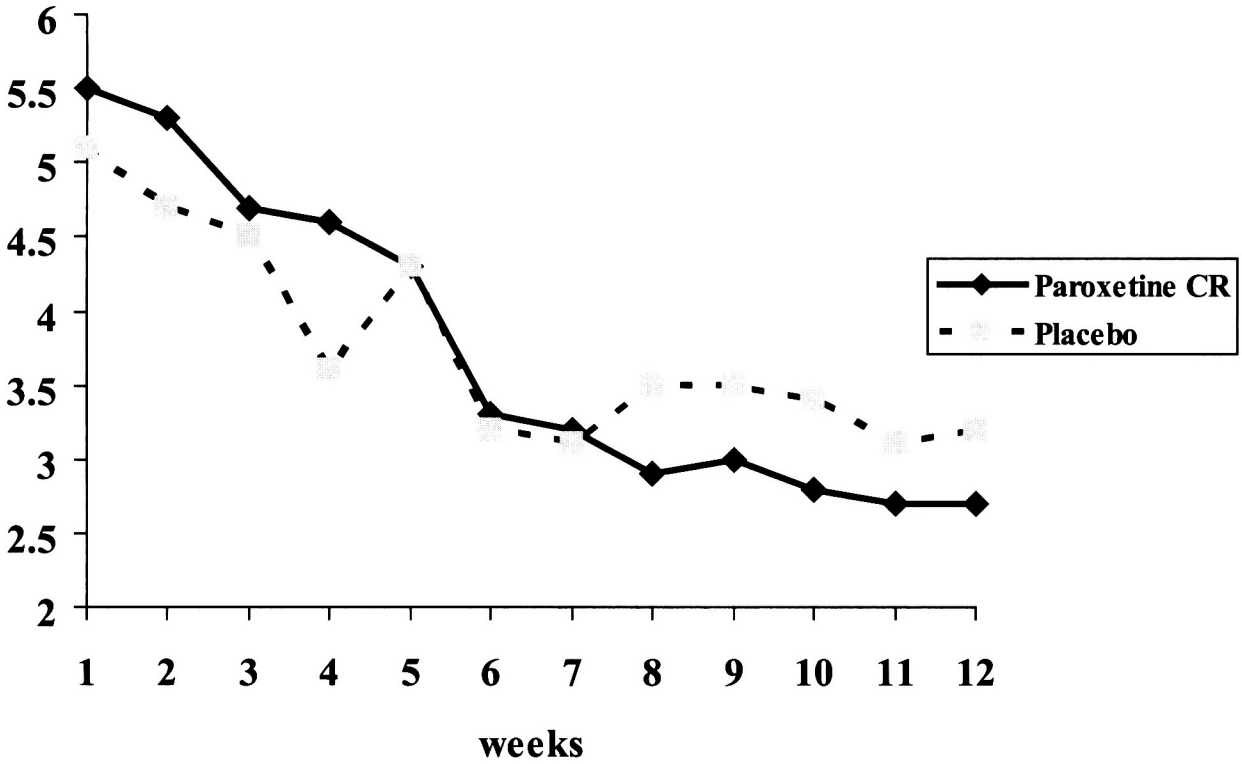
Symptoms that cumulatively support the diagnosis of IBS: 1. Abnormal stool frequency (for research purposes, "abnormal" may be defined as more than 3 bowel movements per day and fewer than 3 bowel movements per week); 2. Abnormal stool form (lumpy/hard or loose/watery stool); 3. Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation); 4. Passage of mucus; 5. Bloating or feeling of abdominal distention

The diagnosis of a functional bowel disorder always presumes the absence of a structural or biochemical explanation for the symptoms.[a] Adapted from Thompson et al.[41] and Drossman et al.[17]

to AEs comparable between the paroxetine-CR (N = 3) and the placebo (N = 2) groups. The treatment-emergent AEs occurring in ≥5% of subjects were not significantly different between the two treatment groups. Drowsiness was the most common AE in both groups (Table 2).

Differences in weight gain were not found between the paroxetine-CR group (from 160.1 lbs. to 162.3 lbs.) and the placebo group (from 170.1 lbs. to 176.7 lbs.; $t = 0.954$, $p = 0.344$ at Week 0; $t = 1.174$, $p = 0.344$ at Week 12). Two subjects in the paroxetine-CR group and one in

**FIGURE 2. Changes in Interactive Voice-Response System (IVRS) Composite Pain Scores During the Study**




Intent-to-treat (ITT) analysis with the last observation carried forward (LOCF).

**TABLE 2. Adverse Events Occurring in ≥5% of Subjects During the Study, N (Percent)**

| | Paroxetine-CR (N = 36) | Placebo (N = 36) |
|---|---|---|
| Drowsiness | 13 (36.1) | 9 (25.0) |
| Dry mouth | 10 (27.7) | 6 (16.6) |
| Female genital disorders[a] (N = 63; paroxetine-CR group = 31; placebo group = 32) | 8 (25.8) | 4 (12.5) |
| Erectile dysfunction[a] (N = 9; paroxetine-CR group = 5; placebo group = 4) | 1 (20.0) | 0 (0.0) |
| Nightmare/vivid dreams | 6 (16.6) | 5 (13.8) |
| Poor sleep | 6 (16.6) | 5 (13.8) |
| Fatigue | 6 (16.6) | 5 (13.8) |
| Increased appetite | 5 (13.8) | 3 (8.3) |
| Constipation | 3 (8.3) | 3 (8.3) |
| Headache | 3 (8.3) | 7 (19.4) |
| Anxiety | 3 (8.3) | 2 (5.5) |
| Weight gain | 3 (8.3) | 1 (2.8) |
| Sweating | 2 (5.5) | 3 (8.3) |
| Nausea | 2 (5.5) | 3 (8.3) |

No comparisons were significantly different between the two treatment groups.
[a]Gender-specific analysis.

the placebo group had ≥7% weight gain. There were no serious AEs in either group during the study.

## DISCUSSION

The present study failed to find a statistically significant difference between paroxetine-CR and placebo groups on the primary efficacy measure (IVRS Composite Pain Scores), although a numerically higher reduction was seen in the paroxetine-CR group than in the placebo group. However, there were noticeable differences between paroxetine-CR and the placebo group on the secondary efficacy measures. There were significantly more subjects showing CGI–I scores of 1 or 2 and ≥1-point reduction in CGI–S scores in the paroxetine-CR group than in the placebo group. Our findings suggest that paroxetine-CR may provide global benefit in patients with IBS even though it did not improve symptoms of abdominal pain.

In open-label studies,[13,30] we have previously demonstrated some beneficial effects and good tolerability of SSRIs in patients with IBS. Of 20 patients with IBS, 13 (65.0%) reported a ≥50% reduction in abdominal pain and 11 (55.0%) experienced a ≥50% reduction in pain frequency on paroxetine-IR. On the CGI–I scores at the end of treatment, 8 out of 17 patients (47.0%) on paroxetine-IR were considered Much or Very Much Improved.[13] Citalopram was also found to be beneficial and well-tolerated in patients with IBS.[30] In that study, 80.0% of patients (12/15) on citalopram reported a ≥50% reduction in the presence of abdominal pain, and 67.0% showed a ≥50% reduction in frequency of the pain symptoms. Approximately one-half of the patients met criteria for remission of abdominal pain (≥70% improvement).

There have been several placebo-controlled studies of SSRIs for treatment of IBS patients. In the first such study,[31] with paroxetine-IR (20 mg–40 mg/day), the drug significantly improved the primary outcome measure, general well-being (63% in the paroxetine-IR group versus 26% in placebo) but not the symptoms of abdominal pain and bloating, which is similar to our findings. Fluoxetine (20 mg/day) was also studied in patients with IBS, demonstrating a nonsignificant 10% therapeutic difference on global symptom relief without improvement in abdominal pain severity. Possible explanations include inadequate power to detect the difference (40 subjects) and possible under-dosing of fluoxetine.[34] Another study with fluoxetine (20 mg/day) showed that fluoxetine was superior to placebo in improving symptoms of pain, bloating, and constipation in 44 pain- and constipation-predominant IBS patients.[35] A 6-week crossover trial of citalopram in IBS patients (3 weeks: 20 mg/day; 6 weeks: 40 mg/day) also showed that citalopram significantly improved abdominal pain, bloating, impact of symptoms on daily life, and overall well-being, as compared with placebo.[33]

Taken together, currently-existing placebo-controlled studies show outcomes different from our study on the primary efficacy measure of pain symptoms in patients with IBS. There are several possible explanations for these differences. First, we did not control for diet, whereas Tabas et al.,[31] for instance, studied patients with IBS who did not respond to a high-fiber diet. Second, we excluded patients with current mood or anxiety disorders (but not with subsyndromal mood or anxiety symptoms or a past history of mood or anxiety disorders), whereas other studies did not. Since psychosocial factors are linked to development of IBS, excluding patients with mood or anxiety disorders may decrease the likelihood of response to an SSRI for IBS symptoms.[6] Third, we used daily IVRS to measure outcomes; this method is less susceptible to recall bias than weekly measures. A lack of power could also be the most likely explanation for the negative findings on our primary outcome measure, although it is possible that the paroxetine-CR is not efficacious for the treatment of abdominal pain symptoms of IBS. Another difference was that the primary outcome measure in the present study was narrower than in previous studies, which adopted overall well-being, using a 5-point Likert scale, and defined improvement as a 0.5-point increase in overall well-being.[31]

In some studies, the primary efficacy measure was comparable to our secondary outcome measures, which did show significant differences favoring paroxetine-CR over the placebo group. We should also look at the dose-titration in the present study. Paroxetine-CR was started at 12.5 mg/day and increased biweekly in 12.5-mg/day increments, the maximum dose being 50 mg per day. The mean dose of paroxetine-CR was 30.0 mg/day (corresponding to paroxetine-IR 22.5 mg/day) in the present study. In the previous two controlled trials,[31,34] which failed to distinguish from placebo on the abdominal pain measure, the doses of paroxetine-IR were also low compared with those used in studies of paroxetine-CR in other chronic pain syndromes, such as fibromyalgia.[36]

Also, in a 6-week crossover trial of citalopram in IBS patients (3 weeks: 20 mg/day; 6 weeks: 40 mg), a substantial further improvement was obtained after 6 weeks, although it is unclear whether this reflects prolongation of the treatment period or doubling of the citalopram dose.[33] Full-dose SSRIs have been proposed as leading to a ther-

apeutic response in patients with IBS.[37] Meanwhile, treatment of IBS patients with SSRIs may need to be individualized in accordance with the predominant IBS subsymptom (e.g., fluoxetine for pain and constipation-predominant IBS patients),[35] a suggestion supported by findings that each SSRI has different effects on visceral hypersensitivity,[34] small-bowel transit time, and colon relaxation.[28] Paroxetine was associated with a reduction of orocaecal transit time in both healthy-control subjects and IBS patients, but not with whole-gut transit time, which may be beneficial to constipation-dominant IBS patients.[31,47] Constipation could also increase transit time, thereby increasing absorption, whereas patients with diarrhea-predominant symptoms may benefit from the anticholinergic effects of paroxetine, particularly at higher doses.

There were no major safety issues with paroxetine-CR in patients with IBS. We should note that there were trends toward increases in selected side effects in the paroxetine-CR group (e.g., female genital disorders), as compared with the placebo group, although there were no statistically significant differences. The dropouts due to AEs were comparable between the two treatment groups (paroxetine-CR: N = 3/30; placebo: N = 2/28), although the overall dropout rate was 19.4%. In contrast to our finding, the dropouts due to AEs were high in a recent large, placebo-controlled study of desipramine in IBS patients (the desipramine group: 57.5%, versus placebo: 27.3%), indicating favorable tolerability of paroxetine-CR over TCAs.[46] There were no significant changes in clinical measures such as heart rate, blood pressure, or weight.

The strengths of the present study were the following: 1) administration of a structured psychiatric interview; 2) use of Rome II criteria to define IBS; 3) exclusion of patients with current psychiatric illnesses that might affect treatment outcome; 4) being the first double-blind, placebo-controlled study of paroxetine-CR in IBS; and 5) use of daily symptom rating by use of IVRS, which can reduce placebo response.

The principal limitation of this study was the small sample size, perhaps leading to inadequate power to detect differences from placebo. Additional limitations of the study include recruitment of subjects through advertisement, which can lead to selection bias. The majority of our patients were female and Caucasian, limiting the generalization of our results.[48] Finally, the dose-titration and maximum dose were somewhat slow and low, respectively.

In conclusion, although paroxetine-CR was not distinguished from placebo on the primary outcome of composite pain scores on IVRS, the inability to detect a difference may be related to inadequate power. Paroxetine-CR offered some benefit over placebo on secondary outcome measures. Therefore, adequately powered studies may clarify the role of paroxetine-CR in IBS.

*This research was presented in part at the Annual Meeting of the American Psychiatric Association, Atlanta, GA, May 21–26, 2005.*

*This study was supported by a collaborative research grant from GlaxoSmithKline.*

*DISCLOSURE: Dr. Masand is a consultant for Bristol-Myers Squibb Company, Cephalon, Inc.., Eli Lilly and Company, Forest Pharmaceutical Laboratories Inc., GlaxoSmithKline, Janssen Pharmaceutica, Jazz Pharmaceuticals, Organon, Inc., Pfizer Inc., U.S. Pharmaceuticals Group., Targacept Inc., and Wyeth Pharmaceuticals. He is on the speaker's bureau of Astra-Zeneca, Bristol-Myers Squibb Company, Forest Pharmaceutical Laboratories, Inc., GlaxoSmithKline, Janssen Pharmaceutica, Pfizer Inc., U.S. Pharmaceuticals Group., and Wyeth Pharmaceuticals. He has received research support from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Cephalon, Inc.., Eli Lilly and Company, Forest Pharmaceutical Laboratories Inc., GlaxoSmithKline, Ortho McNeil Pharmaceutical, Inc., Janssen Pharmaceutica, and Wyeth Pharmaceuticals, and is an employee of i3CME. Dr. Patkar is a consultant for Bristol-Myers Squibb Company, GlaxoSmithKline, and Reckitt Benckiser; he is on the speaker's bureau of Bristol-Myers Squibb Company, GlaxoSmithKline, and Reckitt Benckiser, and has received research support from National Institutes of Health, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Forest Pharmaceuticals, Inc., GlaxoSmithKline, Janssen Pharmaceutica, McNeil Consumer and Specialty Inc., Organon, Inc., Jazz Pharmaceuticals, and Pfizer Inc., U.S. Pharmaceuticals Group. Dr. Pae has received research support from GlaxoSmithKline. Mr. Krulewicz is an employee of GlaxoSmithKline and owns common stock in the company.*

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