History of Depressive and Anxiety Disorders and Paroxetine Response in Patients With Irritable Bowel Syndrome: Post Hoc Analysis From a Placebo-Controlled Study

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Objective: Although irritable bowel syndrome (IBS) is highly comorbid with depressive and anxiety disorders, information on the clinical implications of this comorbidity is limited. We investigated whether a history of depressive and/or anxiety disorders was associated with response to treatment in a double-blind, randomized, placebo-controlled trial of paroxetine controlled release (CR) in IBS.

Method: Seventy-two IBS subjects (diagnosed using Rome II criteria) were recruited from August 2003 to November 2005 and randomly assigned to receive flexibly dosed paroxetine CR (dose, 12.5–50 mg/day) or placebo for 12 weeks. The Mini-International Neuropsychiatric Interview (MINI-Plus version) was used to ascertain current (exclusionary) or past diagnoses of depressive and anxiety disorders. Subjective depression, anxiety, and stress were assessed at entry and throughout the trial using the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Perceived Stress Scale (PSS). Severity of IBS symptoms was determined by the Composite Pain Score (CPS), administered via Interactive Voice Response System, and the Clinical Global Impressions scale (CGI). The primary outcome was treatment response defined as ≥ 25% reduction in CPS from randomization to end of treatment. A post hoc analysis (multivariate logistic regression) was done to evaluate whether a history of depressive and/or anxiety disorder was associated with response to medication.

Results: Baseline demographic and clinical characteristics (CPS, BDI, BAI, PSS, CGI scores) were similar between groups (history of depressive/anxiety disorder vs. no history). In multivariate logistic regression analysis, treatment response was not predicted by history of depressive and/or anxiety disorder (OR = 0.58, CI = 0.29 to 1.68, p = .32) or drug status (paroxetine CR vs. placebo) (OR = 1.26, CI = 0.68 to 3.21, p = .19). Drug status was significantly associated with the secondary outcome variable of treatment response as defined by a CGI improvement score of 1 to 2 (OR = 12.14, CI = 2.9 to 48.4, p < .001). Paroxetine CR was safe and well tolerated during the study.

Conclusions: History of depressive and/or anxiety disorder was not associated with response of IBS symptoms to paroxetine CR. Conclusions are limited due to insufficient statistical power. Further research is needed to clarify the role of selective serotonin reuptake inhibitors in the treatment of IBS and to elucidate the treatment ramifications of comorbid psychiatric disorders.

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Irritable bowel syndrome (IBS) is a functional gastrointestinal disease characterized by chronic abdominal discomfort with associated changes in stool 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 U.S. population, with a slight predominance in women.[3] IBS results in significant morbidity, with patients reporting 3 times as many absences from school and work compared to those without the disorder.[4] The average number of days off work per year is estimated between 8.5 to 21.6 days, with considerable medical costs and impaired quality of life.[4,5]

Bidirectional comorbidities between psychiatric illness and IBS are common. Studies have shown that 50% to 90% of patients in treatment for IBS have current or past psychiatric comorbidity, most commonly mood and anxiety disorders.[2,6,7] It has been suggested that psychiatric comorbidity is specific to those with IBS who seek treatment, but data now indicate that the association of depressive and anxiety disorders is independent of

treatment-seeking status.[6,8,9] Additionally, IBS patients have been shown to have features associated with depression and anxiety, including high rates of psychosocial stress,[10–12] frequent trauma and abuse history,[5,13,14] high prevalence of depressive and anxiety disorders in family history,[15] common heritability,[16] and response to antidepressant medications.[17–19] These shared characteristics between IBS and depression/anxiety as well as potentially shared pathophysiology have led authors to group IBS and other functional physical ailments (including chronic fatigue syndrome, migraine, fibromyalgia, and atypical facial pain) into "affective spectrum disorder."[20] The efficacy of antidepressant medications for IBS has been established in multiple randomized placebo-controlled trials with tricyclic antidepressants.[17–19] More recent reports using selective serotonin reuptake inhibitors (SSRIs) have been mixed, and to date have consisted of case reports, open-label studies, and a few small double-blind, placebo-controlled studies.[21–28]

Overall, the associations between IBS and psychiatric disorders warrant further clarification, and in particular the impact of these associations on treatment expectations may be important. The current post hoc analysis evaluates whether a past history of (but not current) depressive or anxiety disorder was associated with response to treatment in a 12-week randomized controlled trial of paroxetine controlled release (CR) in the treatment of IBS; patients with current depressive or anxiety disorders were excluded from the study due to concern that paroxetine treatment of these disorders might indirectly affect gastroenterological symptoms and confound the assessment of paroxetine effects on IBS. The results of the primary efficacy analysis have been submitted for publication (P.S.M., C.U.P., S.K., et al.). For the purpose of this analysis, we decided to combine subjects with history of depressive and anxiety disorders because there was a substantial overlap between the 2 disorders, both disorders have been shown to respond to paroxetine, and we believed the combined group would increase the power to detect an effect.

METHOD

Design

This was a randomized, double-blind, placebo-controlled trial of paroxetine CR (flexible dose 12.5 to 50 mg/day) for 12 weeks in IBS. The study was approved by the institutional review boards of Duke University, Durham, N.C., and Thomas Jefferson University, Philadelphia, Pa., and performed under an investigator IND (investigational new drug application) assigned by the U.S. Food and Drug Administration.

Subjects

Subjects were recruited through clinical referrals and newspaper advertisement. All subjects provided written informed consent prior to participating in the protocol. Eligible subjects included men and women, 18 to 65 years of age, who had a confirmed diagnosis of IBS using Rome II diagnostic criteria of at least 12 weeks in a preceding 12-month period of abdominal pain or discomfort, associated features (e.g.. relief with defecation), and altered bowel function (abnormal stool frequency and form) in the absence of a structural or organic explanation for the condition.[29,30] Additional criteria for eligibility were (1) had ≥ 1 year of symptoms, (2) were able to maintain their usual diet, (3) had a documented full colonoscopy/flexible sigmoidoscopy in the past to rule out structural disorders, (4) were able to comply with the study procedures, and (5) had a Beck Depression Inventory (BDI) score of ≤ 23 at screening and after placebo lead-in. Eligible subjects were required to discontinue all prescription medications for IBS. Approved methods of contraception were required for all women of childbearing potential who participated in the study.

Exclusion criteria were (1) severe concurrent medical disease such as heart disease, cardiac arrhythmia, and glaucoma; (2) current psychotic, depressive (major depressive disorder or dysthymic disorder), anxiety, or bipolar disorder or substance dependence/abuse, anorexia nervosa, or bulimia based on an interview with the Mini-International Neuropsychiatric Interview (MINI); (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 prior to 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) female patients who were pregnant or lactating.

Concomitant medication exclusions included psychotropics, analgesics, muscle relaxants, steroids, and hypnotics except over-the-counter analgesics (acetaminophen up to 4 g/day, ibuprofen up to 1.2 g/day, and naproxen up to 660 mg/day) as rescue pain medication. Concomitant medications such as antihypertensives that were not prescribed for IBS required a minimum of 4 weeks at a stable dose.

Assessment of Major Depression and Anxiety Disorders

The MINI is a brief structured interview designed conjointly by American and European psychiatrists to diagnose Axis I disorders as well as antisocial personality disorder according to DSM-IV and ICD-10 criteria. For the purposes of this study, we used the sections of the instrument (MINI-Plus version) exploring current or past episodes of mood disorders (major depression, dysthymic disorder), anxiety disorders (generalized anxiety disorder,

panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder [PTSD]), somatoform disorders, substance use disorders, psychotic disorders, eating disorders, and adjustment disorder. The MINI has been shown to be reliable in multicenter clinical trials and in epidemiologic and clinical studies.[31] The MINI-Plus was selected over other screening instruments because of its ease of administration, the relatively brief training needed for its use, its broad coverage, and its reported quick administration time.

When reporting frequencies of depressive or anxiety disorders, it is worth noting that those with current diagnoses of depressive disorders or anxiety disorders were excluded from the study at the time of screening.

Other Assessments

The BDI[32] is a validated, 21-item self-report instrument that assesses depressive symptoms in the previous week. The Beck Anxiety Inventory (BAI)[33] is a self-report 21-item instrument to measure severity of anxiety symptoms. The Perceived Stress Scale (PSS)[34] is a 10-item, self-report scale that measures the degree to which situations in one's life over the past month are appraised as stressful. Items are designed to assess how unpredictable and uncontrollable respondents find their lives.

Primary Efficacy Measure

The primary efficacy measure was proportion of responders as defined by ≥ 25% reduction in Composite Pain Scores (CPS; frequency × duration) recorded on the telephone-based Interactive Voice Response System (IVRS)[35] from baseline 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. 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 established.[35]

Secondary Efficacy Measures

The secondary outcome measures included proportion of subjects per group with a Clinical Global Impressions-Improvement (CGI-I) score of 1 (very much better) or 2 (much better) at end of treatment or a decrease of 1 point or more on the Clinical Global Impressions-Severity of Illness (CGI-S) scores from randomization to end of treatment. The CGI-S and CGI-I[36] have been widely used as physician-rated, global measures of improvement in clinical trials. The CGI-S provides scores ranging from 1 (normal, not ill) to 7 (among the most extremely ill). The CGI-I scores range from 1 (very much better) to 7 (very much worse).

Study Procedures

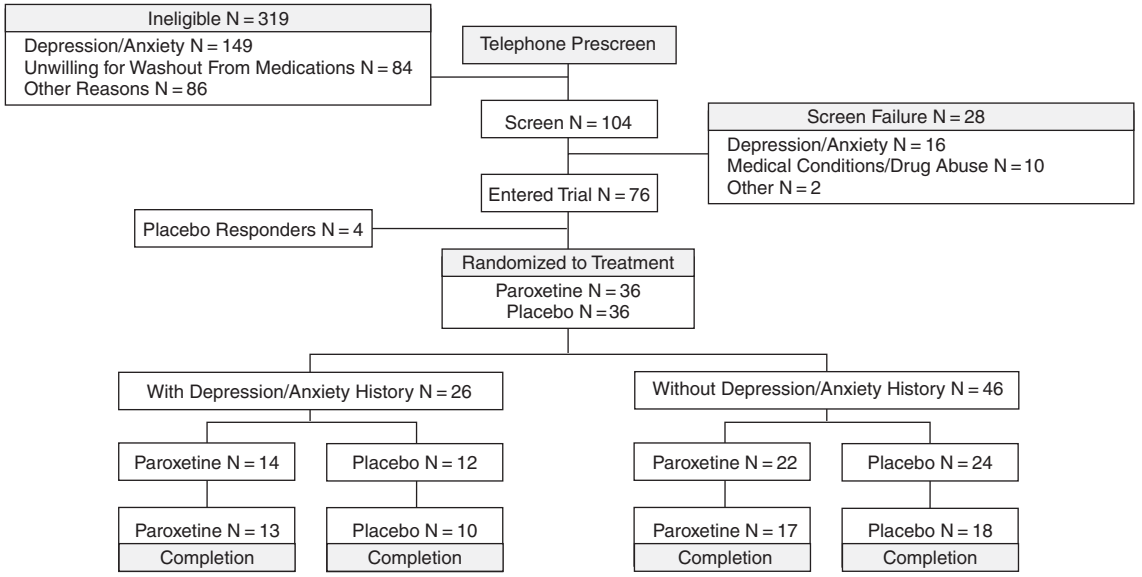
The study was conducted at 2 sites, Duke University Medical Center and Thomas Jefferson University.

Study procedures are described in a forthcoming report (P.S.M., C.U.P., S.K., et al., manuscript submitted). The screening phase (visit 1) included a review of clinical history, establishing any psychiatric comorbidity based on the structured MINI[31]; a physical examination; urine drug and pregnancy screen; and routine laboratory tests to examine complete blood count, liver and renal function, thyroid status, and electrolytes. The screening visit was followed by a 1-week, single-blind, placebo run-in phase (visit 2). Subjects who had a 25% or greater reduction in CPS at the end of the placebo run-in phase were considered as placebo responders and excluded from the study. At visit 3, subjects were randomly assigned to receive paroxetine CR or placebo in a double-blind fashion for the next 12 weeks. Paroxetine CR was started at 12.5 mg/day and increased biweekly (every other week) in 12.5-mg/day increments, the maximum dose being 50 mg/day based on tolerability and response. 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 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.

Data Analysis

Analysis was intent-to-treat (ITT) with last observation carried forward (LOCF). Chi-square analysis was used for all categorical associations, and analysis of variance (ANOVA) or t tests and paired t tests were used to examine differences for all continuous variables. In multivariate logistic regression, we determined if a history of depression and/or anxiety disorders was an independent predictor of response to treatment on primary and secondary endpoints. All statistical significance was 2-tailed and set at $p < .05$. Bonferroni correction was applied for multiple comparisons as appropriate. Fisher exact tests were used to calculate power to detect a difference between treatment response rates between the 2 groups. We found that we had very little power (10%) to determine a difference. Statistical analysis was done using the SPSS 10.0 for Windows program (SPSS Inc.; Chicago, Ill.).

Figure 1. Subject Disposition Throughout the Trial



RESULTS

Figure 1 summarizes subject disposition during the randomized trial.

Comorbid Depressive and Anxiety Disorders

Four hundred twenty-three patients were screened over the phone; 319 were found to be ineligible, and 104 subjects were asked to come in for an on-site screening visit. Twenty-eight subjects were excluded at the on-site screening, 76 subjects met the entry criteria and entered the placebo-run phase, and 72 were randomly assigned to receive paroxetine CR or placebo.

Current depressive and/or anxiety disorders were recorded for 46.7% of the 319 patients excluded via the telephone screening and 50% of the 32 excluded at the on-site screening. Of the 72 randomized subjects, 36.1% had a lifetime history of depressive and/or anxiety disorders; the most common lifetime diagnoses were major depression (N = 6, 8.3%) and PTSD (N = 8, 11.1%). Table 1 shows the distribution of depressive and anxiety disorders in subjects with IBS who were excluded during the screening process and those who enrolled in the study.

For the purpose of analysis, we divided the subjects into 2 groups: those who had a history of depressive and anxiety disorders (N = 26) and those without such a history (N = 46). Comparing the baseline characteristics, we found that a greater proportion of subjects with a history of depressive and anxiety disorders reported a history of sexual and/or physical abuse (N = 16 [61.5%]) compared to the rates reported by subjects without a history of anxiety and depressive disorders (N = 16 [34.7%]; $\chi^2 = 8.68$, df = 2, $p < .05$). There were no significant differences between the 2 groups in pain (CPS), anxiety (BAI), depression (BDI), perceived stress, or global impression of severity of illness (CGI-S) scores at baseline. Table 2 summarizes the baseline comparisons between the 2 groups.

Table 1. Depression and Anxiety Disorders in Irritable Bowel Syndrome, N (%)[a]

Subject Group	Depressive Disorders	Depressive and Anxiety Disorders	Anxiety Disorders
Telephone screen failure (N = 319)	87 (27.3)	104 (32.6)	128 (40.1)
On-site screen failure (N = 16)	5 (31.3)	4 (4.0)	7 (43.8)
Randomized subjects (N = 72)	9 (12.5)[b]	5 (6.9)[c]	12 (16.7)[d]

[a]Lifetime diagnoses reported in sample after excluding current depressive and anxiety disorders.
[b]Drug, N = 4; placebo, N = 5.
[c]Drug, N = 3; placebo, N = 2.
[d]Drug, N = 7; placebo, N = 5.

The average dosage of paroxetine CR was 31.6 ± 6.8 mg (range, 12.5–50 mg) for subjects with a history of depressive and anxiety disorders and 32.8 ± 8.4 mg (range, 12.5–50 mg) for subjects without such a history.

History of Depressive and Anxiety Disorders as Predictor of Response

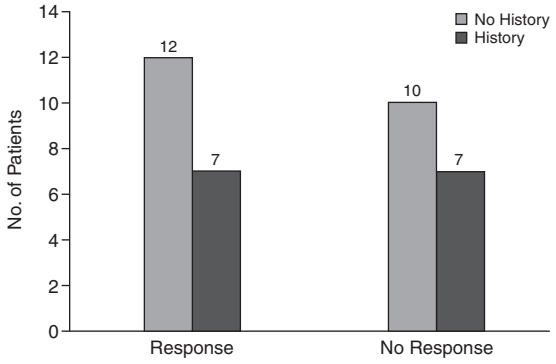
Primary outcome. Multivariate logistic regression showed that treatment response as defined as a ≥ 25% reduction in CPS was not associated with history of

Table 2. Baseline Characteristics of Irritable Bowel Syndrome Subjects With and Without a History of Depressive and/or Anxiety Disorders[a]

Characteristic	History of Depressive and/or Anxiety Disorders (N = 26)	No History of Depression and/or Anxiety Disorders (N = 46)
Demographic variables		
Male, N (%)	3 (11.5)	6 (13.0)
Female, N (%)	23 (88.5)	40 (87.0)
Age, mean (SD), y	48.7 (8.8)	49.1 (10.3)
Race, N (%)		
White	17 (65.4)	37 (80.4)
African American	9 (34.6)	9 (19.6)
Rating scale scores, mean (SD)		
CGI-S	3.9 (0.3)	3.9 (0.4)
Depression (BDI)	6.7 (5.1)	4.9 (4.6)
Anxiety (BAI)	6.8 (5.7)	5.5 (4.9)
Stress (PSS)	26.8 (9.3)	25.3 (10.3)
Pain (CPS)	5.9 (5.2)	5.6 (4.8)

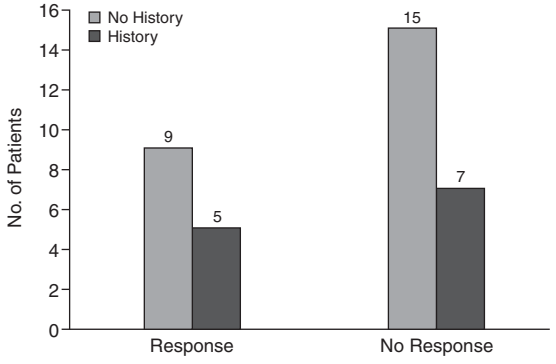
[a]No statistically significant differences between groups.
Abbreviations: BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, CGI-S = Clinical Global Impressions-Severity of Illness, CPS = Composite Pain Score, PSS = Perceived Stress Scale.

Figure 2. Distribution of History of Depressive and/or Anxiety Disorders Among Responders and Nonresponders in the Paroxetine CR Group (N = 36)[a]



[a]Treatment response was defined as ≥ 25% reduction in Composite Pain Score to the end of treatment. Fisher exact test, p = .68.
Abbreviation: CR = controlled release.

Figure 3. Distribution of History of Depressive and/or Anxiety Disorders Among Responders and Nonresponders in the Placebo Group (N = 36)[a]



[a]Treatment response was defined as ≥ 25% reduction in Composite Pain Score to the end of treatment. Fisher exact test, p = .37.

depressive and/or anxiety disorders (OR = 0.58, 95% CI = 0.29 to 1.68, p = .32) or drug status (paroxetine CR) (OR = 1.26, CI = 0.68 to 3.21, p = .19).

There were no significant differences in the number of responders between subjects with (N = 11/26, 42.3%) or without (N = 22/46, 47.8%) history of depression and anxiety disorders (Fisher exact test, p = .48). We also examined the proportion of responders in the drug and the placebo groups separately. There were no significant differences in subjects with or without history of depressive and/or anxiety disorders who responded to paroxetine CR (depression/anxiety history N = 7/14, 50.0% no history N = 12/22, 54.5%; Fisher exact test, p = .68) or to placebo (depression/anxiety history N = 5/12, 41.6%; no history N = 9/24, 37.5%; Fisher exact test, p = .37). Figures 2 and 3 summarize the distribution of history of depressive and anxiety disorders among responders and nonresponders in the paroxetine CR and placebo groups, respectively.

Average dosages of paroxetine CR between the responder/nonresponder groups were not significantly different in subjects with or without history of depression and anxiety (32.3 mg and 31.7 mg among responders and nonresponders in those with a history of depression and anxiety, respectively; 33.1 mg and 31.3 mg in the group without history of depression and anxiety, respectively).

Secondary outcomes. On the secondary outcome of a CGI-I score of 1 or 2, logistic regression showed that history of depressive and anxiety disorders did not predict treatment response (OR = 0.51, CI = 0.24 to 1.46, p = .36), while the drug status (paroxetine CR) was significantly associated with treatment response (OR = 12.14, CI = 2.9 to 48.4, p < .001). The responder rate did not differ between subjects with (N = 13/26, 50.0%) or without history of depression/anxiety (N = 18/46, 39.1%; overall Fisher exact test, p = .18) when response was defined as a CGI-I score of 1 or 2 at the end of treatment. Similarly, there were no significant differences in the rates of depressive and anxiety disorders among responders and nonresponders defined on the basis of changes in CGI-S scores (response defined as a ≥ 1-point reduction in scores during treatment; p = .28).

After 12 weeks of treatment, although there were significant reductions over time in several of the outcome measures within each group, there were no striking differences in outcome between subjects with and without history of depression and/or anxiety. Table 3 summarizes changes in primary and secondary outcomes between subjects with and without history of depression and/or anxiety.

Table 3. Changes in Clinical Variables From Baseline to the End of Treatment (week 12) in Irritable Bowel Syndrome Subjects With and Without a History of Depressive and/or Anxiety Disorders, Mean (SD)[a]

Variable	History of Depressive and/or Anxiety Disorders (N = 26)	No History of Depression and/or Anxiety Disorders (N = 46)
Pain (CPS)	–2.8 (2.3)[b]	–2.4 (2.6)[b]
Depression (BDI)	–2.7 (1.4)[b]	–1.8 (1.1)
Anxiety (BAI)	–3.8 (1.7)[c]	–2.3 (1.6)[b]
CGI-S[d]	–1.2 (0.4)[c]	–1.0 (0.4)[c]
CGI-I[d]	–2.7 (0.5)[c]	–2.6 (0.4)[c]

[a]Paired t tests were performed to determine mean changes from randomization to end of treatment.
[b]$p < .05$.
[c]$p < .01$.
[d]Wilcoxon ranked test performed.
Abbreviations: BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CPS = Composite Pain Score.

Due to the small number of subjects, data were not analyzed separately for subjects with history of depressive disorder (N = 9) and anxiety disorders (N = 12) to determine if there was a differential effect of type of depressive or anxiety disorder on treatment response.

The dropout rate in the study was 19.4% (N = 14). There was no difference in rate of dropouts between those with a history of depression/anxiety (N = 3/26, 11.5%) and those without such a history (N = 11/46, 23.9%) (p = .44).

Adverse Events

There were no serious adverse events during the study. We should note that there were trends toward increases in selected side effects with the paroxetine CR group (e.g., female genital disorders) compared to the placebo group, although there were no statistically significant differences. The number of dropouts due to adverse events was comparable between the 2 treatment groups (paroxetine CR N = 3/30; placebo N = 2/28). There were no significant changes in laboratory measures such as heart rate, blood pressure, or weight.

DISCUSSION

This post hoc analysis was conducted after the initial randomized controlled trial showed that paroxetine CR did not separate from placebo on the primary efficacy measure of reduction in Composite Pain Scores but did separate from placebo on the secondary efficacy measure of CGI-I score (P.S.M., C.U.P., S.K., et al., manuscript submitted). The present study did not find a significant effect of a history of depression and/or anxiety to predict treatment response to paroxetine CR in IBS on the primary efficacy measure of proportion of responders (response defined by ≥ 25% reduction in CPS score) or on any of the secondary measures. This lack of significant effect persisted when measures were compared within treatment arms, such that history of depressive and/or anxiety disorder failed to predict treatment response to paroxetine CR or to placebo; the sample size within arms was relatively small as noted.

There are multiple potential explanations for the findings, and the lack of overall effect of paroxetine CR on the primary efficacy measure makes the post hoc analysis of the effect of depression and/or anxiety history more challenging. First, response of IBS to paroxetine CR may be independent of psychiatric history, and IBS patients with remitted depressive or anxiety disorders may be phenomenologically no different from IBS patients without such a history. Although it has been observed that IBS patients with comorbid current depression have more severe symptoms[37,38] and may be more likely to seek treatment for IBS,[11] data suggest IBS patients with depression in remission have no worse IBS symptoms than IBS patients without psychiatric history.[37] On the other hand, a recent retrospective chart review by Sayuk and colleagues[39] suggests that a history of depression and/or anxiety may actually predict poor treatment response, side effects, and premature discontinuation of antidepressants in "functional gastrointestinal disorders." The issue of how depression and/or anxiety history affects treatment response to antidepressants in many disorders remains mysterious. Studies of antidepressant medications in fibromyalgia, another "affective spectrum disorder,"[16] have failed to associate treatment response with a history of depression (references 40 and 41 and C.U.P., C.H., P.S.M., et al., manuscript submitted). Data on paroxetine treatment for PTSD show no association of treatment response with history of depression,[42] whereas it has been shown that history of depression predicts treatment refractoriness to medications (which included antidepressants and benzodiazepines) in panic disorder.[43,44]

Second, it is possible that current (as opposed to past) depressive or anxiety disorders are associated with better or worse treatment response of IBS to paroxetine CR; we excluded patients who met criteria for current depressive and/or anxiety disorders on the MINI-Plus in order to avoid confounding the primary efficacy measure. However, it has been suggested that patients with mild to moderate anxiety should be included in clinical IBS studies to more accurately reflect the target patient polulation.[8] Third, IBS appears to be a complex and heterogenous disease with contributions from biological and psychological mechanisms. In a study of the link between depression and IBS, current depression, "catastrophizing," and control variables collectively accounted for only 21% of the variance in pain severity.[38] It may be that a specific variable such as history of depression and/or anxiety accounts for a too small proportion of the

variance in treatment outcome to be significant in a study of this type.

In this study, paroxetine CR was well tolerated and did not appear to affect patient retention. In contrast, the dropouts due to adverse events were high in a recent large placebo-controlled study of desipramine in IBS patients (desipramine group 57.5% vs. placebo 27.3%),[45] indicating favorable tolerability of paroxetine CR over a tricyclic antidepressant.

The strengths of the present study were (1) administration of structured psychiatric interview; (2) use of Rome II criteria to define IBS; (3) exclusion of patients with current psychiatric illnesses, which yielded a "cleaner" subject sample; and (4) daily symptom rating using IVRS, which can reduce the placebo response rate.

The principal limitation of this study was the small sample size leading to inadequate power (10%) to detect differences between subjects with a history of depressive and/or anxiety disorders and those without such a history. Additional limitations of the study include recruitment of subjects through advertisement, which can lead to selection bias. As noted, it has been controversial whether treatment-seeking IBS patients differ in severity or comorbidity from those in the community who have not come to medical attention; it is not known to what extent subjects recruited through advertising mimic treatment-seekers versus population-based samples. Similar to the epidemiology of IBS in the population,[46] our study subjects tended to be white women. The bias in our sample is similar to that in other studies. Although we attempted to minimize the effect of current depressive and anxiety symptoms by excluding MINI-positive volunteers and volunteers with high BDI scores, we cannot rule out that subsyndromal symptoms may have affected results. Of note, subjects with history of depressive and/or anxiety disorders had mildly higher baseline scores on the BDI and BAI, but this difference in means was not significant. Finally, the paroxetine CR dose titration and maximum dose were somewhat slow and low, respectively. This may have blunted efficacy in our study and reduced our ability to detect differences in treatment response between subjects with a history of depressive and/or anxiety disorders and subjects without such a history.

In conclusion, history of depressive and/or anxiety disorder did not predict treatment response of IBS symptoms to paroxetine CR based on the primary outcome variable of proportion of treatment responders (based on Composite Pain Scores obtained via IVRS). Additionally, history of depressive and/or anxiety disorder did not show predictive value on the secondary measure of proportion of treatment responders as determined by CGI scores (despite a significant effect of paroxetine CR on CGI scores in the primary efficacy analysis). Insufficient statistical power was a chief limitation of this study. Adequately powered studies may clarify the role of paroxetine CR in IBS and the influence of psychiatric history variables in treatment response. Additional research is warranted to elucidate the utility of SSRIs in IBS and to better characterize the interplay between depressive and anxiety disorders and IBS.

Drug names: desipramine (Norpramin and others), ibuprofen (Motrin, Ibu-Tab, and others), naproxen (Naprosyn, Naprelan, and others), paroxetine (Paxil, Pexeva, and others).

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