CLINICAL–ALIMENTARY TRACT

Cognitive-Behavioral Therapy Versus Education and Desipramine Versus Placebo for Moderate to Severe Functional Bowel Disorders

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See editorial on page 249.

Background & Aims: Studies of antidepressants and psychological treatments in functional bowel disorders (FBD) are methodologically limited. The aim of this study was to assess the clinical efficacy and safety of cognitive-behavioral therapy (CBT) against education (EDU) and desipramine (DES) against placebo (PLA) in female patients with moderate to severe FBD (irritable bowel syndrome, functional abdominal pain, painful constipation, and unspecified FBD). We also evaluated the amenability of clinically meaningful subgroups to these treatments. *Methods:* This randomized, comparator-controlled, multicenter trial enrolled 431 adults from the University of North Carolina and the University of Toronto with moderate to severe symptoms of FBD. Participants received psychological (CBT vs. EDU) or antidepressant (DES vs. PLA) treatment for 12 weeks. Clinical, physiologic, and psychosocial assessments were performed before and at the end of treatment. *Results:* The intention-to-treat analysis showed CBT as significantly more effective than EDU ($P = 0.0001$; responder rate, 70% CBT vs. 37% EDU; number needed to treat [NNT], 3.1). DES did not show significant benefit over PLA in the intention-to-treat analysis ($P = 0.16$; responder rate, 60% DES vs. 47% PLA; NNT, 8.1) but did show a statistically significant benefit in the per-protocol analysis ($P = 0.01$; responder rate, 73% DES vs. 49% PLA; NNT, 5.2), especially when participants with nondetectable blood levels of DES were excluded ($P = 0.002$). Improvement was best gauged by satisfaction with treatment. Subgroup analyses showed that DES was beneficial over PLA for moderate more than severe symptoms, abuse history, no depression, and diarrhea-predominant symptoms; CBT was beneficial over EDU for all subgroups except for depression. *Conclusions:* For female patients with moderate to severe FBD, CBT is effective and DES may be effective when taken adequately. Certain clinical subgroups are more or less amenable to these treatments.

The functional bowel disorders (FBD) characterized by abdominal pain with altered bowel habit are prevalent in society and are associated with impaired health-related quality of life and increased health care costs.[1,2] These are disorders of brain-gut function with altered gastrointestinal motility, visceral hypersensitivity, and central dysregulation involving neuroendocrine, autonomic, attentional, and pain-regulatory pathways.[3,4] Available treatments for these disorders depend on the nature of the symptoms and their severity.[3] Patients with mild to moderate symptoms may respond to dietary modifications, lifestyle changes, or medications directed at gut function (e.g., loperamide for diarrhea, fiber or osmotic laxatives for constipation, anticholinergic drugs for pain). However, patients with moderate to severe

Abbreviations used in this paper: BDI, Beck Depression Inventory; CBT, cognitive-behavioral therapy; CI, confidence interval; DES, desipramine; EDU, education; FBD, functional bowel disorders; FBDSI, Functional Bowel Disorder Severity Index; IBS, irritable bowel syndrome; IBS-QOL, irritable bowel syndrome quality of life; ITT, intention to treat; NNT, number needed to treat; PLA, placebo.

0016-5085/03/$30.00
doi:10.1016/S0016-5085(03)00669-3

symptoms are frequently refractory to such treatments and experience greater psychosocial disabilities and comorbidities that also require proper attention and treatment to achieve clinical benefit.[5]

Although prescribing antidepressants and psychological treatments for patients with moderate to severe FBD is intuitively evident, has been extensively reviewed,[6–8] and is commonly practiced,[1,3,9] to date no conclusive data from well-designed studies have emerged. In part, study design limitations as well as variable outcome assessments have led to controversy on the value and utility of these treatments.

This study is the largest randomized trial to assess the efficacy of desipramine (DES), a tricyclic antidepressant, and cognitive-behavioral therapy (CBT) against their placebo (PLA) conditions for female patients with moderate to severe FBD. We hypothesized that either active treatment, CBT, or DES would each be better than their control conditions (education [EDU] and PLA, respectively) and would not be significantly different from each other. In addition, we evaluated the relative benefits of these treatments on clinically meaningful subgroups: those with moderate and severe FBD, those with and without a history of depression and sexual or physical abuse, and those with predominant diarrhea and constipation. We hypothesized that subjects with severe FBD, a history of abuse, and no depression would respond less favorably to active treatment than their complementary groups (i.e., moderate FBD, no abuse, and depression).

Patients and Methods

Participants

Between July 1996 and October 2001, female study participants were recruited by self-referral from community or hospital-based advertising or by medical or gastroenterology physician referral in community or university-based practices at 2 medical centers in Chapel Hill, a rural/suburban area in North Carolina (UNC), or in Toronto, an urban city in Ontario, Canada. The hospital ethics committee at each participating center approved the protocol, and each study participant gave informed written consent. Literate women (who were screened to achieve at least a seventh-grade reading level) aged 18–70 years with moderate to severe abdominal pain with or without altered bowel habit (FBD) for at least 2 days per week for 6 months or more were eligible to participate. Eligible participants were excluded if they had heart disease, glaucoma, pregnancy, urinary retention, bipolar disorder, schizophrenia, or substance abuse/dependency; any gastrointestinal disorder that would explain the gastrointestinal symptoms; another psychiatric disorder that would preclude participation in the study; an unwillingness to discontinue anticholinergic medication, calcium channel blockers, or antidepressants (for 3 months); had previously taken DES; or did not use an acceptable method of birth control. A trained research coordinator determined participant eligibility under the supervision of the physician investigators (D.A.D. and N.E.D.), who also addressed difficult decisions relating to eligibility through medical record review or interview with the patient or her physician.

Clinical, Psychosocial, and Physiologic Assessments

The research coordinator at each site who was not involved in the treatment administered a battery of clinical and psychosocial questionnaires in person before treatment to assess prognostic variables. The research coordinator also assessed clinical and psychosocial variables in person at the end of treatment and by mail at quarterly intervals for 1 year after treatment to assess the predictors of the treatment effects. Participants were paid $50 to complete the self-report questionnaires, which included demographic information, sexual and physical abuse history,[10] and several other psychosocial and health care utilization measures previously used in our research.[5,11,12] Participants also filled out a diary card daily for 14 days before the study visit and at the end of the 12-week treatment period to assess daily abdominal pain on the McGill Pain Questionnaire[13] and, on a 100-mm visual analogue scale, stool consistency using the Bristol Stool Form Scale[14] and concurrent medication use. Severity of the disorder using the validated Functional Bowel Disorder Severity Index (FBDSI)[15] was determined to exclude patients with mild severity (FBDSI, <37) and to classify participants with moderate (FBDSI, 37–110) or severe (FBDSI, >110) FBD symptoms for analysis. Patients filled out questionnaires containing the Rome I diagnostic criteria[16] and were categorized as having irritable bowel syndrome (IBS), painful functional constipation, chronic functional abdominal pain, and unspecified FBD. In addition, the referring physician separately indicated the diagnosis; rated the severity of the condition as mild, moderate, or severe; and indicated any other medical conditions or concurrent medications. Finally, 317 (73.5%) of the 431 study participants received $200 to undergo gastrointestinal physiology testing by a research technician before and at the end of the 12 weeks of treatment. A barostat balloon was inserted into the rectum, and a series of distentions was performed to estimate the threshold for the urge to defecate and for painful distention using a tracking technique.[17] Physiologic testing was undertaken to assess the mediating effects of sensation threshold, along with treatment and other psychosocial variables, on outcome. The results of the psychosocial and physiologic tests are reported elsewhere.[18]

Interventions

CBT versus EDU. One half of the participants received one-on-one hourly sessions from the same trained psychologist at each site with an intervention of either (1) 12 weekly hour-long sessions of CBT originally developed by Beck et al.[19] and modified by Toner et al.[20] that focused on modifying the influence of attention, personal appraisal, sex-

related cognitive schemas, and illness attribution as related to the gastrointestinal symptoms as a means to develop more effective coping strategies or (2) 12 weekly modified-attentional control sessions (EDU) with the same therapist providing CBT, where each week the participants reviewed their symptom diaries, read educational materials mainly taken from a book on FBD,[21] and then discussed the information with the therapist. Although the 12 sessions were scheduled to be consecutive (i.e., over 84 days) for both conditions, the treatment period was slightly longer for CBT (median, 108 days) than for EDU (median, 99 days) because of scheduling difficulties.

To assess the process of the interventions, validated measures of expectation of benefit (credibility scale)[22] and the therapist-participant relationship[23] were given to patients after 1 week to ensure that treatment expectations and the therapeutic relationship were equivalent across the 4 treatment arms and between sites. In addition, we evaluated expectation-of-treatment benefit for each arm after treatment was completed. The items assessed in the credibility scale were as follows: "How logical does this type of therapy seem to you for helping functional bowel symptoms?" and "How confident are you that this treatment will be successful in reducing your bowel symptoms?" Finally, the Cognitive Scale for FBD[24] was given before and after psychological treatment to assess improvement in maladaptive cognitions.

DES versus PLA. The other half of the participants received a medication intervention from a registered nurse or physician's assistant with 12 weekly visits to review the patient's clinical status. Participants received either (3) DES, a tricyclic antidepressant administered as 1 pill (50 mg) per day for 1 week, 2 pills (100 mg) per day for 1 week, and then 3 pills (150 mg) per day from week 3 to week 12, or (4) PLA administered in the same fashion. Adverse events were monitored; when clinically appropriate, the dosage level was held or reduced and reevaluated on subsequent weeks with the goal of keeping participants as close to 3 pills per day as possible. At 6 weeks of treatment, a blood DES level (EmitR Desipramine Immunoassay; Syva Co., Palo Alto, CA) was obtained to determine whether toxic levels of medication were present and, if so, the code was broken and the subject was informed to decrease or stop the medication. The treatment period for DES and PLA was the same for both groups (median, 85 days).

Quality control of study conduct. Quality control measures and study protocol monitoring were initiated before the study began and continued throughout the study period. This involved the following: (1) the use of standardized CBT, EDU, and DES/PLA manuals developed for this study; (2) 4-day training sessions for all psychologists and drug study coordinators; (3) monthly within-site and also between-site conference calls of study personnel to review study progress and address problematic issues; (4) monthly supervisory telephone calls between investigators and treatment personnel, with intervention when any clinically relevant psychological (B.B.T. and D.A.D.) or medical issues (D.A.D. and N.E.D.) arose during the course of the study; and (5) audiotaping of all sessions and the selection of 3 tapes per study subject to assess adherence to the treatment protocol. This was evaluated by 2 independent raters and was supervised by one of the investigators (B.B.T.).

Objectives and Outcomes

The primary objective was to assess the benefit of CBT and DES against their control conditions for moderate to severe FBD using a clinically relevant outcome measure. Our primary hypothesis was that active treatment, CBT, and DES would each be better than their respective PLA conditions and would not be significantly different from each other. The secondary hypotheses in the subgroup analyses were as follows: participants with (1) severe FBD and (2) abuse history would respond less favorably to these treatments than study participants with moderate FBD or no abuse history, (3) participants with moderate to severe depressive symptoms (Beck Depression Inventory [BDI], >16) would respond better than those without these symptoms, and (4) participants with diarrhea-predominant symptoms would benefit from DES more than those with constipation-predominant symptoms.

The primary outcome measure was a composite of the following variables assessed at the end of treatment: (1) satisfaction with treatment (treatment efficacy questionnaire), which consisted of 8 items (e.g., "I am satisfied with the results of my treatment," "My bowel symptoms have improved as a result of treatment," "I am engaging in activities that I would not have done prior to treatment") scored from 1 (strongly disagree) to 5 (strongly agree), and all items were summed to give a summary score[25]; (2) global well-being ("How would you rate your general well-being") scored on a Likert scale from 1 (poor) to 5 (excellent)[12]; (3) 2-week averaged diary card scores of the pain rating index (the average of the intensity score of all pain items endorsed for up to 20 pain descriptors) of the McGill Pain Questionnaire[13]; and (4) health-related quality of life using a 34-item condition-specific measure (IBS-QOL) in which each item is rated on a 5-point Likert scale and then standardized to a 0–100 score, with 100 being the best quality of life.[26,27] These measures were consistent with Rome committee recommendations[28] that subjective global end points (e.g., global well-being, satisfaction with treatment) as well as pain scores and quality-of-life scales be used. Following this, the 4 outcomes comprising the composite measure (see previous text) were analyzed separately as secondary variables. Finally, to achieve clinical relevance, a responder analysis was performed to see if there was a difference in the number of responders by treatment. A responder was defined as a subject who scored ≥ 28 using 8 questions on the satisfaction-with-treatment questionnaire (each question scored as follows: 1, strongly disagree; 2, disagree; 3, neither agree nor disagree; 4, agree; 5, strongly agree) for the 8 items on the satisfaction-with-treatment questionnaire (i.e., a score of 28 is a mean/question score of >3.5). Based on the responder analysis, an estimate of the number needed to treat (NNT) to achieve the desired outcome was calculated.[29]

Determination of Sample Size

Sample sizes were based primarily on treatment comparisons for all study participants, taking into account treatment comparisons within subgroups of moderate and severe FBD. The multiplicity in comparisons among interventions was addressed by the use of a hierarchically closed sequence of tests, first testing for differences between the combined patients with moderate and severe FBD and, if significant, then testing for differences as separate subgroups. Moreover, in the first test, an overall 0.05 significance level was maintained across the 2 pairwise comparisons between experimental interventions and placebo by the Bonferroni–Holm method.[30] If the first test reached significance at 0.05, the results of subsequent tests between individual treatments and their control conditions would be interpreted as confirmatory at the 0.05 level; however, if significance at 0.05 was not reached, subsequent analyses would be considered exploratory. The multiplicity in outcome measures was addressed using a single composite ranking criterion[31,32] to which a single nonparametric test (analogous to the Wilcoxon rank sum statistic) is applicable. We produced the composite ranking by ranking the patients in a comparison (regardless of intervention) for each outcome measure (McGill Pain Questionnaire, global well-being, satisfaction, IBS-QOL) and then averaging the ranks for each patient. With the sample sizes in our study, there is 0.90 power to detect statistical significance with 2-sided tests at $\alpha \leq 0.025$ for at least 1 of the 2 interventions relative to placebo for standard effect sizes (computed as expected difference between 2 groups divided by standard deviation for a continuous outcome measure) of at least 0.50.[33]

Randomization and Masking

Randomization was performed by computer into one of the 4 treatment arms using separate randomization schedules for each severity stratum (moderate or severe) as determined by the FBDSI.[15] The proposed ratio for moderate and severe FBD was 2:1. For each site by severity stratum, participants were randomized in permuted variable-size blocks of 6 and 12 in random order at a ratio of 2:2:1:1 for CBT, DES, EDU, and PLA. Masking occurred so that only persons not involved in clinical assessment or treatment were aware of the randomization allocation or the DES blood levels. The randomization was known to persons in the Biometry core doing the randomization, the pharmacists dispensing the drug to the drug study coordinator, and the members of the Data Safety and Monitoring Board who periodically monitored the conduct of the study. However, the psychologists and their participants allocated to CBT or EDU were aware of the intervention.

Statistical Methods

To calculate the primary outcome score, each of the component scales in the composite were ranked by site using standardized mid-ranks or modified ridit scores, which are defined as Rank/(No. of Observations + 1) and represent the expected values of the order statistics for the uniform distribution on (0,1).

The average of the 4 rankings was the linear-t composite score. If one or more of the component scales were missing and the subject was not a dropout, the rankings of the remaining scales were averaged. A rank analysis of covariance was then used to compare the composite linear-t score for the 2 active vs. the 2 placebo treatments while adjusting for baseline scores of 3 of the components when possible; the satisfaction scale was obtained only at the end of treatment. The individual component scales were then compared as a secondary analysis. For the scales that followed a continuous distribution (McGill Pain, IBS-QOL, and satisfaction), comparisons were made using a parametric analysis of covariance linear model, when possible adjusting for baseline. Because the general well-being schedule was categorical in nature, a logistic regression was used, adjusting for the baseline score. This score was averaged over 14 days and dichotomized according to a clinically relevant definition of ≥ 3 (good/very good/excellent) and < 3 (poor/fair).

The primary analysis was performed as intention to treat (ITT). Of the 94 subjects who dropped out of the study, end-of-treatment data were available for 43. Therefore, to analyze the remaining 51 dropouts without end-of-treatment data, we used a hierarchical ranking system related to whether participants left the study due to lack of treatment effect, uncertainty about treatment effect, or unrelated to treatment effect (emergency or severe adverse effects) as follows. (1) Participants who had emergencies or adverse effects or were unavoidably relocated and who received adequate treatment (defined as at least 4 drug treatment visits or 8 psychological treatment visits) were presumed to have still possibly benefited from treatment and were given a median composite score for the total sample of 0.5. (2) Participants who dropped out stating a lack of benefit who received adequate treatment were given a "worst case" score of 0. (3) Participants who did not have adequate treatment or did not fit into the other 2 categories (e.g., schedule problems, distance, change in jobs) were scored in the lower quartile at 0.25. When multiple reasons were given, each case was systematically reviewed to determine the most appropriate ranking toward a conservative estimate.[34] The initial ratings were determined by consensus by 4 of the investigators blinded to treatment allocation (D.A.D., C.B.M., C.J.B., and Y.H.), and additional ratings were independently performed separately for reliability by 2 other investigators (S.I.B. and W.E.W.). There were 2 disagreements for 94 dropouts in the 3-observer comparison, yielding a κ statistic for agreement of 0.95.

A per-protocol analysis involving all participants who completed at least 8 visits of the treatment arms was also performed using the same primary outcome measure. A responder, determined by a mean score of ≥ 3.5 on the satisfaction scale, was compared using χ^2 analysis. Finally, exploratory subanalyses were performed to assess differential responses to treatment with the following pretreatment variables: (1) moderate (FBDSI, < 110) and severe (FBDSI, ≥ 110) symptoms, (2) abuse history and no abuse history, (3) depressive symptoms (BDI, ≥ 16) and no depressive symptoms (BDI, < 16), and (4) predominant diarrhea, constipation, and mixed

stool pattern (Bristol Stool Form Scale scores over 2 weeks averaging between 1 and 2 for diarrhea and 6 and 7 for constipation). Analyses were performed as 2-sided tests (SAS version 8.0; SAS, Cary, NC).

Data Safety and Monitoring and Role of Funding Source

Based on National Institutes of Health guidelines, a Data Safety and Monitoring Board was set up consisting of 5 external faculty members in gastroenterology, psychiatry, psychology, and biostatistics. In addition, representatives from the clinical trials section of the National Institute of Diabetes and Digestive and Kidney Diseases attended the meetings. The Data Safety and Monitoring Board met annually with the investigators to review the unblinded data in open session and the ongoing results of the study in closed session without the investigators. They made recommendations to the investigators regarding the monitoring of side effects and recruitment and, on occasion, specific data reports were requested from the biostatistician with the investigators remaining blinded. When the study was completed, the data were unblinded and the investigators performed the analyses based on a priori protocols. The funding source (National Institute of Diabetes and Digestive and Kidney Diseases) had no direct role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

Results

Recruitment

Eligible participants were recruited between July 1996 and October 2001. Study participants were screened by telephone or during a visit to the hospital and received their pretreatment and posttreatment assessments at the hospital site at UNC or Toronto.

Participant Flow

Figure 1 indicates the flow of study participants (combined for UNC and Toronto sites) through enrollment, study allocation, and analysis. Of the 1029 participants evaluated, 467 were excluded because of ineligibility. Of the 562 eligible participants, 114 refused to participate and 17 did not enter the study for other reasons. Thus, 431 participants (76.7% of the 562 eligible) were enrolled and randomized either into the psycho-educational treatment group (n = 215) or medication treatment group (n = 216). With regard to the treatment arms, 7% (n = 29) of those allocated for each of the 4 treatment arms did not receive the intervention because they did not show up for the first visit. Thus, 402 of the 431 participants allocated to treatment (93.3% of randomized) actually entered into treatment and were included in the ITT analysis. Of these 402 participants, 308 completed all 12 weeks of treatment and another 13 completed 8–11 sessions, comprising 321 participants (74.5% of the 431 randomized) in the per-protocol analysis. Compared with treatment completers, the 94 dropouts were similar except for (1) fewer white participants (79.8% vs. 86.0%; $P < 0.004$), (2) abuse history (60.6% vs. 45.5%; $P < 0.04$), and (3) greater pain at baseline on the visual analogue scale (41.9 vs. 37.2 mm; $P < 0.05$).

With regard to possible protocol deviations, one of 135 participants on antidepressant medication had a potentially toxic blood level of >800 ng/mL. The medication was discontinued, and a DES level obtained 1 week later was in the therapeutic range. In addition, 12 patients who were prescribed antidepressants (8.9%) had nondetectable blood levels, suggesting either that these patients were rapid metabolizers of the drug or were not adherent to their treatment protocol. There were no deviations from the CBT/EDU protocols.

Baseline Demographic and Clinical Data

Table 1 indicates the demographic and clinical features of the total study population and of the 4 treatment allocation groups. The demographic profile of the study participants was white women in their late 30s with close to 15 years of formal education; one half were married or cohabitating. The clinical profile shows that more than 80% had IBS and two thirds had moderate disease severity with moderate abdominal pain (38.5 mm on the visual analogue scale) and averaged 2 bowel movements per day. Almost one half had some history of physical or sexual abuse. Analysis of the baseline variables by site (not shown in Table 1) indicated that UNC had more black participants ($P = 0.0001$). There were no significant between-site differences in any of the baseline clinical variables. Additionally, because we randomized within site, the primary efficacy comparisons are not affected in subsequent statistical analyses. Therefore, all data were combined in later analyses. There were no baseline differences across the treatment conditions for any of the listed demographic or clinical variables.

Numbers Analyzed

The treatment assignments of the 431 randomized participants are shown in Figure 1, yielding 402 participants for the ITT analysis. The primary reasons for dropouts in the psychological treatment arms related to difficulties getting to treatment sessions (e.g., work, child care, too far), whereas the primary reason for the medication group related to adverse events or not being satisfied or comfortable with the treatment. Thus, 321 of 402 (79.9%) in the ITT group were available for the per-protocol analysis (Figure 1). Subsequent results reported in the tables include only participants with nonmissing values.

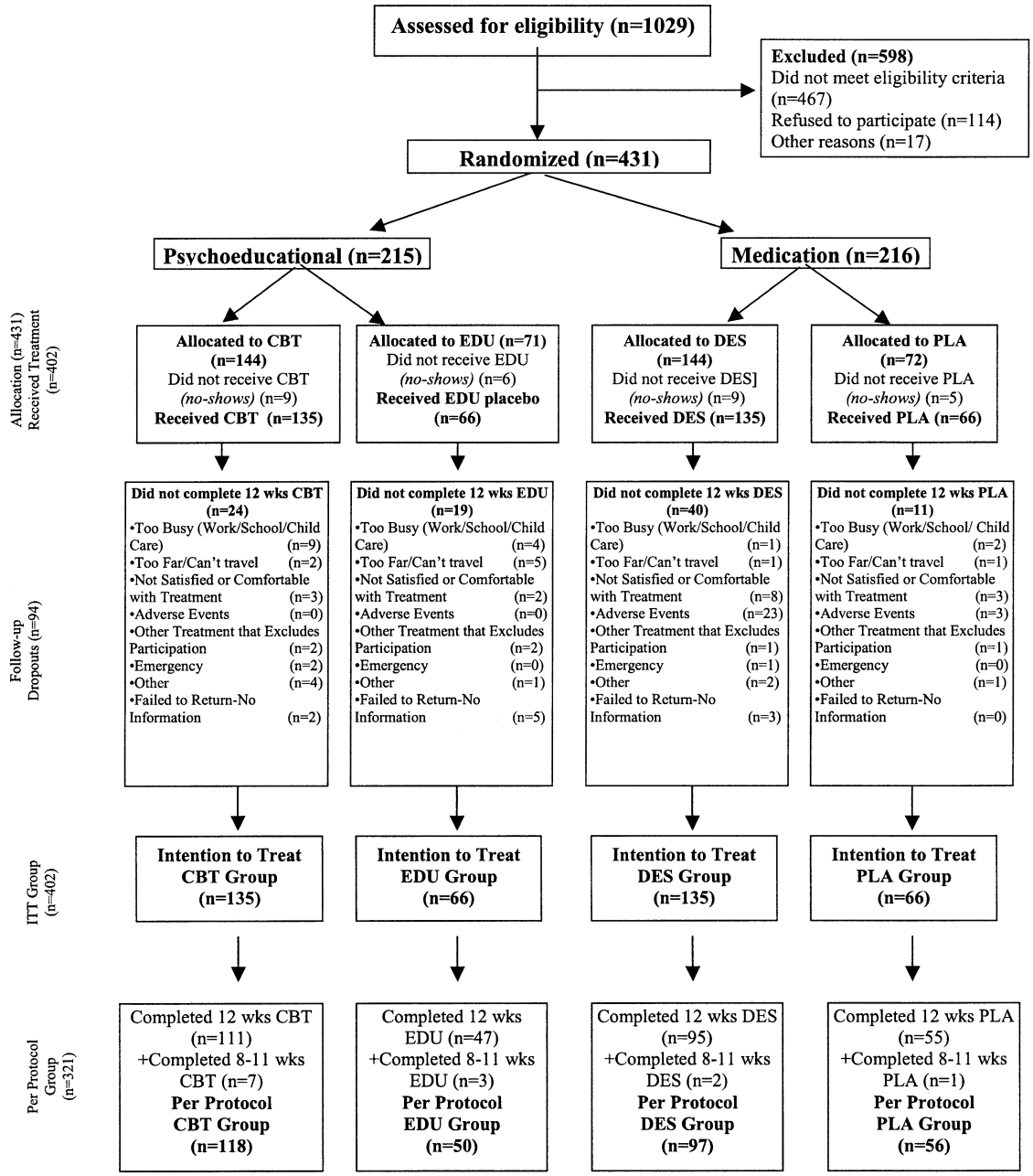

Figure 1. Flow of study participants (combined for UNC and Toronto sites) through enrollment, study allocation, and analysis.

Process Measures and Compliance

For the psychological arm, after adjusting for multiple comparisons, there were no differences at the start of treatment on the credibility scale between sites or between CBT and EDU groups. There was some improvement in the cognitive scale score for the CBT group (change score, 1.05 ± 3.26 relative to baseline); for the EDU group, the change score was 0.88 ± 1.97 (CBT vs. EDU, $P < 0.21$). The change scores for all subgroups where clinical benefit was achieved were in the expected direction, favoring CBT over EDU, but these comparisons were not statistically significant (range, $P < 0.10$ to $P < 0.20$). The credibility (expectation of benefit), while being no different at baseline, was significantly greater for CBT than for EDU ($P < 0.001$) after treatment. This indicates that the study participants were more confident in the benefit of CBT over EDU at the end of treatment.

For the medication arm, there were no differences on the credibility scale between DES and PLA before or after treatment. Of the 216 participants prescribed pills (drug or PLA), 16% took the full dosage of 3 pills per day, 38% averaged at least 2 pills per day, 17% averaged at

Table 1. Baseline Demographic and Clinical Information: Total Randomized Sample and by Treatment

Characteristic	Total sample (n = 31)	DES (n = 144)	PLA (n = 72)	CBT (n = 144)	EDU (n = 71)
Age, n = 431 (yr ± SD)	38.6 ± 12.0	39.7 ± 12.0	40.1 ± 12.1	37.9 ± 11.8	36.1 ± 11.8
Education, n = 431 (yr ± SD)	14.8 ± 2.8	14.7 ± 2.7	14.8 ± 3.2	14.9 ± 2.8	14.7 ± 2.7
Ethnicity, n = 431 (%)					
White	84.5	84.7	80.6	84.0	88.7
Black	10.0	9.0	11.1	11.1	8.5
Asian American	1.9	2.8	2.8	1.4	0.0
Hispanic	1.4	1.4	1.4	1.4	1.4
Other	1.6	1.4	4.2	1.4	0.0
Native American/Canadian	0.7	0.7	0.0	0.7	1.4
Married, n = 431 (%)					
Single	33.9	34.0	31.9	31.9	49.4
Married/cohabitating	49.7	50.7	51.4	50	45.1
Divorced/separated	13.2	12.5	11.1	16.7	9.9
Widowed	3.3	2.8	5.6	1.4	5.6
FBDSI, n = 431 (%)					
Mild (0–36)	3.5	4.2	5.6	2.1	2.8
Moderate (37–110)	67.8	63.9	69.4	68.8	71.8
Severe (>110)	28.9	31.9	25.0	29.2	25.4
FBD diagnosis (%)					
Rome diagnosis, n = 431					
IBS	78.0	79.9	79.2	77.8	73.2
Functional constipation	10.7	9.0	5.6	12.5	15.5
Chronic functional abdominal pain	7.4	6.9	8.3	7.6	7.0
Unspecified FBD	3.9	4.2	6.9	2.1	4.2
Physician diagnosis, n = 425					
IBS	87.2	91.0	81.9	86.8	85.9
Functional constipation	3.3	1.4	4.2	4.2	4.2
Chronic functional abdominal pain	4.9	3.5	5.6	4.9	7.0
Unspecified FBD	3.3	3.5	6.9	1.4	2.8
Sexual/physical abuse, n = 431 (%)					
None	42	43.1	36.1	46.5	36.6
Some	58	56.9	63.9	53.5	63.4
Urge threshold pressure, n = 211 (mm Hg, mean ± SD)	22.2 ± 8.6	23.8 ± 9.5	21.6 ± 7.4	20.7 ± 7.3	22.7 ± 10.5
Pain threshold pressure, n = 206 (mm Hg, mean ± SD)	25.4 ± 11.7	25.6 ± 10.9	27.8 ± 13.6	24.0 ± 11.0	25.2 ± 12.5
Self-reported health, n = 429 (1–5 mean ± SD)	3.0 ± 0.9	2.8 ± 0.9	3.1 ± 1.0	3.1 ± 0.9	3.1 ± 0.9
Physician visits in 6 months, n = 429 (mean ± SD)	5.5 ± 7.2	6.4 ± 8.8	4.8 ± 5.1	5.4 ± 6.8	4.7 ± 5.7
Physician phone calls for gastrointestinal problems in 3 months, n = 430 (mean ± SD)	0.9 ± 2.2	0.9 ± 2.6	0.9 ± 2.2	0.8 ± 1.5	0.9 ± 2.5
Visual analogue scale Pain, n = 429 (0–100 visual analogue scale, mean ± SD/14 days)	38.5 ± 20.6	38.5 ± 22.0	38.3 ± 22.1	39.9 ± 18.9	36.3 ± 19.5
No. of stools/day, n = 431 (mean ± SD/14 days)	2.2 ± 1.6	2.3 ± 1.6	2.1 ± 1.4	2.1 ± 1.6	2.0 ± 1.8
Stool consistency (Bristol Stool Form Scale), mean ± SD	4.1 ± 1.3	4.1 ± 1.3	4.0 ± 1.3	4.1 ± 1.3	4.1 ± 1.1
McGill Pain, n = 427 (Average of pain rating index, mean ± SD)	13.4 ± 9.9	13.5 ± 10.2	12.2 ± 8.5	14.1 ± 10.3	12.9 ± 9.4
IBS-QOL, n = 431 (mean ± SD)	65.5 ± 20.3	62.8 ± 20.4	64.3 ± 20.4	67.2 ± 20.7	68.8 ± 18.8
Global well-being (% good, very good, or excellent), n = 431	37.4	38.9	34.7	36.8	38.0

least 1 pill per day, 23% averaged less than 1 pill per day, and 6% took no medication. The number of pills taken related primarily to dose adjustments made by the drug study coordinator. With regard to adherence to treatment, the mean number of pills taken was 162.3 (±82.4) compared with 193.8 (±82.1) prescribed (84% adherence). Fewer pills were prescribed in the active drug group (148.1 ± 87.4) than the PLA group (191.6 ±

Table 2. Composite Outcome Scores and Its Component Outcome Variables: ITT Sample by Treatment

	DES vs. PLA			CBT vs. EDU		
End point	DES group (n = 135)	PLA group (n = 66)	*P*	CBT group (n = 135)	EDU group (n = 66)	*P*
Composite score, n = 395 (mean ± SE)	**0.49 (0.02)**	**0.45 (0.02)**	**0.16**	**0.49 (0.02)**	**0.40 (0.02)**	**0.0001**
Satisfaction n = 325 (mean ± SE) (posttreatment score only)	27.91 (0.87)	24.12 (1.19)	0.011	29.10 (0.52)	25.75 (0.76)	0.0004
IBS-QOL, n = 336 (mean ± SE)[a]	76.31 (1.47)	72.02 (2.01)	0.09	76.55 (1.16)	73.60 (1.72)	0.156
Global well-being, n = 319 (% "good, very good, excellent")[a]	52.5%	46.4%	0.79	47.4%	34.8%	0.04
McGill average daily pain, n = 302 (mean ± SE)[a]	8.94 (0.62)	10.73 (0.83)	0.09	9.52 (0.54)	10.13 (0.89)	0.56
Responder n/total n (%)[b]	64/107 (59.8)	27/57 (47.4)	0.128	77/110 (70.0)	19/51 (37.3)	<.0001

[a]Adjusted for baseline.
[b]NNT is 8.1 for DES and 3.1 for CBT.

61.8), and adherence was also poorer in the active drug group (80.5%) compared with the PLA group (89.5%). Dose adjustments by the coordinator and adherence rates related primarily to side effects.

Outcomes and Estimation

To proceed to comparison of each active treatment to PLA, and in keeping with the hierarchical analytic design,[30] we first compared the overall effect of active treatment (CBT + DES groups together) against their control conditions (EDU + PLA groups together); there was a significant effect favoring active treatment (P=0.0004) over the control condition in general. This result has no clinical implications; however, by reaching a level of statistical significance, it permitted us to analyze each treatment against its own PLA in a confirmatory manner. Table 2 summarizes results of the ITT analyses for DES vs. PLA (first set of columns) and CBT vs. EDU (second set of columns). The composite measure, derived from the 4 outcome variables of clinical relevance (satisfaction with treatment, IBS-QOL, global well-being, and McGill Pain Questionnaire), was the primary outcome measure. The data in Table 2 show both the composite score results as well as the results of the individual outcome measures comprising the composite score.

ITT analysis. CBT was superior to EDU (P = 0.0001; effect size, 0.51; 95% confidence interval [CI], 0.21–0.81), and DES showed nonsignificant benefit (P = 0.16; effect size, 0.23; 95% CI, 0.07 to 0.52) over PLA. In addition, there was no difference between the effects of DES vs. CBT using the primary composite outcome variable (P = 0.87) and no statistical difference between PLA vs. EDU (P = 0.11). Similar results were obtained for ITT analysis when not imputing the data on the 51 subjects for whom end-of-treatment data were not available.

Further analysis of the individual outcome variables indicates that treatment benefit was explained primarily by the satisfaction scale (treatment efficacy) for medical and psychological treatments (DES vs. PLA, P = 0.011; CBT vs. EDU, P = 0.0004).

We also assessed the proportion of responders in each treatment group. By treatment allocation, 70.0% of the CBT group were responders vs. 37.3% of the EDU group (P = 0.0001), and 59.8% of the DES group were responders vs. 47.4% of the PLA group; this was not statistically significant (P = 0.128). Thus, the NNT was 3.1 for CBT and 8.1 for DES.

Per-protocol analysis. Table 3 shows the results of the per-protocol analysis of each individual treatment against PLA. DES treatment was now significantly better than PLA (P = 0.03; effect size, 0.44; 95% CI, 0.14–0.73), as was CBT over EDU (P = 0.001; effect size, 0.50; 95% CI, 0.2–0.8). The responder analysis indicated that 73.0% responded to CBT vs. 41.3% in the EDU group (P = 0.0002; NNT, 3.2) and 68.5% responded to DES vs. 49.1% for the PLA group (P = 0.021; NNT, 5.2).

Notably, a post-hoc analysis for the DES vs. PLA group that excluded 12 patients on DES but with nondetectable blood levels found an even greater treatment effect (P = 0.002), with an improved responder analysis

Table 3. Composite Outcome Score and Responder: Per-Protocol Sample by Treatment

	DES vs. PLA			CBT vs. EDU		
End point	DES group (n = 97)	PLA group (n = 56)	*P*	CBT group (n = 118)	EDU group (n = 50)	*P*
Composite score, n = 315 (mean ± SE)	0.55 (0.02)	0.48 (0.02)	0.03	0.51 (0.01)	0.43 (0.02)	0.001
Responder n/total n (%)[a]	61/89 (68.5)	27/55 (49.1)	0.02	73/100 (73.0)	19/46 (41.3)	0.0002
Composite score, detectable DES levels, n = 138 (mean ± SE)	0.57(0.02)	0.47 (0.02)	0.01			
Responder n/total n (%)[b]	58/80 (72.5)	27/55 (49.1)	0.006			

[a]NNT is 5.2 for DES and 3.2 for CBT.
[b]NNT is 4.3.

of 72.5% for DES vs. 49.1% in the PLA group ($P = 0.006$; NNT, 4.3). This strongly suggests that antidepressant treatment with DES is effective, provided that the medication is properly taken.

Ancillary (Subgroup) Analyses

Illness severity and psychosocial comorbidity. Ancillary analyses were performed using the per-protocol study sample to address whether there are differential effects of treatment for clinically relevant subgroups. These exploratory analyses identified clinically meaningful subgroups relating to (1) severe and moderate symptoms, (2) some abuse history and no abuse history, and (3) depression (BDI, >16) and no depressive symptoms (BDI, <16). Each of these subgroups was studied between active treatment and PLA with regard to treatment benefit. In general, participants with less severe illness or a history of abuse or no depression responded better to treatment. With regard to the specific treatments, DES was not significantly different over PLA for any of these findings except for marginal benefit for subjects having moderate severity (Table 4, first set of columns). However, CBT showed significant benefit for all groups except for subjects with depression (BDI, >16) (Table 4, second set of columns).

Diarrhea predominant and constipation predominant. DES showed marginally significant benefit for participants with diarrhea-predominant stool form (n = 32; composite score, 0.59 ± 0.04 for DES vs. 0.39 ± 0.06 for PLA; $P = 0.08$), and this was significant in the ITT analysis (N = 57; $P = 0.03$). It was not significant for those with constipation-predominant or normal stool form. There was similar benefit of CBT for either diarrhea-predominant or constipation-predominant FBD.

Adverse Events and Dropouts From Medication Treatment

Table 5 shows the adverse events in the medication arm for any and moderate to severe events (as defined by the study participants). There were no side effects that required hospitalization or emergency evaluation. The most common side effects for DES related to the anticholinergic and antihistaminic effects of the drug: dry mouth, sleep disturbance, dizziness, and constipation. The same side effects were also seen at about one half the

Table 4. Ancillary Analyses (per protocol) of Composite Outcome Score by Severity, Abuse, and Depression Subgroups

		DES vs. PLA			CBT vs. EDU		
		DES	PLA		CBT	EDU	
Subgroup	N	Mean (SE)	Mean (SE)	*P*	Mean (SE)	Mean (SE)	*P*
By severity							
Moderate (FBDSI, <110)	230	0.57 (0.02)	0.49 (0.02)	0.06	0.51 (0.02)	0.44 (0.03)	0.01
Severe (FBDSI, >110)	88	0.53 (0.03)	0.45 (0.05)	0.20	0.52 (0.03)	0.40 (0.05)	0.04
By abuse							
No abuse	140	0.55 (0.02)	0.52 (0.04)	0.58	0.51 (0.02)	0.43 (0.04)	0.04
Some abuse	177	0.56 (0.02)	0.45 (0.03)	0.003	0.51 (0.02)	0.44 (0.03)	0.01
By depression							
Depressed (BDI > 16)	60	0.43 (0.04)	0.43 (0.06)	0.85	0.48 (0.04)	0.50 (0.06)	0.88
Not depressed (BDI ≤ 16)	258	0.58 (0.02)	0.48 (0.02)	0.01	0.51 (0.02)	0.41 (0.02)	0.0002

NOTE. Composite based on end scores, with adjustment for baseline scores.

Table 5. Medication Arm Side Effects, Total and Moderate/Severe

	Total no. of patients (n = 201)			
	DES (n = 135)		PLA (n = 55)	
Side effect	Any side effect (%)	Moderate or severe side effects (%)	Any side effect (%)	Moderate or severe side effects (%)
Dry mouth	48	26	26	11
Sleep disturbance	32	20	20	13
Dizzy/light-headed	4	13	18	9
Constipation	26	16	9	8
Flush/hot flash	23	13	4	2
Tired/drowsy	20	11	28	15
Nervous/jittery	15	9	9	6
Heartburn	13	9	4	2
Nausea	13	8	6	2
Headache	11	8	11	9
Decreased appetite	10	4	2	2
Fast irregular heartbeat	9	6	2	0
Flu/cold	9	4	17	6
Muscle/bone	6	6	13	11
Rash	6	4	3	2

frequency in the PLA group. Moderate to severe side effects usually requiring dosage adjustments were about twice as frequent in the medication arm. Of the 51 dropouts in the DES vs. PLA treatment groups (UNC, 20; Toronto, 31), 29 (56.9%) occurred because of side effects (26 on DES and 3 on PLA). Most reported multiple side effects (mean, 3.5).

Discussion

Among participants with moderate to severe FBD enrolled in a 12-week multicenter treatment trial, we found that CBT showed statistically significant benefit when compared with EDU (composite score, $P < 0.0001$). Because it may be difficult to interpret the clinical meaning of the composite score, we also show clinically significant results as determined by the responder rate (70% vs. 37% EDU) and the NNT (3.1). DES was not significant over PLA ($P = 0.16$; responder rate, 60% vs. 47%; NNT, 8.1) in the ITT analysis. However, statistically significant benefit was achieved secondarily in the per-protocol analysis ($P = 0.01$; responder rate, 69% vs. 49%; NNT, 5.2), and this was enhanced ($P = 0.002$; responder rate, 73% vs. 49%; NNT, 4.3) when 12 of 97 participants allocated to DES with nondetectable DES blood levels were excluded from the analysis. This suggests that DES may be effective for treating FBD, provided that participants can tolerate the side effects and detectable blood levels are achieved.[3] Furthermore, there was no difference between the treatment effect of CBT vs. DES ($P = 0.87$), with the lack of significance of DES vs. PLA explained by the higher placebo effect of PLA than EDU, although there was no statistical difference when PLA was compared with EDU ($P = 0.11$).

To address the issue of multiplicity of analyses, we proposed a priori that the primary outcome variable be a composite measure of 4 clinically meaningful end points: satisfaction with treatment (treatment efficacy),[25] health-related quality of life (IBS-QOL[26]), global well-being,[12] and 14-day averaged abdominal pain (McGill Pain Questionnaire[13]). The outcome item that best explained the composite measure of treatment benefit was satisfaction with treatment, while pain scores were only slightly and not significantly improved. This finding supports recommendations by the Rome II committees[28] and regulatory agencies[35] that subjective global end points (e.g., satisfaction with treatment) be considered as primary outcome variables. Furthermore, the results are consistent with clinical experience when using these particular treatments. Often patients will report that "the pain is still there but I'm managing it better." Physicians and mental health professionals recognize this to be a clinically meaningful response.

Another objective of our study was to identify treatment response of clinically meaningful subgroups. In general, DES was more effective for participants with less severe illness (FBDSI, <110) and a history of abuse, whereas CBT was effective regardless of the level of illness severity or abuse status. Contrary to expectations, participants with depression (BDI-II, >16) did not benefit either from CBT or DES over their control conditions. This may be because participants with depression

may also have more severe illness and other comorbidities that together adversely affect the clinical response,[5,36] or these participants may be less willing or able to engage in and respond to psychological treatment[3,20,37,38] or adhere to an antidepressant regimen.[39] We suggest that clinicians and therapists increase their efforts to communicate the rationale for these treatments to increase the patient's motivation to engage in treatment. Treatment studies involving other medical and psychiatric conditions suggest that combined psychological and antidepressant treatment show greater benefits than monotherapy,[40,41] and this is particularly true for patients with more severe depression or refractory illness.[42,43] Combination treatment might be a rational means to increase benefit in a more refractory clinical population with FBD, although this will require future prospective studies. Finally, we found that participants with diarrhea-predominant symptoms may selectively benefit from DES. Given the large effect difference, the marginal statistic ($P = 0.08$) may be explained by small sample size ($n = 32$). Indeed, we found significant differences when also analyzing this effect in the ITT analysis ($P = 0.03$; $n = 57$). This is consistent with the anticholinergic properties of tricyclic antidepressants and previous data.[44]

Several smaller studies evaluating CBT or antidepressants for patients with FBD (primarily IBS) are supportive of our findings but have methodological limitations. In a review of 15 randomized trials of psychological treatments for IBS[9] using CBT (9 studies), interpersonal psychotherapy (3 studies), relaxation/stress management (2 studies), and hypnosis (1 study), most favored active treatment but only 5 included placebo arms. Of these, 2 were positive and one showed a trend for greater bowel symptom reduction. Several trials compared the active psychological intervention with continuation of standard medical therapy or with monitoring symptoms while waiting to start therapy. However, these control groups are associated with a negative expectancy because patients were referred to these trials if they had failed medical therapy and the participants would not expect to improve while waiting to be treated. In addition, many studies did not include process measures to validate the treatment response. We used a credible, protocol-driven educational placebo condition where the subject had the same number of treatment visits and the therapists administering both treatments were monitored for adherence to each protocol via audiotaped sessions.

With regard to antidepressant treatment, one study of 28 patients found that 150 mg/day DES for 4 weeks was superior to atropine and placebo for abdominal pain, stool frequency, and depressive symptoms.[44] DES was more helpful for diarrhea-predominant symptoms, and the benefit was independent of anticholinergic action or the presence of psychiatric disease. Subsequent meta-analyses have tended to favor tricyclic antidepressants over placebo for chronic nonmalignant pain[45,46] and for IBS.[8] However, the individual studies were limited in their interpretation and generalizability because of the following: (1) small sample size, (2) heterogeneous study populations with inadequate entry criteria, (3) nonstandardized treatment protocols or (if multicenter) failure to assess adherence to protocol across sites, (4) use of measurement instruments not designed specifically for the FBD population, and (5) a variety of outcome measures not always consistent with recommended guidelines. Our study of more than 400 patients with moderate to severe FBD used standardized inclusion criteria, protocol-driven treatments, and clinically relevant and recommended outcome measures and assessed adherence to the protocols and DES blood levels.

Several limitations to the study need to be considered. First, at least moderate side effects occurred in up to one fourth of participants taking DES. Thus, some participants may have become unblinded, although up to 15% of participants on PLA also had similar side effects. Because DES seems to be effective when properly taken, a comparator such as an anticholinergic drug might be included in future studies to reduce the possibility of unblinding. Second, dropouts occurred in 23% (94 of 402 randomized) allocated to treatment; however, end-of-treatment data were obtained for 43 of these dropouts. Thus, for the remaining 51 subjects (13% of those randomized), we used a reliable method to impute the data that anticipated treatment responses based on whether the dropout was due to a poor treatment response, side effects, or reasons unrelated to the study.[34] Of note, there was no difference with and without imputation, suggesting that the data lost from these dropouts are not likely to affect the results. Third, some may consider including all patients with Rome I or II FBD (i.e., IBS, functional abdominal pain, painful constipation, unspecified FBD) as a limitation, because the study is not powered to determine comparative effects. However, the study was designed to access a "usual care" clinical population having abdominal pain with or without bowel dysfunction, and it was sufficiently powered to determine similar effects for participants with IBS as well as for the total sample of FBD. Therefore, the results can apply specifically to IBS but cannot conclusively determine benefit for the other specific FBD.

The study results and conclusions are definitive and generalizable to any patient who fulfills our selection criteria, is treated by our standardized CBT protocol,[20] or is adherent to taking DES as prescribed. The conclusions are best applied to participants with abdominal pain that is moderate to severe in nature, with or without altered bowel habit, and occurring at least 2 days per week. The results may not be generalizable to the larger group of participants with mild FBD as seen in primary care, to men, or to other psychological treatments besides CBT. Although other tricyclic antidepressants may show similar efficacy, they may vary in their side effect profile; further work is needed to determine if dosages <150 mg are as effective. The findings may not apply to patients treated with selective serotonin reuptake inhibitor antidepressants because of their different receptor activity profile. Finally, the data suggest that the predicted outcomes relate primarily to subjective global assessments and quality of life more than to improvements in pain or bowel habit per se.

In conclusion, we found that CBT is effective in treating women with FBD, including IBS. DES is effective only for those able to stay on medication. These treatments most benefit participants with moderate more than severe symptoms and without comorbid depression. Whether other psychological treatments or other classes of antidepressants are effective needs to be determined. With growing evidence that these treatments have synergistic effects, future studies should evaluate the benefit of combined treatment with DES and CBT for the patients not responsive to monotherapy, particularly those with more severe depression.

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Received December 6, 2002. Accepted April 3, 2003.

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Supported by a research grant from the National Institutes of Health (RO1-DK49334).

This study was registered with ClinicalTrials.gov (trial registry no. NCT00006157).

The authors thank the members of the National Institutes of Health Data Safety and Monitoring Board for their support and guidance: Kevin W. Olden, M.D. (chair), E. Jan Irvine, M.D., R. Bruce Lydiard, Ph.D., M.D., Emeran A. Mayer, M.D., Kim Sutton-Tyrell, Ph.D., and W. Grant Thompson, M.D.; Tommie Sue Tralka, Dr. Kurt Kroenke, and Dr. Robert Sandler for their helpful comments; and Sara Liles, Chalice Overy, Catherine Coleman, and Kristin Clark for their assistance in the administration of the project.