Published in final edited form as:

Clin Gastroenterol Hepatol. 2019 July ; 17(8): 1500–1508.e3. doi:10.1016/j.cgh.2018.10.033.

Factors Associated With Efficacy of Cognitive Behavior Therapy vs Education for Patients With Irritable Bowel Syndrome

Jeffrey M. Lackner, PsyD¹ and James Jaccard, PhD² IBS Outcome Study Research Group

¹Divisions of Behavioral Medicine and Gastroenterology, Department of Medicine, Jacobs School of Medicine, University at Buffalo, Buffalo, NY

²School of Social Work, New York University, New York, NY

Abstract

Background & Aims: Among patients with irritable bowel syndrome (IBS), it would be helpful to identify those most likely to respond to specific treatments, yet few factors have been identified that reliably predict positive outcome. We sought to identify pretreatment baseline characteristics that associate with symptom improvement in patients who received empirically validated regimens of cognitive behavior therapy (CBT) or IBS education.

Methods: We analyzed data from the IBS Outcome Study, in which 436 patients with IBS (average age, 41 years; 80% female) were randomly assigned to groups that received to 4 or 10 weeks of cognitive behavior therapy or education. Baseline data were collected from all participants on sociodemographic and clinical features and comorbidities. Interaction analyses used a modified linear probability model with Huber-White robust estimators to identify baseline factors that moderated as a function of treatment condition symptom improvement based on the IBS-version of the Clinical Global Impressions-Improvement Scale.

Results: Whether the primary outcome of IBS symptom improvement was rated by patients or physician assessors blind to treatment 2 weeks after it ended, higher percentages of patients had symptom improvement after CBT compared with EDU among those with low levels of trait anxiety (71.3% vs 34.9%; $P<.05$) or anxiety sensitivity (71.7% vs 38.6%; $P<.05$) and for those with baseline typical levels of trait anxiety (66.0% vs 47.1%; $P<.05$) or anxiety sensitivity (66.3%

Corresponding Author: Jeffrey M. Lackner, Psy.D., Division of Behavioral Medicine, Department of Medicine, University at Buffalo, SUNY, ECMC 462 Grider Street, Buffalo, NY 14215. Telephone: 716-898-5671; Fax: 716-898-3040; lackner@buffalo.edu.

Author Contributions: Dr. Lackner and Dr. Jaccard had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lackner, Jaccard

Acquisition, analysis, or interpretation of data: Lackner, Jaccard

Drafting of the manuscript: Lackner, Jaccard

Critical revision of the manuscript for important intellectual content: Lackner, Jaccard

Statistical analysis: Jaccard

Obtained funding: Lackner

Administrative, technical, or material support: Lackner, Jaccard

Study supervision: Lackner

Disclosures: None .

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vs 47.1%; $P < .05$). For patients with high trait anxiety or anxiety sensitivity, the difference in percentage of responders to CBT vs EDU was non-significant for trait anxiety (60.6% vs 59.2%) and anxiety sensitivity (60.9% vs 55.9%). If patients scored at or below 22 on the Trait Anxiety Inventory, CBT had a statistically significant advantage over EDU. If patients scored at or below 29 on the Anxiety Sensitivity Inventory, there was a statistically significant advantage for CBT vs EDU.

Conclusion: In analyses of outcomes of patients with treatment-refractory IBS, baseline levels of trait anxiety and anxiety sensitivity (fear of arousal symptoms) were associated with improved gastrointestinal symptoms following CBT compared to IBS education. These findings and approaches might be used to optimize selection of treatment for patients with IBS.

Keywords

precision medicine; moderation; predictors; psychological treatments; treatment outcome

Irritable bowel syndrome (IBS) is the most prevalent of all gastrointestinal (GI) disorders. The limited efficacy of medical therapies has led to the development of a number of psychological treatments that target central factors believed to dysregulate brain gut interactions¹. The psychosocial treatment for which there is most empirical support is cognitive behavior therapy (CBT)². While CBT is generally effective in improving chronic and severe IBS symptoms³, a significant proportion of CBT-treated patients neither respond nor respond well enough to register as have achieved clinically meaningful improvement. Given the prevalence of IBS, its public health burden, and limited resources available for effectively managing it, it is important to identify patients for whom treatments are most effective. The specification of prescriptive factors has the potential to lead to more precise clinical decision making, to promote the practice of what the Institute of Medicine⁴ calls “precision medicine”⁵, and to make best use of scarce resources.

Our understanding of what patient factors influence IBS treatment outcomes comes from a few small-scale trials whose only consistent conclusion is that so few reliable predictors of treatment success exist that any additional search is “futile”^{6,7}. Almost all research has focused on identifying non-specific predictors of outcomes for a single IBS treatment rather than predictors that allow us to predict which of two or more treatment types will be most effective. Non-specific predictors identify which patients are more likely to respond to treatment and may point to ways to improve treatment delivery but they do not provide information that informs optimal treatment selection. Moderators are a type of predictor that identify what subgroups differentially respond to one treatment over another and are therefore critical to realizing the treatment matching goals of personalized medicine

Because the empirical literature provides little guidance about how to select the optimal treatment strategy for a particular patient based on his or her baseline characteristics, health care professions often resort to decision-making based on intuition, anecdote, and trial and error. This is an inherently inefficient and unreliable approach that can lead to treatment delays, demoralization, frustration on the part of patients and providers, and costs to the health care system. The purpose of this study was to identify baseline characteristics that

interact (moderate) with treatment type to produce symptom improvement in patients enrolled in a RCT comparing CBT to IBS education.

Baseline variables that we *a priori* expect to influence the effects of CBT over education/support are co-existing anxiety-related personality traits that are regarded as relatively stable biological predispositions⁸. Anxious patients suffer from often intrusive thoughts as well as deficient attention control mechanisms (e.g., distractibility, concentration difficulties⁹). These symptoms have been linked to an attentional focus on threat-related stimuli (e.g., self-focused attention, hypervigilance to threat). Individuals with high trait anxiety (TA) are more inclined to detect and process threat-related information, which interferes with performance on various attentional tasks¹⁰. Highly trait anxious IBS patients also may lack attentional control mechanisms to benefit fully from CBT strategies. To illustrate, one goal of CBT is for patients to learn to apply evidence-based logic to reduce stress arising from prediction errors (mismatch between expected and actual outcome) believed to dysregulate brain-gut interactions¹. For this strategy to work, an individual must have the cognitive resources to disengage attention from threat-related stimuli and reorient it towards cognitive reappraisal. This task may be difficult for high TA patients because their over attention to threat stimuli may “hijack” attentional resources needed for reappraisal exercises (e.g., worry control). We would expect that low TA patients, on the other hand, are more likely to benefit from CBT because they can more easily allocate limited attentional resources to its cognitive demands without interference of threat-related stimuli. An attentional model would also predict that relative to CBT high TA patients might benefit from IBS education because of its lighter cognitive demands. We would expect similar pattern of response for other anxiety-related risk factors such as anxiety sensitivity. Whereas high trait anxiety persons respond fearfully to stressors in general based on previous anxiety experiences, those high in anxiety sensitivity (AS) tend to respond fearfully to arousal symptoms regardless of the intensity or frequency of past anxiety experiences (e.g., “It scares me when my heart beats rapidly”)¹¹. High AS patients believe that arousal sensations (e.g., heart palpitations, blushing, shortness of breath) have harmful or catastrophic consequences such as mental or physical illness, social embarrassment, or loss of control.

We speculate other predictors may impede patients’ ability to attend to and engage in CBT relative to IBS education. These include depression, motivation, medical comorbidities, somatization, illness beliefs, stress, fear of visceral sensations, and interpersonal stressors. We conducted exploratory analyses of their moderating effects on IBS symptom improvement via CBT versus EDU as well.

METHODS

Description of the parent study

The present study is a secondary analysis of the Irritable Bowel Syndrome Outcome Study (IBSOS)¹². The IBSOS is a randomized controlled, parallel group trial that allocated patients from two sites (University at Buffalo, Northwestern University) into either cognitive behavior therapy or education. CBT is a brief, learning-based treatment that teaches patients behavior change skills for improving treatment refractory IBS symptoms. Symptom self-management skills target both dysfunctional patterns of thinking and behaviors believed to

maintain IBS. CBT in the present study was delivered in 4 sessions over 10 weeks (MC-CBT) or once a week for 10 weeks (S-CBT). The education condition (EDU¹²) provides information about IBS, its clinical features, causes, treatments and the role of lifestyle factors (stress, diet, exercise) in the context of a support therapeutic environment without prescribing behavior changes or addressing CBT mechanisms. EDU was delivered in 4 sessions over 10 weeks. Detailed description of the treatments is provided elsewhere^{3, 12}. Adults (18-70 years) suffering from IBS as defined by Rome III criteria¹³ were included provided GI symptoms were at least moderately severe (i.e., occurred at least twice weekly and caused some life interference). Patients were excluded if they presented evidence of current structural/biochemical abnormalities or other primary GI disease that better explained gastrointestinal symptoms; had been diagnosed for a malignancy other than localized basal or squamous cell carcinomas of the skin in the past 5 years; were undergoing IBS-targeted psychotherapy; could not commit to completing all scheduled follow up visits; had an unstable extraintestinal condition or a major psychiatric disorder (e.g., depression with severe suicidality, psychotic disorder); reported a current gastrointestinal infection or an infection within 2 weeks before evaluation; used a gut-sensitive antibiotic during the 12 weeks prior to baseline assessment.¹¹ were included provided GI symptoms were at least moderately severe (i.e., occurred at least twice weekly and caused some life interference). Table 1 presents baseline characteristics of the sample

Outcome Measure

Per Rome recommendations for clinical trials for FGIDs¹⁴, the primary endpoint was global IBS symptom improvement based on the IBS version¹⁵ of the Clinical Global Impressions-Improvement Scale (CGI-I)¹⁶. Patients whose symptoms were rated as “substantially improved” or “moderately improved” qualified as treatment responders. Study gastroenterologists blind to treatment condition completed a physician-version of the CGI¹⁷.

Potential Treatment Moderators

Potential predictors of differential response were assessed at the beginning of a 4-week pretreatment baseline before treatment assignment. Candidate moderators included the age at symptom onset, IBS symptom severity as measured by the IBS-SSS [add citation], the number of comorbid DSM-IV Axis I disorders, as determined by the MINI International Neuropsychiatric Interview¹⁸, depression, as measured by the Beck Depression Inventory-II¹⁹, situational and dispositional anxiety (State-Trait Anxiety Inventory²⁰); somatization (Brief Symptom Inventory-18²¹); perceived stress (Perceived Stress Scale-4)²²; fears of somatic arousal (Anxiety Sensitivity Inventory)²³ and fear of GI symptoms (Visceral Sensitivity Index)²⁴; pain catastrophizing (Coping Strategies Questionnaire²⁵) and treatment motivation (Treatment Self-Regulation Questionnaire²⁶). Number of comorbid medical comorbidities was measured with the IBSOS Medical Comorbidity Checklist^{27, 28}. Control beliefs were measured with the IBS Locus of control Scale²⁹ and the IBS Self-Efficacy scale³⁰. The quality of social relationships was measured with the Inventory of Interpersonal Problems-32³¹.

Statistical Analyses

Analyses focused on outcome data obtained 2 weeks after treatment completion and were restricted to patients who received adequate dosage of the respective treatments (completion of at least 8 sessions of S-CBT, and 3 sessions of M-CBT or EDU) given our focus was on understanding the moderators of treatment efficacy rather than effectiveness (where efficacy is confounded with treatment drop-out; although treatment drop-out was minimal at 9%). Interaction effects between treatment condition and moderators were evaluated using a modified linear probability model (MLPM) with Huber-White robust estimators (to accommodate non-normality and variance heterogeneity). Moderator by condition product terms were used to evaluate the presence of statistical interactions. For justification of the use of the MLPM over logistic regression, see ^{32, 33} as well as online supplement. All analyses included site as a covariate as well as medication status (patient using medication for abdominal pain, bowel symptoms, or for multiple IBS symptoms versus not). Ninety five percent confidence intervals are reported as margins of error, i.e., the maximum absolute half width for the lower versus upper confidence limit relative to the parameter estimate. Missing data were minimal (less than 1%) and treated by chained equation multiple imputation.

RESULTS

Table 2 presents those interaction effects that were statistically significant ($p < 0.05$) when analyzing dichotomous responder status using patient-reported ratings of IBS symptom improvement (1 = substantially or moderately improved, 0 = did not substantially or moderately improve) and for the corresponding gastroenterologist improvement judgments. The columns indicate the estimated percent differences between the CBT and EDU conditions when the moderator is “low” (one standard deviation below its mean), “typical” (at its mean), or “high” (one standard deviation above its mean), respectively. Several of the statistically significant interactions are of theoretical or practical interest, but the most distinctive results surround the construct of anxiety because (a) its moderating effect replicated for both patient and gastroenterologist improvement ratings (which was not true of the other moderators), (b) it was *a priori* predicted based on a strong logic model, and (c) it was statistically significant even after adjusting for family-wise error rates across all moderators using a Holm modified Bonferroni correction. The on-line supplement presents results for all moderators explored, including the product term coefficients as well as breakdowns at low, typical and high values.

The two anxiety constructs that were consistent moderators across both data sources (patient, physician assessments) were anxiety sensitivity (AS) and trait anxiety (TA). Figures 1 and 2 present the estimated differences graphically. When TA was “low”, the estimated difference on patient-reported CGI between the CBT and EDU conditions was $71.3\% - 34.9\% = 36.4\% \pm 15\%$, $p < 0.05$. When TA was at its mean, the estimated difference between the CBT and EDU conditions was $66.0\% - 47.1\% = 18.9\% \pm 10\%$, $p < 0.05$. When TA was “high,” the estimated difference between the CBT and EDU conditions was $60.6\% - 59.2\% = 1.4\% \pm 15\%$, ns. For blind physician ratings, when TA was “low”, the estimated difference between the CBT and EDU conditions was $63.3\% - 33.3\% = 30.0\% \pm 15\%$, $p < 0.05$. When TA was at its mean, the estimated difference between the CBT and EDU conditions was

61.9% – 43.5% = 18.4% $\pm$ 11%, $p < 0.05$. When TA was “high,” the estimated difference between the CBT and EDU conditions was 60.5% – 53.7% = 6.8% $\pm$ 16%, ns.

For patient-reported CGI, when AS was “low”, the estimated difference between the CBT and EDU conditions was 71.7% - 38.6% = 33.1% $\pm$ 15%, $p < 0.05$. When AS was at its mean, the estimated difference between the CBT and EDU conditions was 66.3% - 47.1% = 19.2% $\pm$ 11%, $p < 0.05$. When AS was “high,” the estimated difference between the CBT and EDU conditions was 60.9% - 55.9% = 5.3% $\pm$ 15%, ns. For blind gastroenterologist ratings, when AS was “low”, the estimated difference between the CBT and EDU conditions was 65.2% - 34.2% = 31.0% $\pm$ 15%, $p < 0.05$. When AS was at its mean, the estimated difference between the CBT and EDU conditions was 62.0% - 44.0% = 18.0% $\pm$ 11%, $p < 0.05$. When AS was “high,” the estimated difference between the CBT and EDU conditions was 58.8% - 53.8% = 5.0% $\pm$ 16%, ns.

Anxiety sensitivity and TA were correlated 0.53 ± 0.08 , $p < 0.05$, indicating they share redundant variance that likely reflects a tendency to respond to a range of situations as dangerous or threatening. Of interest is whether this generalized reactivity to threat stimuli is the primary driver of the moderated effect or if there are unique aspects of AS responsible for the moderation. If unique facets of trait anxiety and anxiety sensitivity are responsible for moderation, then when both product terms that reflect statistical interactions (one for each construct) are entered into the equation, one or both of the product terms should be statistically significant. If the primary driver of moderation is a generalized tendency to respond fearfully to threat stimuli, then neither product term should be statistically significant because the common variance is partialled out of each term by virtue of the presence of the other term in the regression equation. For both patient-reported and physician-reported CGI responder status, none of the product terms were statistically significant when both were included in the equation simultaneously. This suggests that the primary source of their moderation effects is a trait-like tendency to respond anxiously to stressors that includes but is not limited to unpleasant physical sensations.

Additional analyses were conducted using an iterative variant of the Johnson-Neyman method³⁴ to identify the cutoff scores on the Trait anxiety scale of the STAI and the ASI where the difference between CBT and EDU became statistically non-significant and thereby no longer favored CBT over EDU in terms of raising the probability of achieving responder status. For TA and patient-reported CGI, the score was 22 (range 0 to 40) and for AS it was 29 (range 0 to 64). For patients scoring at or below 22 on TA CBT will have an advantage over EDU because the probability of responding positively to treatment is statistically significantly higher at that point. For a patient who scores 23 or above, then there is no necessary advantage of CBT over EDU, but there also is no advantage of EDU over CBT. For patients who score at or below 29 on AS, there will be an advantage to triaging them to CBT instead of EDU. EDU has a statistically significant advantage over CBT only at very high scores of AS, i.e., scores of 38 or higher.

DISCUSSION

Our most robust finding involved the moderating effects of trait anxiety and anxiety sensitivity on IBS symptom improvement. CBT-treated patients with lower levels of TA evidenced greater symptomatic improvement than EDU treated patients. The proportion of responders faring better with CBT narrowed as TA increased to the point that there was negligible, non-significant difference between CBT (60.6%) and EDU (59.2%) in patients with higher TA levels (i.e., one SD above the mean). By comparison, the absolute percentage difference between CBT (71%) and EDU (35%) is 36% when TA is low (i.e., one SD below the mean). A similar pattern of data characterized anxiety sensitivity. Our findings are consistent with an information-processing model that predicts that the pervasive and persistent anxiety interferes with the attentional demands of CBT in patients with very high TA or AS. The relatively lighter cognitive demands of education particularly if delivered in the context of a warm and supportive therapeutic relationship may facilitate symptom improvement among high anxiety patients who fare less well in CBT. The expression of empathy, caring and reassurance that comes with support may buffer patients against the pathogenic effects of stress³⁵, while increased knowledge about IBS even in the absence of formal skills training may facilitate the adoption of a biopsychosocial explanatory model of illness that empowers them to take control of symptoms³⁶. In some respects, our data suggest that a sizable proportion of highly anxious patients may do quite well with a less complex treatment than CBT although even among high trait anxious and anxiety sensitivity patients treatment response did not fall below 50%. What is notable is that among this highly anxious subgroup EDU positive treatment response exceeded the 50% cutoff the field often uses to characterize treatments with a robust efficacy profile.

An innovative aspect of this study was specification of cut-off scores for TA (a score of 22) and AS (a score of 29) scales above which CBT no longer had statistical advantage over EDU. Indeed, at very high levels of TA (scores above 37), the results tend to favor EDU over CBT, although care is required in extrapolating the cross-over interaction to a point in the distribution where few individuals reside. For patients with anxiety scores below the respective cutoffs, CBT has advantages over EDU. Because precision medicine is as much a methodology as a goal, the analytic method we used to identify decision cut points for treatment protocol decisions is important in health care environments that value making more efficient use of effective treatment options with scarce resources. Further research is needed to apply this approach to others patients, GI disorders, interventions, outcomes, and candidate moderators both biological (e.g. genetic, neural, motility markers) and behavioral.

In addition to TA and AS, depression, number of diagnosable psychiatric conditions, situational anxiety, and stress moderated IBS symptom improvement from the perspective of the patient but not blind assessors. Generally speaking, these variables can distort information processing such that both negative and neutral stimuli are appraised as more aversive than they are objectively. It is possible that these variables influence patient's perception of improvement of GI symptoms per se and their status as moderators should be treated cautiously. Future research should explore them in more depth. In the meantime, clinical gastroenterologists may find that understanding patients sensitivity to stressors – whether they are somatic (anxiety sensitivity) or more broad based (trait anxiety) – can help

them get the most out of empirically validated non-drug treatments such as CBT. Both AS and TA are heritable, relatively stable and not wholly modifiable and therefore we are not inclined to treat them separately before initiating CBT but their identification through easy to administer and short screening methods (GAD-7³⁷, ASI²³) may optimize health outcomes by setting realistic treatment expectations and personalizing options. For patients who display high TA or anxiety sensitivity, a fear of GI sensations (“When my stomach is upset, I worry that I might be seriously ill”) elicited in a brief GI consultation may be part of a more pervasive anxiety problem that may require greater amount or type of behavioral support than the brief, gut-targeted CBT featured here. In this respect, pattern of results speak to the specificity of our version of CBT for ameliorating GI symptoms, although its neurobiological change mechanisms are not well understood.

Fulfilling the promise of precision medicine has been complicated by a number of factors. Interindividual variability of response within treatments and small effect sizes for most therapies validated through tightly controlled RCTs carried out in research settings has prompted a need to go beyond “horserace questions” of whether treatment A is more effective than treatment B for the average person³⁸ to address the more complex question of what treatment works best for what individual patient? This question is particularly relevant to practicing GEs who struggle to reconcile guideline recommendations of treatments based on their average efficacy with the realities of clinical practice where individual patients are often anything but “average”, varying widely in their response to specific treatments and perhaps not coincidentally characteristics they “bring with them”. While these characteristics are often dismissed as nuisance variables or background noise in both clinical and research settings, they have the capacity to differentially impact outcomes (IBS symptom improvement) deemed important to both patient and provider. Identifying treatment moderators is an important way to establish the efficacy of prescriptive treatments and their effectiveness in “real world” clinical setting where the overwhelming number majority of IBS patients are seen.

One may have expected that those patients with more psychiatric comorbidities would fare poorer in CBT than EDU than those with fewer comorbidities. In fact, there was not sufficient evidence that the number of psychiatric comorbidities impacted the magnitude of treatment effect of CBT or Education. This also was true of the severity of depressive symptoms which Drossman et al. ³⁹ identified as a predictor of poor response to a different version of CBT than featured in this study. Taken together, the moderating effect of TA and AS suggests that what is critical is not the number of psychiatric conditions accompanying IBS but the specific type of condition, namely co-occurring anxiety problems particularly reflecting an enduring tendency to respond fearfully to stressors.

Non-significant findings should be interpreted cautiously as the current study is a secondary analysis of a multisite trial that was powered for the primary outcome question of whether CBT was more effective than EDU. Null findings do not necessarily mean the absence of an effect but rather that the effect was not large enough to be detected given the sample sizes. As such, while findings did not provide evidence for moderation across a range of sociodemographic variables, interpersonal problems, illness beliefs and motivation, the failure to find such effects may be due to reduced power. Results also may not generalize to

different clinical settings or patients undergoing other treatments. Whether the moderating effect of AS or TA extends long term is an important question that is beyond the scope of this study. We confined our analyses to a limited number of behavioral variables that we had hypothesized *a priori* had potential prognostic value. An innovative area of future research is whether TA- related biological processes (HPA axis reactivity to stress, alterations in mitochondrial function, neurotransmitter signaling, etc) have predictive value in identifying patients for whom treatment is most effective. To the extent that genetic composition of the brain influences individual differences in stress reactivity⁴⁰ then neuroimaging may prove useful for predicting which IBS patients may profit most from CBT.

In the meantime, our data shed ng light on the value and means for matching IBS patients to treatments based on their particular characteristics. Data offer a strategy for strengthening the efficiency and efficacy of treatment for IBS and relieving its personal and economic costs of one of the most common and challenging GI disorders confronting both primary care physicians and gastroenterologists.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements.

We thank members of the IBS Outcome Study Research Group: Rebecca Firth, Susan Krasner, Laurie Keefer, Chang-Xing Ma, Chris Radziwon, Michael Sitrin, Darren Brenner, Gregory Gudleski and Len Katz

Grant Support and Disclaimer: Research reported in this manuscript was supported by the NIH/NIDDK Grant 77738 (Dr. Lackner). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

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What you need to know

Even the most effective treatment for IBS do not work for every patient

We sought to identify baseline characteristic that interact with (moderate) with treatment to influence GI improvement

Baseline levels of trait anxiety and anxiety sensitivity moderated improvement in CBT relative to IBS education.

Data provide prescriptive information that can inform optimal selection of treatments recommended in clinical guidelines

Figure 1.
Moderating Effects of Trait Anxiety on Percent of Responders: Patient Reported Outcome

Figure 2.
Moderating Effects of Anxiety Sensitivity on Percent of Responders: Physician Reported Outcome

Table 1.**Baseline Sociodemographic and Clinical Characteristics by Treatment Condition**

Characteristic	Overall (n = 436)	MC-CBT (n = 145)	S-CBT (n = 146)	EDU (n = 145)
Age, mean (SD)	41.4 (14.8)	40.9 (14.6)	41.1 (14.4)	42.2 (15.4)
Women, N (%)	350 (80.3%)	124 (85.5%)	112 (76.7%)	114 (79.2%)
Race/ethnicity N (%)				
Non-Hispanic white	390 (89.4%)	133 (91.7%)	128 (87.7%)	129 (89.0%)
African-American	28 (6.4%)	8 (5.5%)	9 (6.2%)	11 (7.6%)
Other or missing	18 (4.2%)	4 (2.8%)	9 (6.2%)	5 (3.5%)
Marital status, N (%)				
Never married	185 (42.4%)	61 (44.1%)	60 (41.1%)	64 (44.1%)
Married	185 (42.4%)	68 (46.9%)	58 (39.7%)	59 (40.7%)
Separated/Divorced	57 (13.1%)	11 (7.6%)	26 (17.8%)	20 (13.8%)
Widowed	9 (2.1%)	5 (3.4%)	2 (1.4%)	2 (1.4%)
Income (\$), mean (SD)	74.0 (54.2)	77.9 (56.4)	73.1 (52.2)	71.3 (54.0)
Education, N(%)				
High school or less	99 (22.7%)	31 (21.4%)	30 (20.5%)	38 (26.2%)
Associate or Vo-tech	65 (14.9%)	25 (17.2%)	22 (15.1%)	18 (12.4%)
College degree	142 (32.6%)	54 (37.2%)	41 (28.1%)	47 (33.1%)
Post-grad degree	127 (29.1%)	35 (24.1%)	52 (35.6%)	40 (27.6%)
Missing	3 (0.7%)	0	1 (0.7%)	2 (1.4%)
Employment status, N (%)				
Employed full- or part-time	277 (63.5%)	92 (63.4%)	91 (62.3%)	94 (64.8%)
Unemployed	109 (25.0%)	38 (26.2%)	40 (27.4%)	31 (21.4%)
Homemaker	13 (3.0%)	4 (2.8%)	5 (3.4%)	4 (2.8%)
Retired	33 (7.6%)	9 (6.2%)	9 (6.2%)	15 (10.3%)
Missing	4 (0.9%)	2 (1.4%)	1 (0.7%)	1 (0.7%)
Predominant bowel type, N (%)				
Constipation	130 (29.8%)	43 (29.7%)	40 (27.4%)	47 (32.4%)
Diarrhea	188 (43.1%)	59 (40.7%)	67 (45.9%)	62 (42.8%)
Mixed	98 (22.5%)	33 (22.8%)	35 (24.0%)	30 (20.7%)
Undifferentiated	20 (4.6%)	10 (6.9%)	4 (2.7%)	6 (4.1%)
Years with IBS, mean (SD)	17.1 (14.4)	15.7 (13.3)	17.7 (13.3)	17.7 (16.4)
Received medical care for IBS (lifetime), N (%)	328 (75.2%)	107 (73.8%)	116 (79.5%)	105 (72.4%)
IBS treatment-naïve, N (%)	10 (2.2%)	4 (2.6%)	3 (1.9%)	3 (1.9%)
Assessment scores, mean (SD)				
IBS Symptom Severity Scale ^a	281.9 (72.1)	278.0 (68.6)	285.1 (76.7)	282.4 (71.0)
Brief Symptom Inventory ^{35,a}				
Anxiety	4.50 (4.50)	4.22 (4.26)	4.27 (4.41)	5.02 (4.81)
Depression	3.97 (4.29)	4.07 (4.47)	3.82 (4.33)	4.03 (4.09)
Somatization	4.22 (3.93)	4.16 (4.31)	4.00 (3.56)	4.54 (3.91)

Characteristic	Overall (n = 436)	MC-CBT (n = 145)	S-CBT (n = 146)	EDU (n = 145)
Global Severity Index	12.7 (11.0)	12.4 (11.6)	12.1 (10.5)	13.6 (10.8)
Medical comorbidities ⁴¹ , #	4.6 (4.9)	4.8 (5.2)	4.3 (4.7)	4.8 (5.0)
Psychiatric comorbidities ⁴² , #	1.2 (1.6)	1.1 (1.5)	1.3 (1.7)	1.2 (1.7)
Medication use for IBS symptoms, (N, %)	292 (67.0%)	94 (64.8%)	95 (65.1%)	103 (71.0%)
Pain medication	35 (8.0%)	9 (6.2%)	13 (8.9%)	13 (9.0%)
Bowel medication	271 (62.2%)	86 (59.3%)	87 (59.6%)	98 (67.6%)
Multi-symptom medication	20 (4.6%)	6 (4.1%)	7 (4.8%)	7 (4.8%)
Psychiatric medication	26 (6.0%)	8 (5.5%)	12 (8.2%)	6 (4.1%)

^a
(notes: = Higher scores indicate more severe symptoms; IBS-SSS 300 = Severe)

Table 2:**Moderation Analysis for Patient Reported CGI Responder Status**

	% Difference at SD Below Mean	% Difference at Mean	% Diff at SD Above Mean
<u>Patient Reported Outcome</u>			
Psychiatric comorbid #	31.4% * $\pm 14\%$	19.7% * $\pm 10\%$	8.1% $\pm 14\%$
Depression	31.1% * $\pm 15\%$	19.4% * $\pm 11\%$	7.6% $\pm 16\%$
Trait anxiety	36.4% * $\pm 14\%$	18.9% * $\pm 10\%$	1.4% $\pm 15\%$
State anxiety	35.3% * $\pm 15\%$	19.2% * $\pm 10\%$	3.1% $\pm 15\%$
Anxiety sensitivity	33.1% * $\pm 14\%$	19.2% * $\pm 10\%$	5.3% $\pm 15\%$
Stress	31.4% * $\pm 14\%$	19.6% * $\pm 11\%$	7.8% $\pm 15\%$
<u>Physician Reported Outcome</u>			
Trait anxiety	30.0% * $\pm 15\%$	18.4% * $\pm 11\%$	6.8% $\pm 16\%$
Anxiety sensitivity	31.0% * $\pm 15\%$	18.0% * $\pm 11\%$	5.0% $\pm 16\%$

(Notes: Entries are percent difference between CBT conditions and EDU condition. Difference when moderators are ignored is 19.7%. Entries following $\pm$ are margins of error that reflect the half width of 95% confidence intervals about the parameter estimate;

* $p < 0.05$; SD = standard deviation; sample size for CBT group is 253 and for EDU it is 136).