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Factors That Predict Magnitude, Timing, and Persistence of Placebo-Like Response in Patients With Irritable Bowel Syndrome

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Abstract

BACKGROUND AND AIMS: Placebo response impedes the development of novel irritable bowel syndrome (IBS) therapies and the interpretability of randomized clinical trials. This study sought to characterize the magnitude, timing, and durability of IBS symptom relief in patients undergoing a non-drug placebo-like control.

METHODS: One hundred forty-five Rome III-diagnosed patients (80% F, M age = 42 years) were assigned to education/nondirective support delivered over a 10-week acute phase. Treatment response was based on the IBS version of the Clinical Global Improvement Scale completed 2 weeks after treatment ended. Candidate predictors were assessed at baseline (eg, emotion regulation, pain catastrophizing, distress, neuroticism, stress, somatization, gastrointestinal-specific anxiety) or clinically relevant points during treatment (patient-provider relationship, treatment expectancy/credibility).

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Authors' Contributions:

Authored the study concept and design: Jeffrey M. Lackner, Brian M. Quigley, and Paul Enck. Drafted the manuscript: Jeffrey M. Lackner, Brian M. Quigley. Critically revised the manuscript for important intellectual content: all authors. Contributed to the statistical analysis: Brian M. Quigley. Obtained funding; Jeffrey M. Lackner. Supervised the study: Jeffrey M. Lackner, Gregory D. Gudleski, Christopher D. Radziwon, and Susan S. Krasner.

Conflicts of Interest:

The authors disclose no conflicts.

Ethical Statement:

The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research. Ethical approval was approved by site-specific institutional review boards.

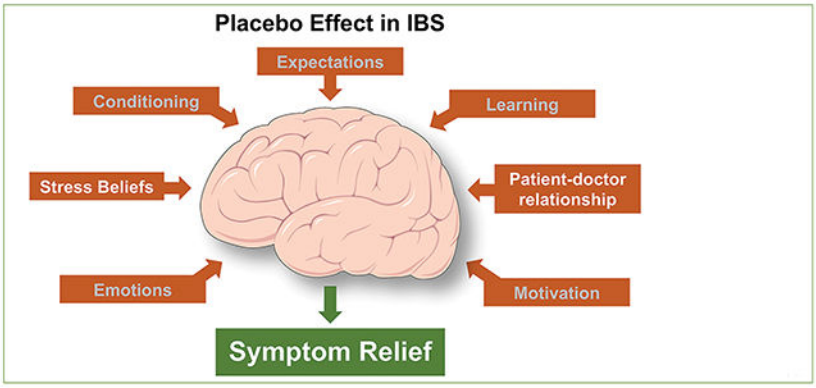
Reporting Guidelines:

Helsinki Declaration, STROBE.

RESULTS: Midtreatment response was associated with lower levels of stress and somatization at baseline and greater patient-provider agreement on treatment tasks ($P < .001$). Treatment response was associated with baseline gastroenterologist-rated IBS severity, anxiety, ability to reappraise emotions to reduce their impact [cognitive reappraisal], and agreement that provider and patient shared goals from provider perspective ($P < .001$). The day-to-day ability to reappraise emotions at baseline distinguished rapid from delayed placebo responders ($P = .011$).

CONCLUSION: Patient beliefs (eg, perceived stress, cognitive reappraisal) impacted the magnitude, timing, and persistence of placebo response measured at midway point of acute phase and 2 weeks after treatment discontinuation. Baseline beliefs that patients could alter the impact of stressful events by rethinking their unpleasantness distinguished rapid vs delayed placebo responders. Collaborative agreement between doctor and patient around shared tasks/goals from the clinician perspective predicted placebo response.

Graphical Abstract



Keywords

Placebo Effect; Emotion Regulation; Randomized Clinical Trials; Expectancies

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder affecting 5%–10% of the world's population.[1] Its clinical symptoms (abdominal pain with altered bowel habits such as diarrhea or constipation) are often refractory to available medical and dietary treatments.[2] When effective, medical therapies provide clinically meaningful relief in less than 50% of patients.[3]

Because IBS lacks a "gold standard" of treatment, candidate therapies develop in the context of randomized clinical trials that use placebo arm[4] as a comparator for characterizing the incremental benefit of a particular approach above and beyond the generic effects of simply initiating treatment due to the therapeutic benefit of clinical attention and common contextual factors that emerge as practitioners interact with patients (ie, therapeutic alliance, the mobilization of hope and optimism) not delineated as key theoretical properties believed to induce the proposed therapeutic effect. A relatively large (40%) placebo response in IBS trials[5,6] obscures potentially useful, mechanistic, and pharmacodynamically induced symptom changes among agents that do reach market.[7] This begs the question of what individual difference factors distinguish placebo responders. For clinical researchers,

understanding the factors that predict placebo response can inform the design of more sophisticated trials that precisely characterize therapeutic benefit due to specific (vs general) effects. For clinical gastroenterologists, harnessing the mechanisms underlying a placebo response can inform clinical decisions that optimize the therapeutic value of any treatment because, in clinical practice, the route to symptom relief is immaterial, whether it passes through active (drug action) or nonspecific pathways.

The search of placebo patient predictors in IBS patients has come from meta-analyses and secondary analyses from placebo-controlled trials and has struggled to answer the question of "who is a placebo responder?" Previous research has generally focused on baseline personal characteristics (eg, age, sex) and study design factors (eg, trial duration, number of sites, or study arms) with unreliable prognostic strength[8] or clinical utility for researchers or clinicians. Factors that arise during acute phase after treatment is initiated (eg, patient-provider dynamics[9]) when the placebo response is defined are not featured in meta-analyses of published trial data.[10,11] This limitation partly reflects the demands of efficacy trials that prioritize pre- and post-treatment data over that collected during acute phase, when the putative mechanisms underpinning placebo effects play out. The expectation that one can benefit from a treatment, for example, is optimally assessed after its rationale is delivered but before a clinically thorough regimen is provided, meaning that it cannot be fruitfully assessed at baseline along with other personal characteristics when treatment rationale is not fully disclosed. The same applies to relational factors such as patient-physician interactions[12] that define the context where treatment is delivered and placebo response presumably incubates.

Many methodological limitations of placebo analyses in IBS trials are effectively addressed in well-designed behavioral trials that collect broader set of data as part of mechanistic analyses aimed at characterizing factors that explain why, when, and how behavioral treatments work.[13,14] Because a placebo is inherently a psychological phenomenon[15–17] (its effects are that portion of the treatment effect that is induced by psychological rather than physical means), behavioral trials provide a rich source of information for understanding the general contours of how patients respond to nonspecific therapies because they tend to assess a larger pool of psychosocial variables that underpin placebo-like response (eg, patient beliefs[18]) than drug trials and are not subject to disclosure policy of industrial sponsors.[11]

In the present study, we aimed to identify responders who were assigned to a nonspecific control arm in a psychological (behavioral) trial that served as a highly credible, acceptable placebo-like comparator for the effects of general factors common to all treatment modalities. Common factors include belief in the credibility of treatment and the likelihood it will induce clinically meaningful symptom relief (ie, expectancy), the therapeutic alliance between clinician and patient,[19] and a clear and compelling biomedical treatment rationale for why patient has developed symptoms, and the role that assigned treatment has in relieving symptoms.[20] We were particularly interested in understanding the rate of response (rapid vs delayed), whether the rapidity of response predicted treatment response in the placebo-like nonspecific comparator, and whether (or not) patient characteristics and patient-clinician interactions differentially predicted the response patterns. Based on

prior research[21–23] showing that rapidity of IBS symptom relief influenced trajectory of outcome for both behavioral and pharmacological treatments, we predicted that patients who demonstrated a rapid response by week 5 of 10-week acute phase would have a more sustained placebo response at the end of treatment than those whose response was more delayed (ie, IBS symptom improvement at posttreatment after week 10). A second goal was to explore the psychological makeup of rapid vs delayed placebo responders. We reasoned *a priori* responders to an expectancy-based placebo treatment would be distinguished by cognitive factors (ie, patient beliefs) including the strength of expectancy for improvement, how credible they regarded treatment for relieving their symptoms, control beliefs, their ability to reappraise stressful events in everyday life, pain catastrophizing, and GI-specific anxiety. A final goal was to characterize the strength of behavioral factors in predicting treatment response at mid- and post-treatment. We predicted cognitive and patient-provider interaction factors (eg, collaboration around tasks toward shared goals) would, on the basis of prior research, be more broadly operative at both stages.

Methods

Study Sample

The present study is a secondary analysis of the Irritable Bowel Syndrome Outcome Study, a randomized controlled, parallel group trial that allocated patients into one of 3 conditions (clinic and home-based cognitive behavioral therapy (CBT), education/support) at 2 sites (University at Buffalo, Northwestern University). Adults (18–70 years) whose IBS symptoms were at least moderately severe, unexplained by comorbid organic GI disease, and met Rome III diagnosis for IBS[24] were eligible. Methodological details and information consistent with the Strengthening the Reporting of Observational Studies in Epidemiology checklist[25] (eg, exclusion criteria) are provided elsewhere.[26,27] Of 464 subjects, 145 patients (79% F, M age = 42 years) were randomized to the nonspecific arm that was our primary focus. Ethical approval was approved by site-specific institutional review boards. All authors had access to the study data and reviewed and approved the final manuscript. See Table 1 for sample characteristics.

Treatment Administration

The placebo-like control was structurally equivalent to the active CBT condition (eg, time, attention) and was engineered to include 2 ingredients necessary for a state of the art placebo: (1) a highly acceptable and credible intervention that induces the expectation of therapeutic benefit through support and the opportunity to express their experiences and feelings about the daily symptom burden of their condition and strengthens their understanding of its underlying symptom drivers (eg, stress, dietary triggers, etc.) and guided patient education,[28,29] and (2) attention “much like drug trial combines clinical attention with pill placebo”.[30]

Primary outcome measure.—Per recommendations for functional GI disorders and chronic pain clinical trials,[31,32] the primary outcome measure involved the IBS version[33] of the Clinical Global Impressions-Improvement Scale (CGI-I)[27,34] consisting of 7-point scale rating overall improvement where patients rated as either moderately improved or

substantially improved qualified as placebo responders. Rapid responders met responder criteria for both week 5 (session 2) and posttreatment follow-up (week 12). Delayed responders only met responder criteria at follow-up.

Predictors.—Potential predictor variables were organized into 4 groups (see Table 1). *Demographics* (eg, age, race, sex), *clinical* (eg, MD severity rating,[33] overall IBS severity[35]), and *psychological* (eg, pain catastrophizing,[36] neuroticism,[37] intense worry,[38] distress,[39] perceived stress,[40] ability to reappraise the emotional unpleasantness of a stressful event,[41] control beliefs[42,43]) were assessed at pretreatment baseline. The fourth group (*Nonspecific treatment variables* such as treatment expectancy,[44] quality of doctor-patient relationship[45] rated by both patient and provider) was assessed at end of visit 1.

Statistical Analysis Plan

Data analysis was conducted to examine the demographic, clinical, psychosocial, and treatment-related variables related to global IBS symptom improvement in nondirective support-treated patients. To determine predictors of treatment response, responder status at treatment midpoint and posttreatment were regressed on potential predictors within 4 conceptually distinct domains described above. Zero-order correlations were conducted between the factors in each domain and mid- and post-treatment responses to determine the variables that significantly correlated with response. Variables that showed significant correlation with either response were retained for the regression analyses. Variables were entered in a forward fashion in each regression block such that only the variables that were significant in the previous block were retained for the subsequent blocks.

Individuals who showed rapid response were then compared to individuals who showed delayed placebo response on the variables that were significant in the final regression models. Student's t-tests and corresponding effect sizes (Cohen's *d*) with the 95% confidence intervals were calculated for all these comparisons.

Results

Sample Characteristics and Zero-order Correlations

Table 1 displays the means and standard deviations for all continuous variables and percentage breakdowns for all categorical variables within each of the predictor domains described above, as well as the correlation of each factor with mid- and post-global improvement. Within demographics, no variables significantly predicted mid- or post-treatment global improvement. Within the clinical characteristics domain, only MD rating of IBS severity and impact were significantly correlated with posttreatment response. Among psychological factors, catastrophizing, perceived stress, somatization, depression, and cognitive reappraisal significantly predicted midtreatment response. Posttreatment response was predicted by anxiety. Within the final block of nonspecific treatment predictors, patientrated agreement with providers on treatment tasks and goals was correlated with midtreatment response. Posttreatment response correlated with patient rating of the likelihood treatment would work, patient estimate of the suitability of treatment, patient

and clinician ratings of the expected success of treatment, and provider-rated agreement with patient on treatment goals.

Treatment Response at Midtreatment and Posttreatment

Of 145 placebo-treated patients, 22.1% (n = 31) showed a rapid response by week 5 of the 10-week treatment phase. Among those only demonstrating response posttreatment, 47.3% were categorized as delayed responders (see Table 2).

Predicting Global IBS Improvement at Midtreatment and Posttreatment

The first regression was conducted to identify predictors of global improvement at midtreatment (Table 3). The final regression equation was significant, F (5,114) = 6.02, $P < .001$, and accounted for 17% of the variance in midtreatment global improvement, CGI, $R^2 = 0.174$. Significant predictors were perceived stress, somatization, and patientrated task agreement with provider. Patients high on stress and somatization showed less global improvement at midtreatment; however, those who saw greater agreement with provider on treatment tasks saw greater global improvement.

The regression analysis conducted revealed the strongest predictors of global improvement at posttreatment (Table 3, F (4,111) = 7.92, $P < .001$), accounting for 19% of the variance in posttreatment CGI ($R^2 = 0.194$). Posttreatment global improvement was predicted by MD illness severity rating. More severely ill-rated patients at pretreatment showed greater global improvement at post treatment. Additionally, those with higher anxiety and greater cognitive reappraisal abilities at baseline showed greater global improvement at post treatment. Finally, provider rating of goal agreement at the end of session 1 was positively related to post treatment global IBS improvement.

Variables Distinguishing Responders at Treatment Midpoint From Responders at End of Treatment

As Table 2 shows, among those with a placebo-like response at midtreatment, 75% maintained response at posttreatment; among those not showing response at mid treatment, 40% showed positive response at posttreatment. An analysis was conducted to determine if predictor variables identified in the previous analyses distinguished between rapid sustained and delayed responders (see Table 4). Only cognitive reappraisal significantly distinguished the 2 groups with rapid responders more reliant on their ability to rethink stressful events than delayed responders, odds ratio = 1.14 (95% confidence interval = 1.01 / 1.29). When age and sex were added as covariates, the difference between these rapid and delayed responders on cognitive reappraisal continued to be significant.

Discussion

This study shows that patient beliefs had an impact on the timing and persistence of placebo response measured midway during a 10-week acute phase and posttreatment 2 weeks after treatment ended (week 12). Particularly important beliefs were baseline patients' beliefs that they could alter the impact of stressful events by reframing their unpleasantness (ie, cognitive reappraisal) in everyday life. Cognitive reappraisal ability was the only

variable that predicted both mid and end of treatment placebo-like responses. The ability to reappraise stressful events to reduce their subsequent impact differentiated IBS patients who evidenced a rapid and enduring placebo response from those who achieved a more delayed positive treatment response posttreatment.

Further research is needed to see whether a reappraisal thinking style is a stable phenotype across other nonspecific treatments (eg, pill or dietary placebo). In the meantime, there is reason to believe that study findings are not idiosyncratic to behavioral placebo. The finding that baseline ability to rethink the unpleasantness of stressful events to reduce their impact (cognitive reappraisal) distinguished rapid vs delayed placebo maps onto neuroimaging research[46] shows a positive correlation between cognitive reappraisal scores and placebo analgesia-induced activation in prefrontal cortex regions that also showed increased placebo-induced functional connectivity with the midbrain periaqueductal gray, a key node of the "top down" (inhibitory) pain-modulating circuit and the main output pathway of the limbic system. The fact that these findings were observed in healthy controls administered a topical cream as a placebo analgesia agent supports the generalizability of study findings (namely that the placebo effect was related to individual differences in cognitive reappraisal). The finding that cognitive reappraisal predicts both placebo analgesia and psychological placebo is a striking finding that contributes to what is known about placebo responses in general.

Clinical Implications

The prognostic value of how patients regulate date-today emotions may have important implications for clinical gastroenterologists, for whom the relative contribution of specific vs general effects is subordinate to their overarching goal of optimizing therapeutic benefit of a prescriptive therapy. People vary in when and how they modulate emotions of stressful events and their capacity to regulate their emotional fallout.[47,48] Some use tactics designed to alter the way they behaviorally respond to emotionally charged events (emotional suppression) once an emotion is full-blown (eg, hide feelings and pretend not to feel upset, maintain composure). Others rely more proactively on their ability to reframe an event in a way that dampens its emotional impact (cognitive reappraisal). In this study, cognitive reappraisal differentiated rapid vs delayed responders in the placebo condition. It is possible that people who use cognitive reappraisal as a pre-emptive way of neutralizing an adverse emotional response may have a stronger understanding of the relationships linking situational triggers to their responses consisting of thoughts, emotions, somatic sensations like pain, and behaviors, understand when these triggers and chains go haywire, and are primed to benefit from what a placebo offers. Low-intensity strategies that teach more adaptive reappraisal skills may help pharmacologically treated IBS patients get the most out of medications by optimizing their general effects. This may call for physicians to exploit both the specific and general effects of a pharmacotherapy by not focusing exclusively on its intrinsic pharmacodynamic effects but simultaneously emphasizing the added value that comes to patients who believe they can regulate emotions through practical emotion regulation strategies (eg, the ability to identify and label emotions, understand their purpose, knowing how beliefs about a situation can influence reactions). This can be challenging for physicians whose biomedical training emphasizes detachment (eg, staying calm and maintaining a dispassionate professional attitude toward the patient with the goal

of optimizing medical objectivity necessary for clinical decision-making) through emotional suppression tactics. Alternative regulatory strategies that emphasize emotional engagement through empathy, encouragement, and psychosocial talk are important to patients and have been linked to clinical competence and performance as well as the quality of the physician-patient relationship.[49–52]

Limitations and Future Directions

Our findings should be interpreted in light of several limitations. First, the generalizability of data depends to some extent on the assumption of uniformity among a psychological placebo, sham surgery, or pill placebo.[53] To be sure, there are notable differences in the composition of these placebos, route of administration, and the context in which and by whom they are delivered. The unifying and defining characteristics of placebos (ie, what makes a placebo compound a placebo treatment) are that they are delivered in a healthcare context whose activating properties include 2 ingredients: clinical attention and a credible biomedical treatment rationale that is a sufficiently acceptable and credible intervention to induce expectation of therapeutic benefit.[30] Placebo effects are defined by procedural commonalities across modalities, not their technical differences. In drug-placebo studies, placebo-enhancing properties (eg, positive expectancy) are delivered via an inert chemical compound. In this study, education and support are vehicles that constitute a state of the art psychological placebo.[30,54] The alternative term “attention control” condition is regarded as “too restrictive”[53] because it does not capture relational components of nonspecific condition (eg, provider-patient interactions).

Building a cohesive body of knowledge about the placebo effect requires a shared lexicon of nonspecific processes that underlie the general effects of treatments we as researchers and clinicians offer, whether they are behavioral, pharmacological, procedural, etc. The efforts are stymied if sham procedure, pill placebo, and psychological control researchers use language that treats their respective nonspecific effects as specific to the procedure with which they have familiarity or allegiance. For these reasons, we have subscribed to the definition of placebo interventions in clinical trials.[55] as *“a control intervention with similar appearance as the experimental treatment but void of the components in the experimental intervention whose effects the trial is designed to evaluate”*[56] *In this respect, education*/support *functions as a placebo. At the same time*, we have deferentially used the term “placebo-like” in this paper to reflect our acknowledgment of differences between a psychological placebo and pill placebo featured in IBS drug trials and lack of clear consensus about terminology among placebo researchers.[57]

This study, like all outcome studies, is subject to selection bias that arises from recruiting volunteers. It is very possible that enrolled subjects (recruited from 2 geographically distinct clinics) may have been more psychologically minded than volunteers to a drug trial, but this would not explain the between-group differences between the placebo (44%) and experimental (CBT, 58%) arms on global IBS improvement.[27] We do not believe that regression to the mean or temporal change effects[58] (eg, natural history) account for findings, as we have previously found that an untreated control group of IBS patients showed persistent IBS symptoms 3 months posttreatment follow-up, not observed in the

experimental condition. Further, the sample presented with highly treatment-refractory (eg, chronic, impaired quality of life[2]), symptoms whose average illness duration (17 years) was well outside the range (1–9 years postdiagnosis) where one can expect prolonged symptom-free periods.[59,60] Had symptom relief reflected fluctuating temporal changes, we would see a more "waxing and waning" symptom course posttreatment than relatively stable symptom pattern we observed[61] after treatment was discontinued.

Our sample represented a relatively homogeneous sample (eg, 80% female, mostly Caucasian), and results may not generalize to more diverse populations elsewhere. It is not clear whether the pattern of these data would generalize to other measures of alliance such as the Patient-Physician Relationship Scale.[62] We used the Working Alliance Inventory,[45] the most common measure used in behavioral outcome research to measure practitioner-provider interactions. Its conceptual model holds that working relationship between patient and provider consists of 3 elements: agreement on the goals of the treatment, agreement on the tasks to achieve these goals, and the quality of a personal bond made up of reciprocal positive feelings between patient and practitioner. An optimal alliance presumably occurs when patient and practitioner agree on the goals of treatment and view the techniques used to achieve them as credible and efficacious toward achieving treatment goals. Our data dovetail with other research showing that the collaborative agreement on the goals of treatments is critical to shaping health outcomes.[14,19,63] The fact that the emotional bond between practitioner and patient did not emerge as a predictor does not mean that an empathic and supportive bond is unimportant, only that it is subordinate to agreement around tasks/goals in predicting placebo-like effects during and after acute phase. Our data build on the seminal work of Drossman[19] by accentuating the strong therapeutic value of practitioners and IBS patients collaborating around shared goals and tasks. It is possible that task/goal agreement is particularly vital in shaping the alliance-outcome relationship as it relates to symptom improvement regardless of modality or the theory upon which it is based. The magnitude of effect sizes needs to be appreciated in light of operative nonspecific processes common to all treatment and independent of their specific effects, which were not our focus. Finally, one may wonder whether the effects are due to noneven distribution of nonspecific factors such as placebo-expectancy, alliance, etc.). In fact, nonspecific factors were evenly distributed across both conditions by virtue of randomization process and exerted a therapeutic impact during acute phase. This emphasizes a methodological strength of the study (and a limitation of the field in general), which is to conduct more regularly scheduled assessment at baseline and during acute phase. We do not believe that the relationship of cognitive appraisal and treatment response is cofounded by treatment, given that cognitive appraisal was assessed at pretreatment baseline before treatment began.

Conclusion

The strength of placebo responsiveness is subject to the influence of patient factors that precede treatment delivery (rethinking or reinterpreting stressful situations in everyday life in a way that reduces their subsequent impact) and specific elements of provider-patient interactions that occur while treatment is delivered particularly *practitioners*' estimation that patients agree on their goals and tasks to achieve them. We believe this line of research can help identify factors that drive placebo response and narrow the patient-provider

"mismatch"[3] that undermines the quality, satisfaction, and efficiency of IBS care regardless of what treatment is delivered.

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Data Transparency Statement:

Data from the Irritable Bowel Syndrome Outcome Study [(V1)/https://doi.org/10.58020/waer-b554] reported here are available for request at the NIDDK Central Repository (NIDDK-CR) website, Resources for Research (R4R), https://repository.niddk.nih.gov/.

Abbreviations used in this paper:

CBT	cognitive behavioral therapy
CGI	Clinical Global Impressions Scale
F	female
GI	gastrointestinal
IBS	irritable bowel syndrome
M	mean

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Table 1.

Sample Characteristics and Zero-Order Correlations With IBS Clinical Improvement

			r	r
Variable	**Mean (SD)**	**%**	**Mid Tx CGI**	**Post Tx CGI**
Demographics				
Age	42.19 (15.43)		0.013	−0.110
Gender (% female)		79.2%	−0.007	0.019
College or postgraduate		60.8%	−0.095	−0.024
Employed full time		54.2%	−0.169	−.001
Hispanic		2.8%	−0.148	0.031
Race (% White)		91.0%	0.000	0.074
Married		49.0%	0.010	−0.004
Income $40k or less		19.4%	0.028	0.132
Clinical characteristics				
IBS-C		32.4%	−0.139	−0.116
IBS-D		42.8%	0.121	0.074
IBS-M/U		24.8%	0.011	0.040
Age at symptom onset	24.45 (13.77)		0.030	0.012
Duration of symptoms (years)	17.74 (16.39)		−0.012	−0.114
Satisfaction with previous treatment	4.89 (2.51)		−0.063	0.102
Medical comorbidities, #	4.76 (4.97)		−0.151	−0.072
Psychiatric comorbidities, #	1.19 (1.71)		−0.161	0.153
MD rating of IBS severity	4.22 (0.86)		0.021	0.214[a]
MD rating of IBS impact	4.52 (1.23)		−0.033	0.207[a]
IBS symptom severity (IBS-SSS)	282.40 (71.02)		−0.029	0.102
Psychological factors				
Pain catastrophizing	2.60 (1.70)		−0.233[b]	0.024
Neuroticism	20.15 (5.62)		−0.160	0.152
Intense worry	25.35 (9.37)		−0.120	0.078
Perceived stress	6.82 (3.13)		−0.288[b]	0.037

Variable	Mean (SD)	%	r Mid Tx CGI	r Post Tx CGI
Anxiety sensitivity	23.31 (12.35)		−0.096	0.083
Somatization	4.54 (3.91)		−0.262[b]	0.020
Depression	4.03 (4.09)		−0.192[a]	0.098
Anxiety	5.02 (4.81)		−0.131	0.223[a]
Global distress	13.59 (10.81)		−0.225[b]	0.143
Cognitive reappraisal	28.09 (6.25)		0.227[b]	0.155
Emotional suppression	13.11 (5.36)		0.061	0.017
IBS Locus of control	90.58 (14.80)		−0.038	0.035
IBS Self-efficacy	97.60 (24.65)		0.144	−0.055
Nonspecific treatment factors				
Credibility of treatment - patient	7.10 (2.03)		0.119	−0.015
Importance of treatment goal - patient	72.25 (20.87)		−0.137	0.061
Likelihood of achieving of treatment goal - patient	59.37 (26.83)		0.140	0.206[a]
Expectancy that symptoms will improve - patient	54.95 (23.19)		0.115	0.134
Estimate of suitability of treatment - patient	7.46 (2.19)		0.138	0.186[a]
Expected success of treatment - patient	6.86 (2.00)		0.108	0.249[b]
Estimate of suitability of treatment - provider	5.86 (1.73)		−0.069	−0.038
Expected success of treatment - provider	5.45 (1.47)		0.077	0.220[a]
Working alliance- goal agreement - patient	14.99 (3.74)		0.220[a]	0.122
Working alliance- task agreement - patient	13.50 (3.63)		0.174[a]	0.092
Working alliance- bonding - patient	16.30 (3.25)		0.059	0.053
Working alliance- goal agreement - provider	21.59 (3.26)		0.124	0.276[b]
Working alliance- bonding - provider	18.27 (1.90)		0.150	0.079

[a] $P < .05$.

[b] $P < .01$.

Table 2.

Responder Status Based on Patient CGI at Midtreatment and Posttreatment

Midtreatment status	Nonresponder post	Responder post	Total
Nonresponder midtreatment	61	40	101
	60.4%	39.6%	100%
Responder midtreatment	7	21	28
	25.0%	75.0%	100%
Total	68	61	129
	52.7%	47.3%	100%

CGI, Clinical Global Impressions Scale where treatment responder = much/very much improved at posttreatment follow-up.

Table 3.

Logistic Regression Outcomes for Midtreatment and Posttreatment Placebo-Like Response

	Midtreatment response			Posttreatment response	
Step		**b**	**Step**		**b**
Model 1	Perceived stress	−0.290	Model 1	MD rating IBS severity	0.247
Model 2	Perceived stress	−0.239	Model 2	MD rating IBS severity	0.257
	Somatization	−0.215		Anxiety	0.211
Model 2	Perceived stress	−0.255	Model 3	MD rating IBS severity	0.267
	Somatization	−0.248		Anxiety	0.254
	Task agreement - patient	0.246		Cognitive reappraisal	0.227
			Model 4	MD rating IBS severity	0.242
				Anxiety	0.249
				Cognitive reappraisal	0.189
				Goal agreement (provider)	0.238

b, beta weight.

Table 4.

Comparisons of Rapid Responders vs Delayed Responders on Characteristics Related to Treatment Response

Variable	Delayed responders (wk. 12)	Rapid responders (wk. 5-Post)	t	d (95% CI)
n	39	21		
Perceived stress	7.38 (2.99)	6.00 (3.07)	t = 1.70, *P* = .095	d = 0.46 (−0.08/0.99)
MD rating IBS	4.30 (0.69)	4.43 (0.87)	t = −0.63, *P* = .265	d = −0.17 (−0.70/0.36)
Depression	5.23 (4.69)	3.52 (3.35)	t = 1.47, *P* = .146	d = 0.40 (−0.14/0.92)
Somatization	5.18 (4.38)	3.38 (3.60)	t = 1.61, *P* = .113	d = 0.43 (−0.10/0.97)
Anxiety	7.05 (5.07)	4.52 (4.38)	t = 1.93, *P* = .058	d = 0.52 (−0.02/1.06)
Cognitive reappraisal	27.75 (4.38)	31.14 (5.53)	**t = −2.62, *P* = .011**	**d = −0.71 (−1.25/−0.16)**
Emotional suppression	12.32 (4.97)	14.86 (5.59)	t = −1.81, *P* = .075	d = −0.49 (−1.02/0.05)
Goals agreement patient	15.29 (3.76)	16.19 (3.63)	t = −0.89, *P* = .188	d = −0.24 (−0.78/0.29)
Tasks-agreement patient	13.79 (3.37)	14.29 (3.63)	t = −0.52, *P* = .602	d = −0.14 (−0.67/0.39)
Goal agreement- provider	22.05 (3.06)	22.76 (3.08)	t = −0.86, *P* = .393	d = −0.23 (−0.76/0.30)

CI, confidence interval; d, effect size. Bold indicates $P < .05$.