Psychological Predictors of Response to Open-Label Versus Double-Blind Placebo in a Randomized Controlled Trial in Irritable Bowel Syndrome

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ABSTRACT

Objective: There is growing evidence that open-label placebo (OLP) may be an efficacious treatment of chronic and functional conditions. However, patient-level predictors of response to OLP have not been clearly identified. The aim of this study is to evaluate the psychological predictors of response to OLP and to compare this to double-blind placebo (DBP) and no-pill control (NPC).

Methods: This study is a secondary analysis of data collected in a 6-week randomized controlled trial evaluating placebo effects in irritable bowel syndrome (IBS). The primary outcome was change in IBS severity. Hierarchical linear regression identified predictors of placebo response in general and compared them between those randomized to OLP, DBP, and NPC. Predictor variables included personality traits, generalized anxiety, depression, visceral sensitivity (a measure of symptom-specific anxiety), and pain catastrophizing.

Results: A total of 210 participants (mean age = 42.3 years, 73.3% female) were included. Regression models revealed that visceral sensitivity was a predictor of response to OLP and NPC but not DBP. Interestingly, the effects were opposite, with high visceral sensitivity predicting less improvement in NPC and more improvement in OLP. Pain catastrophizing was a negative predictor of response to OLP (i.e., high pain catastrophizing was associated with less improvement in OLP). Neither visceral sensitivity nor pain catastrophizing played a significant role for response to DBP.

Conclusions: IBS participants who score low on the Pain Catastrophizing Scale but high on the Visceral Sensitivity Index seem to benefit particularly from OLP. Our study suggests that different psychological mechanisms may be involved in DBP and OLP interventions.

Key words: placebo effect, open-label placebo, placebo mechanisms, irritable bowel syndrome, randomized-controlled trial.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder affecting approximately 4% of the adult worldwide population (1). IBS is increasingly being referred to as a disorder of gut-brain interaction to highlight the role of the gut-brain (i.e., mind-body) axis in symptom generation. IBS is characterized by abdominal pain and altered bowel habits (constipation and/or diarrhea), and it is associated with a significant reduction in quality of life, high health care utilization, and comorbidities with other chronic conditions (2–4). Treatment options for IBS typically include medical therapy, dietary, and life-style interventions as well as mind-body therapies, and the condition is best managed when approached from a biopsychosocial perspective (5). Less than 25% of IBS patients are very satisfied with their treatment, and innovative therapies are needed (6).

As with other chronic and functional conditions, the placebo effect in IBS is high, with a pooled placebo response rate of 40% in clinical trials (7). Although the placebo effect has largely been viewed as an impediment to demonstrating the efficacy of novel therapies, our team has evaluated whether the placebo effect could be used therapeutically to benefit participants with IBS. In an initial study (8), we demonstrated that prescribing placebo "open-label" (i.e., prescribing placebo without deception or blinding) resulted in a clinically significant improvement in symptoms compared with no treatment. We recently replicated and expanded upon these results in a fully powered study demonstrating that open-label placebo (OLP) was superior to no-pill control (NPC) and as efficacious as double-blind placebo (DBP) (9). In addition, OLP has been shown to be effective in the treatment of other

CBT = cognitive behavioral therapy, **DBP** = double-blind placebo, **GAD-7** = seven-item Generalized Anxiety Disorder, **IBS** = irritable bowel syndrome, **IBS-SSS** = Irritable Bowel Syndrome Severity Scoring System, **NPC** = no-pill control, **OLP** = open-label placebo, **PCS** = Pain Catastrophizing Scale, **PHQ-8** = 8-item depression scale of the Patient Health Questionnaire, **RCT** = randomized controlled trial, **VSI** = Visceral Sensitivity Index

SDC Supplemental Digital Content

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conditions, such as chronic back pain (10,11), allergic rhinitis (12), episodic migraine headache (13), cancer-related fatigue (14,15), and menopausal hot flushes (16). A meta-analysis of 13 randomized controlled trials (RCTs) found a significant overall effect favoring OLP versus no treatment (standardized mean difference = 0.72, 95% confidence interval = 0.39–1.05, $p < .001$) (17). These findings suggest that OLP may be an exciting new mind-body therapy for these conditions that are often treatment refractory and highly distressing to patients.

With growing evidence that OLP may be an efficacious treatment of chronic and functional conditions such as IBS, it is important to begin to understand whether there are patient-level characteristics that predict response to this novel intervention and to evaluate how they might compare with predictors of response to DBP. To date, very little research has been done to evaluate predictors of response to OLP. However, in laboratory models with healthy volunteers, positive expectations clearly correlate with higher placebo responses (18), and research evaluating predictors of response to DBP in IBS trials sometimes suggests that certain psychological factors, such as openness to experience, extraversion, and expectancy, may be implicated in the placebo response (18–22). Data from our recent, large RCT of OLP in IBS (9) found treatment expectancy to be associated with symptom relief in DBP but not OLP, which is consistent with previous OLP trials (11,16). In this study, we aimed to evaluate the psychological predictors of response to OLP, DBP, and NPC using data from our recently completed RCT (9). We hypothesized that personality traits, mental health variables, or the way patients deal with their symptoms may predict placebo responses. Given the lack of prior research on psychological predictors of OLP and whether they might differ from predictors of DBP, the present study should be considered hypothesis generating as opposed to hypothesis confirming.

METHODS

Study Design and Participants

This study is a secondary analysis of data collected in a large, 6-week RCT evaluating placebo effects in IBS ($N = 308$). Only 210 participants were included in the current analysis because a) we only included participants who completed the whole trial and had no missing data, and b) we did not analyze all treatment groups. The methods and results of the parent study are described in detail in the previously published protocol article (23) and in the publication of the primary findings of our parent study (9). Ethical and regulatory approvals were obtained from the Institutional Review Board for the Protection of Human Subjects at Beth Israel Deaconess Medical Center. All participants gave written informed consent.

Among other eligibility criteria, participants had to meet the Rome IV criteria for IBS, and their symptoms had to be at least moderately severe (defined as a score of ≥175 on the IBS Severity Scoring System [IBS-SSS] (24)). The parent study included a nested, double-blind, placebo-controlled RCT of enteric-coated peppermint oil (180 mg) to create ethical conditions for a DBP group. The inclusion of an active treatment arm was required to establish a true DBP condition without deceiving the participants (9), but the purpose of the study was to investigate and compare the placebo conditions. Participants were randomized in a 2:2:2:1 ratio to one of four groups as follows: a) NPC, b) OLP, c) DBP, and d) double-blind peppermint oil. Following the strategy of our published parent study (9), double-blind peppermint participants ($n = 46$) are not included in this article because the aim of the article and prespecified analysis plan is to identify the potential psychological predictors of placebo effects in OLP and DBP.

Before giving informed consent, all participants in the parent study received the same, semiscripted introduction to the study, which included three major points about placebo effects: a) placebo intake can cause clinically significant symptom relief in double-blind conditions; b) it is not known whether placebos can also be effective when applied "open-label," that is, without concealment; and c) it is not necessary to believe in the effectiveness of placebos to benefit from the placebo treatment. Depending on their group assignment, they received additional semiscripted information (see the supplement material, http://links.lww.com/PSYMED/A829). Participants in the OLP and DBP groups were instructed to take three pills a day for 6 weeks. Although OLP participants were aware that they were receiving placebo pills, in the DBP group, neither participants nor study personnel knew whether the pills were placebos or peppermint oil capsules. Participants in the NPC group did not receive placebo pills or peppermint oil capsules, but we explained the scientific importance of their group. In all groups, symptom severity was assessed via the IBS-SSS at baseline, after 3 weeks (midpoint) and after 6 weeks (end point). Total change in IBS symptom severity from baseline to end point serves as the outcome for the present analyses. Demographics and psychological measures were assessed at baseline and are included in the analyses to investigate their influence on symptom improvement.

Measures

IBS Severity Scoring System

The IBS-SSS is a well-established self-report instrument to assess IBS symptom severity with proven external validity, test-retest reliability, and sensitivity to change (24). The five items of the IBS-SSS each use a 0–100 visual analog scale to assess pain severity, pain frequency, severity of abdominal distension, satisfaction with bowel habits, and quality of life. The total score (range, 0–500) can be used to distinguish between mild (75–174), moderate (175–299), and severe (300–500) IBS symptoms. A change of at least 50 points is considered to be clinically significant (24).

Psychological Measures

The selection of psychological variables to analyze for IBS improvement was based on the previous literature. First, the personality traits extraversion, openness to experience, and agreeableness, as assessed by the NEO Five-Factor Inventory (25), were selected because they have been associated with a placebo response in IBS when the patient-clinician interaction was augmented with warmth and empathy (19). Second, depression and anxiety symptoms are common comorbidities of IBS (26), and a reduction in anxiety has been associated with larger placebo effects in IBS (27). Therefore, the eight-item depression scale of the Patient Health Questionnaire (PHQ-8), which is a reliable and valid instrument to assess depression severity (28–30), as well as the seven-item Generalized Anxiety Disorder scale (GAD-7), which is a reliable and valid tool to measure the severity of generalized anxiety disorder (31), were included in the analyses. Finally, because pain catastrophizing and visceral sensitivity are linked to IBS severity (32–34), the Pain Catastrophizing Scale (PCS) (35) and the Visceral Sensitivity Index (VSI) (36) were included as potential predictors of symptom improvement. Although the PCS measures catastrophizing thoughts related to pain experience in general, the VSI assesses anxiety that is specific to gastrointestinal symptoms.

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics 24. The significance level was set at $p < .05$. To identify the potential predictors of change in IBS symptom severity, a hierarchical linear regression analysis was conducted. In the hierarchical linear regression, several independent variables are entered block-wise to test whether they contribute incrementally to predicting the outcome. Our outcome variable, symptom severity change, was defined as the difference between IBS-SSS total scores at baseline and at end point. Thus, positive IBS-SSS change scores indicate symptom improvement. Because treatment group was a nominal variable, it could not be included directly in linear regressions. Therefore, two orthogonal

contrast variables were coded: treatment contrast 1 compares NPC with both placebo conditions, whereas treatment contrast 2 compares OLP and DBP (Supplementary Table S1, http://links.lww.com/PSYMED/A829).

The major aims of this study were a) to identify predictors of placebo response *in general* (i.e., OLP and DBP combined) as compared with improvement during NPC, and b) to identify predictors of placebo response that are *specific* to either OLP or DBP. Therefore, we were especially interested in the statistical interactions between each of the two treatment contrasts with the predictor variables to determine whether any of the predictors plays a differential role among the different treatment conditions. Therefore, for each predictor variable, the interaction terms with the two treatment contrasts were also entered into the model. To compute these interaction terms, continuous variables were first centered before multiplying them with the orthogonal treatment contrast variables. Thus, each regression model added a set of new predictor variables (either exploring main or interaction effects) while still including all of the predictor variables from the previous models to control for their influence. In total, eight regression models were tested within the hierarchical linear regression.

The first model (model 1) of the regression included treatment group (treatment contrasts 1 and 2) as well as demographic variables and baseline symptom severity to control for their influence on symptom severity change. Model 2 added interaction terms of treatment contrasts 1 and 2 with the variables included in model 1 to investigate whether the influence of these initial variables on symptom improvement differed between the treatment groups. The purpose of all the following models was to explore potential psychological predictors of both general and treatment-specific symptom improvement. Model 3 included extraversion, openness, and agreeableness, and model 4 added treatment contrast interaction terms with these variables. Model 5 included depression as assessed by the PHQ-8 and generalized anxiety as assessed by the GAD-7, and model 6 added treatment contrast interaction terms with the PHQ-8 and GAD-7. Model 7 included the PCS and VSI, and model 8 added the interaction terms of the treatment contrasts with the PCS and VSI.

To explore significant interaction terms further and to identify specific predictors for the different treatment conditions, sensitivity analyses using the same hierarchical regression models were performed within each group. In these three post hoc analyses, baseline symptom severity and the basic demographics were again included in the first model (model A) to control for their influence. In the models that followed (models B–D), only the variables that had interacted significantly with any of the treatment contrasts were included.

Given the large number of predictors in the multiple regression analyses, we ran tests for multicollinearity, which suggested that these regressions do not suffer from multicollinearity (e.g., the variance inflation factor for all predictors was >5). See the supplementary material, http://links.lww.com/PSYMED/A829, for additional details.

RESULTS

Participant Characteristics

The current analysis includes participants who were randomized to OLP, DBP, or NPC and completed the trial ($n = 211$). Details about power analysis, participant flow, and characteristics are provided in the parent publication (9). Those who were not included in the parent article (e.g., major protocol violations) were also excluded from our analyses. One additional NPC participant was excluded from the current analyses because of missing data on one of the predictor variables. Thus, 210 participants (mean age = 42.3 years, 73.3% female) were included in the current analyses ($n = 68$ in OLP; $n = 71$ in DBP; $n = 71$ in NPC). Table 1 shows the participant characteristics at baseline of all variables included in the analyses.

Predicting Overall Symptom Severity Change

A statistical summary of all eight models is provided in Table 2. Model 1 accounted for 9.6% of the variance in symptom severity change, and this model was statistically significant ($R^2 = 0.096$; $F(5,204) = 4.31$; $p = .001$). Models 2 to 7 did not account significantly for additional variation in symptom severity change (Table 2). Model 8, in which the interaction terms for the two treatment contrasts with both the VSI and PCS had been added as a new block, contributed significantly to predicting the outcome by accounting for an additional 5.1% of variance in symptom severity change ($R^2 = 0.273$; $F(4,177) = 3.07$; $p = .018$).

The coefficients of all predictors included in the two significant models are shown in Table 3, whereas predictor coefficients of all

TABLE 1. Participant Characteristics at Baseline

	NPC ($n = 71$)	OLP ($n = 68$)	DBP ($n = 71$)
Sex, *n* (%)			
Female	50 (70.4)	52 (76.5)	52 (73.2)
Male	21 (29.6)	16 (23.5)	19 (28.4)
Age, M (SD), y	40.65 (16.54)	43.60 (17.95)	42.55 (19.59)
Baseline IBS-SSS, M (SD)	268.63 (67.88)	282.12 (57.79)	280.03 (68.29)
NEO-FFI personality traits, M (SD)			
Extraversion	27.17 (8.34)	27.79 (7.24)	28.35 (8.20)
Openness	30.42 (6.26)	32.01 (6.38)	32.92 (6.91)
Agreeableness	35.31 (5.43)	36.38 (5.97)	35.62 (5.84)
PHQ-8, M (SD)	5.66 (5.61)	4.49 (4.20)	5.24 (4.97)
GAD-7, M (SD)	5.55 (5.67)	3.96 (4.29)	4.65 (4.26)
PCS, M (SD)	15.30 (11.00)	15.99 (10.95)	15.76 (12.06)
VSI, M (SD)	40.31 (18.67)	43.51 (14.68)	45.58 (16.38)

NPC = no-pill control; OLP = open-label placebo; DBP = double-blind placebo; M (SD) = mean (standard deviation); IBS-SSS = Irritable Bowel Syndrome Severity Scoring System (score range, 0–500); NEO-FFI = NEO Five-Factor Inventory (score range for each scale, 0–48); PHQ-8 = depression scale of the Patient Health Questionnaire (score range, 0–24); GAD-7 = seven-item Generalized Anxiety Disorder scale (score range, 0–21); PCS = Pain Catastrophizing Scale (score range, 0–52); VSI = Visceral Sensitivity Index (score range, 0–75).

TABLE 2. Statistical Summary of the Multiple Regression Models

Model	R^2	SE of the Estimate	Change Statistics			
			F	df_1	df_2	p
1	**0.096**	90.74	**4.31****	5	204	**.001**
2	0.132	90.23	1.39	6	198	.22
3	0.139	90.55	0.54	3	195	.66
4	0.184	89.56	1.73	6	189	.12
5	0.198	89.27	1.61	2	187	.20
6	0.205	89.81	0.44	4	183	.78
7	0.222	89.33	1.99	2	181	.14
8	**0.273**	87.36	**3.07***	4	177	**.018**

Significant effects are highlighted in bold format.

Outcome variable is symptom severity change from baseline to end point (measured by the IBS-SSS). Model 1 includes treatment contrasts 1 and 2, sex, age, and baseline symptom severity. Model 2 additionally includes interaction terms of treatment contrasts 1 and 2 with sex, age, and baseline symptom severity. Model 3 additionally includes extraversion, openness, and agreeableness. Model 4 additionally includes interaction terms of treatment contrasts 1 and 2 with extraversion, openness, and agreeableness. Model 5 additionally includes depression as assessed by PHQ-8 and anxiety as assessed by the GAD-7. Model 6 additionally includes interaction terms of treatment contrasts 1 and 2 with the PHQ-8 and GAD-7. Model 7 additionally includes the PCS and the VSI. Model 8 additionally includes interaction terms of treatment contrasts 1 and 2 with the PCS and VSI.

SE = standard error; *df* = degrees of freedom; IBS-SSS = Irritable Bowel Syndrome Severity Scoring System; GAD-7 = seven-item Generalized Anxiety Disorder scale; PCS = Pain Catastrophizing Scale; VSI = Visceral Sensitivity Index.

*Significant effect with $p < .05$.

**Significant effect with $p < .01$.

other models are provided in the supplementary material (Table S2, http://links.lww.com/PSYMED/A829). In model 1, the first treatment contrast had a significant influence on the outcome ($\beta = -0.191$; $p = .005$), indicating that symptom improvement was significantly greater in the placebo groups than in NPC. Treatment contrast 2 did not have a significant effect ($\beta = -0.047$; $p = .48$), indicating that OLP and DBP did not differ significantly in their symptom severity change. Age and sex did not influence the outcome significantly. Although higher baseline symptom severity was associated with greater symptom improvement ($\beta = 0.212$; $p = .002$), this is most likely due to the statistical artifact of regression toward the mean. In model 8, baseline symptom severity is the only predictor variable with a significant main effect ($\beta = 0.250$; $p = .002$). However, several interaction terms of treatment contrast 1 with other predictors have significant effects in this model. This indicates that agreeableness, the VSI, and the PCS might play a different role for symptom severity change in the two placebo conditions compared with NPC. It is important to note that none of the interaction terms of treatment contrast 2 with other predictors are statistically significant, which means that the predictors that are further explored hereinafter do not significantly differ between OLP and DBP.

Predicting Treatment-Specific Symptom Severity Change

To further explore the influence of agreeableness, visceral sensitivity, and pain catastrophizing on the effects of the different treatment conditions, they were included as predictors in three post hoc hierarchical regression analyses conducted separately for each treatment condition. Age, sex, and baseline symptom severity were also included in these sensitivity analyses to control for these basic characteristics. Table 4 represents the main statistics of these analyses, with Model D representing the final model in the linear regression.

No-Pill Control

Higher visceral sensitivity was associated with less symptom improvement during NPC ($\beta = -0.507$; $p = .004$). In contrast, higher agreeableness was associated with *greater* symptom improvement during NPC ($\beta = 0.309$; $p = .021$).

Open-Label Placebo

In OLP, the VSI and PCS were both significant predictors (Table 4). The effect of the PCS was negative ($\beta = -0.461$; $p = .005$), indicating that symptom improvement—that is, a beneficial OLP effect—was associated with lower pain catastrophizing at baseline. Surprisingly, the VSI had a positive effect ($\beta = 0.369$; $p = .030$), which suggests that higher visceral sensitivity was associated with greater symptom improvement in OLP. This is remarkable for two reasons: a) VSI had a *negative* effect in NPC, and thus, its influence is the opposite in OLP as compared with NPC, and b) the VSI and PCS have opposite effects in OLP, although, because they measure similar constructs, they are positively correlated, and this positive correlation is even very high ($r(68) = 0.63$; $p < .001$ in OLP). Furthermore, neither VSI nor PCS had significant effects when included in the analysis without each other. This becomes evident in model C as presented in Table 4, where PCS is not included and the influence of the VSI is not significant, which is also true vice versa (data not shown). This OLP-specific phenomenon of significant but opposite effects of the VSI and PCS on the one hand, but nonsignificance when included without the respective other variable on the other hand (Figure 1), is very robust: It is evident in a regression analysis only including these two variables as predictors, and it is still evident in a multiple regression analysis controlling for all demographic and psychological variables that have been included in the overall analysis (data not shown). This indicates that the effect of the VSI suppresses the effect of the PCS and vice versa when they are included separately. Thus, only when the influence of the respective other is controlled, that is, the overlapping part is taken out, the unique parts of these two variables seem to predict the treatment outcome. As a consequence, these unique parts of the two questionnaires might present actual psychological OLP mechanisms, which is outlined in the Discussion section.

Agreeableness had a significant, negative effect in OLP but only when the VSI and PCS were also included (model B: $\beta = -0.138$, $p = .30$; model D: $\beta = -0.266$, $p = .048$). Thus, the influence of agreeableness in OLP might be opposite than in NPC but does not seem to be as robust as the positive effect in NPC.

Double-Blind Placebo

Baseline symptom severity had a significant effect on symptom severity change in DBP (p values of all models $\leq .007$). None of the other predictor variables influenced the outcome of DBP treatment significantly (Table 4). Although we cannot interpret a statistical difference between OLP and DBP because the respective interaction effects in the overall regression were not significant (see the Predicting Overall Symptom Severity Change section), it is remarkable that the noticeable effects of the VSI and PCS in the OLP condition are not evident in DBP, and even close to zero (p values $\geq .91$).

DISCUSSION

This study reports the results of a secondary analysis of a large RCT evaluating placebo effects in IBS. The primary aim of the

TABLE 3. Predictor Coefficients of Significant Linear Regression Models

	b (95% CI)	SE	*β*	*p*
Model 1				
Constant	−22.38 (−92.13 to 47.37)	35.38		.528
Treatment C1[a]	−12.64 (−21.42 to −3.87)	4.45	**−0.191****	**.005**
Treatment C2[b]	−5.48 (−20.67 to 9.72)	7.71	−0.047	.478
Sex	14.46 (−13.53 to 42.46)	14.20	0.068	.310
Age	0.18 (−0.51 to 0.88)	0.35	0.035	.603
Baseline IBS-SSS	0.31 (0.11 to 0.50)	0.10	**0.212****	**.002**
Model 8				
Constant	−83.45 (−208.03 to 41.13)	63.13		.188
Treatment contrast 1 (C1)[a]	−0.29 (−17.51 to 16.92)	8.72	−0.004	.973
Treatment contrast 2 (C2)[b]	0.76 (−31.82 to 33.34)	16.51	0.007	.963
Sex	8.71 (−21.26 to 38.67)	15.18	0.041	.567
Age	0.09 (−0.69 to 0.87)	0.40	0.017	.821
Baseline IBS-SSS	0.36 (0.13 to 0.59)	0.12	**0.250****	**.002**
Interaction C1 by sex	−19.38 (−39.74 to 0.97)	10.32	−0.248	.062
Interaction C1 by age	−0.34 (−0.93 to 0.25)	0.30	−0.089	.252
Interaction C1 by baseline IBS-SSS	−0.11 (−0.26 to 0.05)	0.08	−0.105	.180
Interaction C2 by sex	−6.91 (−44.99 to 31.18)	19.30	−0.052	.721
Interaction C2 by age	0.31 (−0.59 to 1.20)	0.45	0.050	.498
Interaction C2 by baseline IBS-SSS	−0.10 (−0.40 to 0.20)	0.15	−0.055	.501
Extraversion	−0.63 (−2.57 to 1.32)	0.99	−0.053	.525
Openness	1.86 (−0.27 to 3.98)	1.08	0.129	.086
Agreeableness	0.50 (−2.15 to 3.15)	1.34	0.030	.711
Interaction C1 by extraversion	−0.27 (−1.65 to 1.11)	0.70	−0.033	.701
Interaction C1 by openness	1.16 (−0.38 to 2.70)	0.78	0.111	.138
Interaction C1 by agreeableness	2.19 (0.27 to 4.12)	0.98	**0.184***	**.026**
Interaction C2 by extraversion	1.54 (−0.83 to 3.91)	1.20	0.102	.202
Interaction C2 by openness	−0.59 (−3.13 to 1.95)	1.29	−0.034	.646
Interaction C2 by agreeableness	−2.84 (−5.99 to 0.30)	1.59	−0.145	.076
Depression (PHQ-8)	−0.19 (−4.78 to 4.40)	2.33	−0.010	.934
Anxiety (GAD-7)	2.96 (−1.78 to 7.69)	2.40	0.151	.219
Interaction C1 by PHQ-8	1.51 (−1.76 to 4.79)	1.66	0.120	.363
Interaction C1 by GAD-7	−1.76 (−5.01 to 1.50)	1.65	−0.139	.288
Interaction C2 by PHQ-8	−1.01 (−6.58 to 4.56)	2.82	−0.040	.720
Interaction C2 by GAD-7	−1.16 (−7.12 to 4.80)	3.02	−0.043	.701
PCS	−0.94 (−2.51 to 0.63)	0.80	−0.113	.240
VSI	−0.09 (−1.22 to 1.03)	0.57	−0.016	.872
Interaction C1 by PCS	1.51 (0.33 to 2.68)	0.60	**0.252***	**.013**
Interaction C1 by VSI	−1.14 (−1.90 to −0.38)	0.38	**−0.303****	**.003**
Interaction C2 by PCS	−1.48 (−3.29 to 0.32)	0.92	−0.147	.107
Interaction C2 by VSI	1.26 (−0.19 to 2.70)	0.73	0.170	.087

Significant effects are highlighted in bold format.

Outcome variable is symptom severity change from baseline to end point (measured by the IBS-SSS).

CI = confidence interval; SE = standard error; C1 = contrast 1; C2 = contrast 2; IBS-SSS = Irritable Bowel Syndrome Severity Scoring System; PHQ-8 = depression scale of the Patient Health Questionnaire; GAD-7 = seven-item Generalized Anxiety Disorder scale; PCS = Pain Catastrophizing Scale; VSI = Visceral Sensitivity Index.

[a]Comparison of no-pill control to both placebo conditions.

[b]Comparison of open-label placebo to double-blind placebo.

*Significant effect with $p < .05$.

**Significant effect with $p < .01$.

current study was to identify whether there are baseline psychological characteristics that predict response to OLP and/or DBP in IBS. We were interested in addressing predictors overall as well as identifying whether there were distinct characteristics that

TABLE 4. R^2 and Coefficients of Hierarchical Linear Regressions Within Each Treatment Group

	NPC	OLP	DBP
Model A, R^2 (p)	0.014 (.81)	0.069 (.20)	**0.159** (.009)**
Sex, β (p)	−0.007 (.96)	0.025 (.83)	0.159 (.16)
Age, β (p)	0.120 (.33)	0.072 (.56)	−0.004 (.97)
Baseline IBS-SSS, β (p)	−0.003 (.98)	**0.259* (.037)**	**0.372** (.002)**
Model B, R^2 (p)	**0.085* (.028)**	0.085 (.30)	0.159 (.98)
Sex, β (p)	−0.056 (.64)	0.073 (.57)	0.160 (.18)
Age, β (p)	0.082 (.50)	0.100 (.42)	−0.003 (.98)
Baseline IBS-SSS, β (p)	0.070 (.57)	**0.264* (.033)**	**0.372** (.002)**
Agreeableness, β (p)	**0.285* (.028)**	−0.138 (.30)	−0.004 (.98)
Model C, R^2 (p)	**0.148* (.032)**	0.090 (.58)	0.159 (.96)
Sex, β (p)	−0.093 (.44)	0.080 (.54)	0.161 (.19)
Age, β (p)	−0.061 (.65)	0.116 (.37)	−0.004 (.98)
Baseline IBS-SSS, β (p)	0.163 (.20)	0.227 (.11)	**0.369** (.006)**
Agreeableness, β (p)	0.226 (.079)	−0.142 (.29)	−0.003 (.98)
VSI, β (p)	**−0.322* (.032)**	0.079 (.58)	0.007 (.96)
Model D, R^2 (p)	0.197 (.052)	**0.203** (.005)**	0.159 (.92)
Sex, β (p)	−0.137 (.25)	0.139 (.27)	0.163 (.19)
Age, β (p)	−0.084 (.52)	0.096 (.43)	−0.003 (.98)
Baseline IBS-SSS, β (p)	0.100 (.43)	0.226 (.087)	**0.368** (.007)**
Agreeableness, β (p)	**0.309* (.021)**	**−0.266* (.048)**	−0.002 (.99)
VSI, β (p)	**−0.507**(.004)**	**0.369* (.030)**	−0.001 (>.99)
PCS, β (p)	0.330 (.052)	**−0.461** (.005)**	0.015 (.92)

Significant effects are highlighted in bold format.

Outcome variable is symptom severity change from baseline to end point (measured by the IBS-SSS). Detailed regression statistics are provided in the supplementary material (Tables S3–S6, http://links.lww.com/PSYMED/A829).

NPC = no-pill control; OLP = open-label placebo; DBP = double-blind placebo; IBS-SSS = Irritable Bowel Syndrome Severity Scoring System; VSI = Visceral Sensitivity Index; PCS = Pain Catastrophizing Scale.

*Significant effect with $p < .05$.

**Significant effect with $p < .01$.

predicted OLP compared with DBP. When interpreting our results, the exploratory nature of this study must be considered, which limits any clear conclusions but only allows for a careful discussion of potential implications. In this sense, the findings of this study suggest that there may be different underlying psychological mechanisms influencing response to OLP, which may not play a significant role in response to DBP.

Model 1 in our hierarchical regression supports the main finding of the original study that DBP and OLP were not different from each other in symptom improvement, but both were superior to NPC (9). Subsequent blocks entered into our regression model revealed that gastrointestinal-specific anxiety (measured by the VSI) was a predictor of response to OLP and NPC but did not play a role for response to DBP. Interestingly, the effects in OLP and NPC were opposite, with high VSI predicting less improvement in NPC and more improvement in OLP. At the same time, pain catastrophizing (measured by the PCS) was a negative predictor of response to OLP; that is, high pain catastrophizing was associated with less improvement in OLP, whereas it had a positive but statistically not significant effect in NPC. The fact that the PCS and VSI had opposite effects from each other in OLP (VSI associated with improvement, PCS associated with worsening of symptoms) is notable because these scales have a strong, positive correlation. In addition to this, when each scale was added to the model alone, neither was significant in OLP. These findings suggest a *suppressor effect* of these two variables, meaning that only after controlling for their shared variance did either variable become significant. In other words, despite being strongly and positively correlated, there are unique aspects of each scale, and those unique aspects seem to have opposite predictive values in OLP.

Upon inspection of the individual items in the PCS and the VSI, it is apparent that both scales measure anxiety and distress related to physical symptoms. However, the PCS seems to measure qualities of hopelessness and helplessness (e.g., "I feel I can't stand it anymore"), whereas the VSI includes a greater sense of self-efficacy in regard to the potential to influence or cope with one's symptoms (e.g., "Because of fear of developing abdominal discomfort, I seldom try new foods"). We hypothesize that the quality of flexible or conditional thinking ("if I do x, my symptoms will improve") is a predictor of improvement in OLP, whereas inflexible thinking and helplessness in coping with symptoms ("no matter what I do, I will feel bad") may impair response to OLP.

One possible interpretation of our findings is that the psychological mechanisms behind OLP may be similar to those of cognitive behavioral therapy (CBT). In CBT, efficacy depends on the patient actively engaging with the treatment. Patients are taught to evaluate, challenge, and eventually change dysfunctional negative cognitions. Thus, cognitive flexibility is a hallmark of CBT.

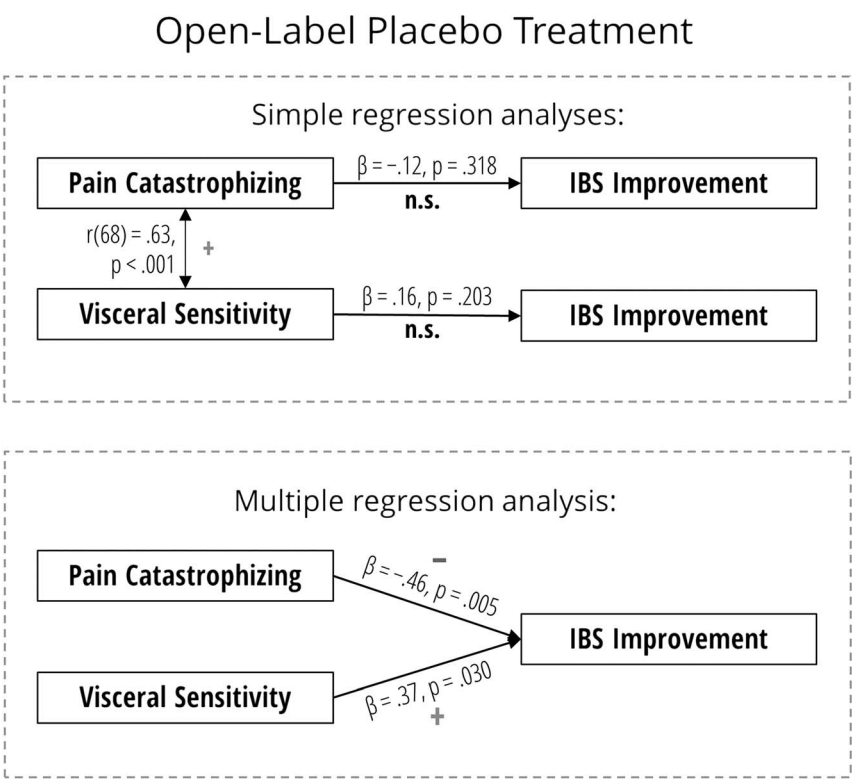

FIGURE 1. Visualization of the suppressor effect in the OLP group. A, The Pain Catastrophizing Questionnaire and the Visceral Sensitivity Index are positively correlated and do not predict IBS improvement significantly in separate simple regression analyses. B, When entered together into the regression model, both contribute to the prediction of IBS improvement significantly but in opposite directions. This indicates that unique aspects of both instruments play a role for OLP treatment success, but because of their shared variance, both variables suppress each other's effect when entered separately. OLP = open-label placebo; IBS = irritable bowel syndrome.

Although OLP does not explicitly involve learning of any specific skill like CBT does, the implicit message of OLP treatment is that participants have the power to heal themselves. Therefore, active engagement may play a similar role to that in CBT, and both interventions may initiate similar mindsets or general orientations. Also, OLP is a paradoxical situation ("this inert pill may help") that may require cognitive flexibility. The unique component of the VSI, which seems to reflect a sense of self-efficacy and conditional, that is, flexible thinking, may thus potentiate OLP treatment, although cognitive flexibility was not assessed directly. In contrast, the unique PCS component of helplessness and hopelessness may interfere with OLP treatment because participants who feel helpless or hopeless have a reduced sense of self-efficacy. This interpretation is consistent with our previous qualitative research, indicating that "hope" had an important role in response to placebo (18,37). Finally, the negative association of agreeableness with OLP outcome may derive from the association between high levels of agreeableness and passivity. In a treatment that depends on the patient having a sense of self-efficacy, passivity is likely to hinder efficacy.

In direct contrast to OLP treatment, the implicit message of pharmacological treatment (and therefore DBP treatment) is that the problem can be fixed by an external agent (i.e., the pill), and that aside from compliance with the treatment regimen, no particular agency or self-efficacy is required of the participant. Under these conditions, the psychological characteristics of the participant should not be of particular importance, which is consistent with the near zero effects of the VSI, the PCS, and agreeableness on DBP outcomes. Although OLP and DBP did not significantly differ regarding these predictors, the near zero effects in DBP are remarkable given that the same variables had a clear and strong impact in OLP. Thus, although active engagement may be required to benefit from OLP, passive commitment seems to be sufficient for DBP treatment success.

Finally, participants assigned to the NPC condition received no treatment and thus were given no explicit or implicit messages about treatment. Thus, our finding of higher VSI scores predicting worse symptoms in NPC participants may simply reflect the association of gastrointestinal-specific anxiety with IBS symptom severity that has been reported previously (38). However, given that the unique components of the VSI and the PCS seemed to influence NPC outcomes in a similar but opposite pattern as in OLP, it seems likely that self-efficacy and the ability of flexible thinking might play a role in NPC participants as well. In this instance, persons with high levels of conditional thinking and self-efficacy might be frustrated by assignment to a no-treatment condition when they were hoping to "do something" about their symptoms by entering a clinical trial. In contrast, persons who feel rather helpless and have little hope for treatment success might be less upset about being assigned to a no-treatment condition.

Our finding that psychological predictors may play a different role in OLP and DBP is in line with the results of our parent study, which demonstrated that treatment expectancy was correlated with treatment success in DBP but not in OLP (9). This finding is additionally supported by other OLP clinical studies that found no

correlation between positive expectations and response to OLP (11,16), and by an experimental OLP study indicating that optimism played a role in deceptive placebo application but not in OLP (39). Differences in clinical or psychological profiles between those who respond to OLP and those who respond to DBP are also supported by emerging genetic evidence. Studies suggest that one particular polymorphism of the catechol-*O*-methyltransferase predicts response to DBP (40), whereas an entirely different polymorphism of catechol-*O*-methyltransferase predicts response to OLP (15,41). Our study and these other emerging findings may a provide a preliminary direction to understanding why some people respond to the paradoxical OLP but not to DBP or to "impure placebos" (i.e., medications used in clinical practice that have little or no pharmacological effect but are given for their potential to serve as placebos) and how their psychological profiles might differ (42).

This study is one of the first to investigate potential psychological predictors of OLP effects and to attempt to disentangle them from DBP mechanisms. However, there are several limitations to note. First, the exploratory nature of these secondary analyses must be considered. In some instances, we have interpreted differences between the two placebo groups in post hoc regression models even when the interactions in the overall model were not significant. However, because this study is the first to compare psychological predictors of placebo response between OLP and DBP, we feel that this analysis could be justified so long as it was clearly indicated as exploratory. Related to this limitation, although the opposite influence of the VSI and the PCS on OLP outcome is very robust in the post hoc regression models, the interpretation of this curious phenomenon remains tentative. Our discussion of potential underlying OLP mechanisms is post hoc interpretations, because these constructs were not measured directly. Future OLP trials should include explicit measures of self-efficacy, hope, and cognitive flexibility to verify our hypothetical interpretation. Second, our analyses were limited to baseline characteristics because we did not have follow-up data available for psychological variables. Future studies should evaluate change in these variables as potential predictors of response to placebo.

In conclusion, the findings of our exploratory analyses emphasize that different mechanisms may be involved in DBP and OLP interventions. IBS participants who score low on the pain catastrophizing questionnaire but high on the VSI may be more likely to benefit from OLP. Although passive commitment, as required for pharmacotherapy, seems to be sufficient to benefit from DBP, we hypothesize that for OLP, the participants' active engagement may be crucial for the treatment success. OLP, in presenting its paradoxical conundrum to participants, may engage psychological mechanisms similar to those in psychotherapy.

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