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Visceral sensitivity as a mediator of outcome in the treatment of irritable bowel syndrome

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Abstract

Patients with irritable bowel syndrome (IBS) experience anxiety about visceral sensations, leading to avoidance behaviors and hypervigilance that maintain IBS symptoms. The current study used data from a clinical trial that compared a treatment aimed at reducing anxiety about visceral sensations (interoceptive exposure; IE) to an attention control (AC) and a CBT-based stress-management treatment (SM) to examine whether changes in visceral sensitivity mediated IBS symptom and quality of life outcomes. Data from participants who completed one of the three treatments ($N = 76$) were subjected to mediation analyses. Visceral sensitivity mediated treatment outcomes across all outcome measures and across all treatment groups, with no differences between IE and the other treatment groups. This finding suggests that psychosocial treatments for IBS may work by decreasing visceral sensitivity, and the degree to which visceral sensitivity is decreased is related to outcome, suggesting IE may be the preferable treatment option.

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder affecting 10–15% of the population (Brandt, et al 2002, Saito, et al 2002). IBS is characterized by abdominal pain or discomfort associated with altered bowel habits (i.e., constipation and/or diarrhea), and is

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often accompanied by sensations of urgency, distention, or incomplete evacuation (Longstreth, 2005). Evidence suggests that IBS is associated with hypervigilance and hypersensitivity to visceral sensations as well as autonomic arousal to visceral events (Naliboff et al., 1997; Verne et al., 2001; Tillisch et al., 2005). Furthermore, these features may be at least partly explained by enhanced central stress responsiveness to gastrointestinal symptoms (Mayer et al., 2001). In turn, GI symptomspecific anxiety leads to increased pain sensitivity and poor coping responses (Labus et al 2004; Hazlett-Stevens et al., 2003). Consequently, visceral anxiety is seen as a primary affective disturbance in IBS and as the mediating variable between other risk factors (e.g., neuroticism, trait anxiety, worry) and IBS symptom severity (Labus et al., 2005).

Based on this model, a cognitive behavioral treatment (CBT) for IBS that included interoceptive exposure to visceral sensations was evaluated in a randomized clinical trial (Craske et al., 2011). This treatment was developed using CBT for panic disorder as a model; specifically, anxiety about the somatic sensations are targeted through cognitive restructuring and repeated exposure to the sensations while modifying maladaptive safety behaviors and other avoidance behaviors associated with somatic sensations (see Craske et al., 2011, for a detailed review). Findings from this trial indicated that the interoceptive exposure condition showed significant improvement in bowel symptom severity and was found to be superior to attention control on a measure of visceral sensitivity and superior to both attention control and a CBT stress-management condition on quality of life measures (Craske et al., 2011).

The interoceptive exposure directly targeted fears of visceral sensations, whereas stress management targeted stress reactions to daily life events. Thus, these two different CBT approaches for IBS are driven by different purported mediators. Changes in visceral sensitivity would be hypothesized to be a mediator specific to the interoceptive exposure treatment relative to the stress management treatment. The current study, using data from the Craske et al. (2011) clinical trial, aimed to answer the following questions: (1) Do changes in VS during treatment mediate outcomes across treatment groups? and (2) Do changes in VS during treatment mediate outcomes in the IE condition more than the AC and SM conditions?

Measures

Participants

Participants were recruited from a digestive disease clinic at a large university in California, and from community advertisements. Participants had to be diagnosed with IBS based on the Rome II diagnostic criteria in order to be eligible. The Rome criteria are a consensus-based symptom criteria system for functional gastrointestinal disorders analogous to the DSM for psychiatry disorders. Participants were excluded if they (a) had another significant chronic pain condition; (b) had a major mental disorder such as schizophrenia, bipolar disorder or substance use disorder (anxiety disorders and depression without suicidal ideation were not exclusions); or (c) were taking narcotic pain medication. Participants who took IBS symptomatic medications (e.g. anti-diarrheal medications) or antidepressants were asked to maintain a stable dose throughout the study.

171 participants completed initial screening. Sixty were deemed ineligible and one dropped before randomization, leaving 110 participants who were randomized. After randomization, 11 participants (10%) declined to participate, withdrawing before beginning treatment. An additional 23 participants were treatment dropouts (23% of 99 who began treatment), defined as not completing at least 8 of 10 sessions. Thus, 76 participants were treatment completers. All of the treatment completers completed the post-treatment assessment. Follow-up data was collected for 61 of the treatment completers. Treatment completers with available follow-up data were included in the analyses.

The total randomized sample was primarily female (74.3%) and the mean age was 39.47 (SD = 13.50). The sample was primarily Caucasian (72.3%), with 9% African-American, 9.7% Asian-American/Pacific Islander, 3.9% Native-American, 1.9% Hispanic, and 3.1% other race/ethnicity. With regard to bowel habit, 34.1% reported constipation, 36.0% reported diarrhea, and 29.9% reported mixed constipation/diarrhea based on proposed ROME II criteria. For more information about the sample, see Craske et al. (2011).

Measures

Outcome Measures

Primary Outcome Measures

Bowel Symptom Composite Score: We previously validated the use of 21 point numerical ratings scales for individual IBS symptoms, including overall symptom severity (Spiegel et al 2008). Herein, a composite bowel symptom severity index (BSS) was created from standardized scores from individual symptom ratings of overall gastrointestinal symptoms, lower abdominal pain, lower abdominal bloating, and lower abdominal discomfort. Each scale was anchored from (0) no symptoms to (20) most intense symptoms imaginable, and referred to the past two weeks. The average of the four standardized scores comprised the BSS value. This measure was administered at pre, post, and follow-up assessment.

Secondary Outcome Measure

IBS-Quality of Life: (Patrick et al., 1998). The IBS-QoL is a 34-item measure of the degree to which IBS symptoms affect lives (5-point scale). The measure shows excellent internal consistency (Cronbach's $\alpha = .95$), good test-retest reliability ($r = .86$), and convergent validity. We examined two of the eight IBS-QOL subscales, Interference (e.g., "I feel I get less done because of my bowel problems") and Food Avoidance (e.g., "I have to watch the kind of food I eat because of my bowel problems"), since these measure aspects of IBS impact not covered by the primary outcomes.

Presumed Mediator of Outcome

Visceral Sensitivity Index (VSI; Labus et al., 2004): Anxiety related specifically to IBS symptoms and misappraisal of them was assessed using this 15-item scale. Participants rated how much they agreed with statements such as "No matter what I eat, I will probably feel uncomfortable" on a 6-point Likert scale. This scale shows good internal consistency (Cronbach's $\alpha = .93$), as well as good convergent, discriminant, content, and predictive

validity (Labus et al., 2004; Labus et al., 2007). This measure was administered at pre-, mid-, post-, and follow-up assessments.

Procedures

Individuals who appeared to meet initial eligibility requirements during a telephone assessment were invited for an initial screening visit. During the screening visit, participants were given information about the study, provided informed consent, and were further screened for eligibility. The screening included a medical history and physical exam, including a diagnostic assessment for IBS conducted by a gastroenterologist or nurse practitioner experienced in the diagnosis of functional bowel disease and the exclusion of organic disease. Participants completed the baseline assessment measures at this time. Eligible participants were randomized to one of the three treatment conditions: Attention Control, CBT-Stress Management, or CBT-Interoceptive Exposure. Treatment conditions were matched on number and duration of sessions (i.e., 10 sessions each lasting approximately 50 min). Participants completed a mid-treatment assessment at Week 5, a post-treatment assessment following treatment, and a follow-up assessment three months after treatment ended.

Attention control condition (AC)—The AC protocol was based on the control group developed for a prior trial examining cognitive-behavioral therapy for IBS (Toner et al., 1998; Drossman et al., 2003). The components of the AC treatment included: (a) reviewing diary cards of daily symptoms; (b) receiving and reading educational material about IBS; and (c) discussing the reading material with the therapist¹.

CBT-Stress management (SM)—SM consisted of (a) education about IBS symptoms and their relationship to stress; and (b) skills training in progressive muscle relaxation (PMR); (c) methods for identifying and challenging erroneous thoughts about stressful life events; and (d) application of relaxation and cognitive restructuring skills to an individualized hierarchy of external stressful situations (e.g., interpersonal conflict, work deadlines) that were not directly related to the experience of IBS sensations. The goal of SM was to reduce cognitive and physical stressful reactions to daily life events, which was presumed to reduce IBS symptoms as a reaction to stress.

CBT- Interoceptive exposure (IE)—The IE protocol was based on CBT for panic disorder (Barlow & Craske, 2006). The IE protocol adapted for an IBS population (de Cola, 2001) targeted erroneous beliefs about IBS symptoms, hypervigilance to IBS symptoms, fear of IBS symptoms, and maladaptive behavioral responses to IBS symptoms. Treatment consisted of (a) education that IBS symptoms reflect conditional reactions to reminders of gastro-distress (e.g., food intake or leaving the house); (b) attentional control skills to learn to shift attention away from rather than perseverate upon unpleasant bodily sensations (Wells et al., 1997); (c) cognitive therapy to challenge threat-laden appraisals of IBS-relevant bodily sensations (e.g., “I have a serious disease”) and behavioral experiments to test the accuracy of thoughts and beliefs; (d) interoceptive exposure involving repeated

¹Protocols for all three conditions are available from the corresponding author

exposure to IBS-relevant visceral sensations (e.g., tightening stomach to produce gut sensations, wearing tight clothing, delaying entrance to the bathroom, eating feared/avoided foods) to reduce fear of the sensations; and (e) in vivo exposure to feared/avoided situations in which IBS sensations were expected (e.g., long road trips, eating at restaurants, going places in which bathrooms were not accessible) while weaning safety signals or safety behaviors (e.g., additional underclothing).

Statistical Analysis

A 2-level hierarchical linear model (HLM) was conducted with Time (pretreatment, mid-treatment, and post-treatment) as the level 1 predictor and VSI score as the outcome variable. A least squares estimates level 2 residual file was obtained from this analysis to compute individual VSI intercepts and slopes for each participant. The residual file contains the ordinary least squares (OL) residuals and fitted values (FV) for each level 1 coefficient ($\hat{Y}_{q0} = \sum \hat{Y}_{qs} W_{sj}$). Adding the OL residuals to the corresponding FV s produces the OL estimate of the corresponding level 1 coefficient β_{qj} . The OL and FV residuals are estimated for the intercept and slope. After generating these individual slope and intercept parameters, a series of linear regression analyses were conducted in SPSS with the outcome measure of interest (i.e., BSI at follow-up, IBS-QOL food avoidance at follow-up, and IBS-QOL interference at follow-up) as the DV. The pretreatment score on the DV was entered as a predictor into the first block of the regression equation and VSI intercept (derived from the HLM residual file) was covaried in the second block. The third block consisted of the VSI slope (derived from the HLM residual file) and Group variables (i.e., IE v. not IE), and the fourth block included the Group $\times$ VSI slope interaction term.

Follow-up scores on the DVs were chosen as indices of outcome instead of post-treatment scores because the VSI slopes included post-treatment scores, thus ensuring temporal precedence. Follow-up scores were also considered to be more important indices of longer-term outcome. In the prior analysis, the DVs as well as the VSI all showed significant decline across treatment, with IE outperforming AC on the VSI and IBS-food avoidance measures at follow-up, and IE outperforming SM on IBS-interference at follow-up (Craske et al., 2010).

Results

For descriptive information on each measure between groups, as well as information on treatment adherence, attrition, credibility, and more detail about treatment outcomes, see Craske et al. (2011).

Does change in visceral sensitivity mediate change in bowel symptom severity outcomes?

A Group $\times$ VSI slope interaction was not observed ($p > .76$). Thus, only main effects were examined. VSI significantly predicted BSS outcome at follow-up, $R^2 = .25$, $\beta = .06$, $t(44) = 3.33$, $p < .01$, with steeper VSI decline slopes across treatment predicting lower BSS scores at follow-up.

Does change in visceral sensitivity mediate change in IBS life interference?

A Group $\times$ VSI slope interaction was not observed ($p > .70$). Thus, only main effects were examined. VSI significantly predicted BSS outcome at follow-up, $R^2 = .08$, $\beta = -1.29$, $t(60) = -3.85$, $p < .001$, with steeper VSI decline slopes across treatment predicting lower life interference at follow-up.

Does change in visceral sensitivity mediate change in food avoidance?

A Group $\times$ VSI slope interaction was not observed ($p > .78$). Thus, only main effects were examined. VSI significantly predicted BSS outcome at follow-up, $R^2 = .07$, $\beta = -1.05$, $t(60) = -2.52$, $p < .05$, with steeper VSI decline slopes across treatment predicting lower food avoidance at follow-up.

Discussion

This study examined whether changes in visceral sensitivity during psychological treatment for IBS mediated changes in bowel symptoms, food avoidance, and life interference due to IBS, and whether the mediating role of visceral sensitivity differed between those who received treatment specifically targeting anxiety about visceral sensations (i.e., interoceptive exposure) compared to other treatments (i.e., stress management and an attention control condition). The primary finding of this study was that changes in visceral sensitivity during psychological treatment for IBS mediated outcomes across treatments, with no differences between the three treatment conditions. In other words, to the extent that IBS treatment reduces visceral sensitivity, greater improvement is seen across a number of IBS outcomes.

The fact that interoceptive exposure treatment outperformed the attention control condition on the VSI at follow-up whereas stress management did not (Craske et al., 2011) suggests that interoceptive exposure may be the preferable treatment option. Furthermore, the finding that changes in VSI mediated outcomes within the interoceptive exposure condition may explain the overall benefits to this treatment condition relative to the other conditions. On the other hand, reductions in VSI also mediated the other treatment conditions, suggesting that change in VSI is a robust mediator of treatment improvement. Perhaps non-specific effects such as monitoring symptoms, receiving medical clearance to participate (which may have indicated to patients that their symptoms were due at least in part to non-medical reasons), and speaking with a therapist about the symptoms in an objective way served to reduce visceral sensitivity overall. Future research should compare these treatments to a pharmacological treatment to parse apart the effects of these non-specific treatment elements. Also, there may be other mechanisms of change that could explain the treatment benefits observed in the CBT-SM condition. In other words, visceral sensitivity may not be the only mediator explaining change, particularly in the CBT-SM condition, which showed significant improvement but did not focus on visceral sensitivity. Exploration of other potential mechanisms, such as cognitive misappraisals (e.g., change in the degree to which one catastrophizes IBS-related outcomes), should be the focus of future investigation.

Finally, relating the current findings to recent neurobiological research may help to more fully understand these mechanisms of action. Although there are no studies directly

examining brain responses associated with visceral anxiety or changes in visceral anxiety in IBS, the growing literature using functional brain imaging suggests several possible brain circuits that might underlie these subjective reports. IBS patients show altered responses in both an emotional arousal circuit (including the anterior cingulate cortex and amygdala) and cortical modulatory circuit (including areas of medial and lateral prefrontal cortex) that may represent the arousal and cognitive aspects of visceral anxiety respectively (Tillisch, Mayer & Labus, 2011; Kennedy et al., 2012); and preliminary evidence suggests that symptom and affective change from CBT for IBS is related to some regions of these circuits (Lackner et al., 2006).

A few limitations of the current study should be noted. First, the sample size was relatively small. Future research should replicate these analyses with larger samples. Second, visceral sensitivity was measured only once during treatment. Thus, in order to use the most appropriate statistical modeling, change slopes were derived from the pretreatment, mid-treatment, and post-treatment scores. An optimal design may have included more data points during treatment, and perhaps one at the final or second-to-last session, which would have also allowed for an examination of whether these slopes mediated post-treatment outcomes. Also, it is possible that change in symptoms occurred before the mid-treatment assessment, which was given at session 5. Indeed, some research suggests that just under one-third of individuals who undergo CBT for IBS respond to treatment within the first four weeks of treatment (Lackner, Gudleski, Keefer, Krasner, Powell & Katz, 2010). Thus, there remains some uncertainty regarding the temporal precedence of change in the mediator before symptom change. However, by limiting our outcome analyses to the follow-up assessment, we retained the important temporal precedence of the VSI change slope before the measurement of the outcome variable. It could be argued that the follow-up assessment outcomes are more important than post-treatment outcomes, as the primary goal of a treatment is to produce longlasting change, not simply immediate relief from symptoms.

The study is one of the first studies to examine mechanisms of change during treatment for IBS. Previous reports have been conflictual, with one study showing that change in IBS symptoms after CBT was not mediated by psychological distress (Lackner et al., 2007), whereas another study did find that mood state (particularly anxiety) mediated bowel symptom outcomes (Jones, Koloski, Boyce, & Talley, 2011). One limitation of the Lackner et al. (2007) study was that presumed mediators were assessed only pre- and post-treatment, without any assessment during the course of treatment. The Jones et al. (2011) study, like the current study, also used a mid-point assessment and found results consistent with the current study. This strengthens the idea that changes in psychological distress during treatment (either anxiety reduction in general, or in the case of the current study, visceral anxiety in particular) mediate bowel symptom improvement. By revealing that reductions in visceral sensitivity during treatment are associated with better IBS outcomes, this study provided support for a model describing IBS as, at least in part, maintained by anxiety about and avoidance of visceral sensations. Indeed, when anxiety about, avoidance of, and hypervigilance toward visceral sensations are reduced, bowel symptoms consequently improve. Thus, attention should be paid to decreasing visceral sensitivity in IBS patients. One such method of decreasing visceral sensitivity is interoceptive exposure, but it may not be the only way in which to reduce visceral sensitivity. Other ways to reduce visceral

sensitivity should be the focus of investigation, as they may present more options for patients to reduce IBS symptoms.

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Highlights

- Visceral sensitivity mediated bowel symptom severity
- Visceral sensitivity mediated quality of life outcomes
- No between-group differences in the effect of the mediator were found