Behavioral avoidance moderates the effect of exposure therapy for irritable bowel syndrome: A secondary analysis of results from a randomized component trial

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ARTICLE INFO

Keywords:
Irritable bowel syndrome
Exposure
Cognitive behavior therapy
Moderation
Piecewise growth models

ABSTRACT

Past research has failed to identify consistent moderators of outcomes in psychological treatments for irritable bowel syndrome (IBS). The aim of this study was to test previously identified mediators as potential moderators of the effects of exposure therapy on IBS symptoms in a previously published randomized component trial. In total, 309 participants with IBS were randomized to internet-delivered cognitive behavioral treatment that included exposure (ICBT) or to the same treatment protocol without exposure (ICBT-WE) and were asked to report on gastrointestinal symptoms at pretreatment, posttreatment and weekly during the treatment. Pre-treatment scores of The Visceral Sensitivity Index (VSI) and The Irritable Bowel Syndrome Behavioral Responses Questionnaire (IBS-BRQ) (i.e., gastrointestinal anxiety and avoidance behavior) were evaluated as predictors and moderators. Piecewise latent growth curve models were employed to evaluate moderators during distinct phases of the trial, prior to and following the onset of exposure in ICBT. Results revealed that pretreatment scores on IBS-BRQ (avoidance) moderated the effect of exposure therapy during the specific phase in which exposure was implemented in ICBT, with higher avoidance scores linked to stronger positive effects of exposure. VSI did not serve as predictor nor moderator. Adding exposure to CBT seems to be especially important for persons with moderate to high levels of avoidance behaviors in order to reduce gastrointestinal symptoms.

1. Introduction

Irritable bowel syndrome (IBS) is a debilitating functional gastrointestinal disorder characterized by abdominal pain in combination with bowel dysfunction (Lovell & Ford, 2012). Psychological treatments, including cognitive behavior therapy (CBT), can be at least moderately effective in reducing symptoms and improving quality of life among individuals with IBS (Ford et al., 2014). Yet, a significant proportion of individuals (approximately 20–40%) do not respond to CBT (Lackner et al., 2010) and the extent literature provides little clues to for whom CBT for IBS is most beneficial. Even less is known about how individual differences interact with single treatment components (e.g., cognitive restructuring, exposure) in CBT to account for heterogeneity in treatment response.

Only a few studies have examined predictors (i.e., variables associated with outcome irrespectively of type of treatment) or moderators (i.e., treatment specific predictors) of effects of CBT in reducing IBS symptoms or improving function to date. The results have been mixed and no clear-cut predictor nor moderator has been identified (Lackner et al., 2010). For example, some studies have found higher psychological distress at baseline to be associated with positive outcomes following CBT (Reme, Kennedy, et al., 2010), whereas other have reported the reverse association (Blanchard et al., 2006) or no association at all (Ljotsson, Andersson, et al., 2013). There is a number of methodological reasons for these conflicting results (e.g., variation across study samples and measures, low power, no comparison condition), but one

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https://doi.org/10.1016/j.brat.2021.103862
Received 7 February 2020; Received in revised form 30 March 2021; Accepted 6 April 2021
Available online 20 April 2021
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exploration could be that studies have not formally examined predictors and moderators based on the theoretical underpinnings of the treatment model. That is, most studies have relied on measures of clinical and demographic characteristics that were collected as part of the original efficacy trial without a clear theoretical rationale to the choice of putative moderators (Blanchard et al., 2006; Lackner et al., 2010). Indeed, the lack of theory in the selection of variables may be one reason why moderators have been so difficult to identify in psychological treatments in general (Kraemer, Wilson, Fairburn, & Agras, 2002; MacKinnon, 2011). An identified moderator (i.e., putative mechanism of change) may serve as excellent candidate moderator variable because it is reasonable to assume that individuals functioning poorly on the moderator at starting point can benefit most from a treatment designed to target this particular moderator (Tein, Sandler, MacKinnon, & Wolchik, 2004). Hence, evaluation of moderation can constitute a test of theory as treatment effects can be expected in one group and not another based on predictions from the underlying theory of treatment change.

CBT protocols that include exposure therapy have emerged as particularly effective treatment approaches for IBS (Shah, Ramos-García, Bhavsar, & Lehrer, 2020) that can produce specific effects that cannot be attributed to nonspecific factors such as for example attention (Craske et al., 2011; Hesser, Hedman, Lindfors, Andersson, & Ljótsson, 2017; Ljótsson et al., 2011, 2014). The theoretical rationale for using exposure-based principles and procedures in the treatment of IBS can be found in the gastrointestinal symptom-specific anxiety model of IBS (i.e., GSA model) (Craske et al., 2011; Ljótsson, Hesser, et al., 2013). The GSA model posits that conditional fear responding and avoidance of symptoms are important mechanisms contributing to IBS symptoms (Labus et al., 2004, 2007). The model has gained considerable support in correlational and experimental research over the last 15 years (Hesser, Hedman-Lagerlöf, Andersson, Lindfors, & Ljótsson, 2018; Labus et al., 2004; Ljótsson, Hesser, et al., 2013).

Based on GSA model, two variables have been proposed to be mediators of exposure therapy on IBS symptoms: IBS-specific anxiety and IBS-specific behavioral avoidance. Both have independently also been identified as mediators of exposure-based CBT for IBS in previous research on adults and children with IBS (Bonnert et al., 2018; Hesser et al., 2018; Ljótsson, Hesser, et al., 2013; Wolitzky-Taylor, Craske, Labus, Mayer, & Naliboff, 2012).

There is, however, a paucity of research on predictors and moderators based on the GSA model. To our knowledge, only one study has examined IBS-specific anxiety as a predictor of outcomes following an exposure-based treatment for IBS. When statistically covarying pretreatment symptom severity in a multivariate regression model, IBS-specific anxiety did not account for significant variation in IBS symptomatology (Ljótsson, Andersson, et al., 2013). This null-finding could be due to fact that the measure employed in that study did not capture processes of key relevance for exposure therapy, such as behavioral avoidance, but could also be due to fact that the exposure-based treatment included other treatment components (e.g., mindfulness practice) besides exposure. That is, if other treatment components were not associated (or reversely associated) with visceral anxiety, the overall correlation between outcomes and the predictor may have been underestimated in the study. Similar, if subgroups responded to the treatment by different mechanisms the overall correlation between IBS-specific anxiety and outcome across subgroups could be deflated. One study showed that higher IBS-specific avoidance predicted more favorable CBT outcome in the form of increased social and work functioning covarying pretreatment levels on the same variable (Reme, Kennedy, et al., 2013); yet, the CBT offered to participants in the that study did not include exposure exercises so it is unclear to what extent the result generalizes to exposure-based CBT. Avoidance behavior may, for example, be a nonspecific predictor rather than a moderator of the effect of exposure therapy. In addition, that study did not examine whether behavioral avoidance was a predictor of changes in IBS symptoms.

To our knowledge no study has evaluated IBS-specific anxiety and avoidance as moderators of the effect of exposure-based CBT for IBS. However, there are findings that do speak to the issue. In a recent analysis of mediators of exposure therapy for IBS, as evaluated in an add-on component study, the mediated effect of IBS-specific avoidance was found to be moderated by baseline scores of the mediator (i.e., moderated mediation). Specifically, higher baseline scores was associated with a stronger effect of exposure (relative to control) on subsequent changes in the mediator (Hesser et al., 2018). The result tentatively suggested that individuals with marked avoidance behavior would benefit more from exposure because of a stronger effect on the postulated mechanism of change (i.e., reduction of avoidance). The finding, however, provided no direct evidence for that IBS-specific avoidance as a moderator of exposure on IBS-symptoms.

The present study aimed to examine moderated effects of GSA variables, i.e., IBS-specific anxiety and IBS-specific avoidance, on IBS-symptoms by using data obtained from the aforementioned component study (Ljötsson et al., 2014). In that study, individuals with IBS were randomly assigned to receive either a full treatment of internet-delivered CBT protocol (ICBT) or a reduced form of the same treatment but without exposure exercises (ICBT-W). Previous analyses showed that effects favored the full treatment with exposure at post-assessment with effects that were sustained at 6-month follow-up (Ljötsson et al., 2014). Treatments were identical up to a certain time point in the study (week 4) and participants reported IBS symptoms on a weekly basis during the treatment phase. This design allowed us test for predictors and moderators during distinct phases of the trial, i.e., before and after exposure component was added to ICBT. We utilized piecewise growth curve modeling to model change and predictors and moderators of change on IBS symptoms during these distinct phases. Thus, this design and analytic procedure made it possible to evaluate the GSA variables as moderators of exposure therapy on IBS symptoms in a more rigorous and detailed way than by aggregating over the entire treatment phase.

Because both treatment conditions in this component study targeted similar GSA processes, we hypothesized that IBS-specific anxiety and IBS-specific behavioral avoidance would both serve as predictors of change in IBS symptoms during the first phase, i.e., higher scores at baseline would be associated with increased symptom reduction across conditions. In the second phase of the trial, at which point exposure was implemented in one of the conditions (ICBT), we predicted that pre-treatment scores on GSA variables would moderate the between-group effect of exposure therapy on IBS symptoms. That is, higher scores on GSA variables would be associated with increased IBS symptom reduction following the treatment with exposure (ICBT) as compared to the treatment without exposure (ICBT-W).

2. Methods

Data were obtained from a previously conducted randomized component study. A brief description of relevant procedures and methods are provided. Full details about the treatments, measures, screening procedures, and participants are presented elsewhere (Ljötsson et al., 2014).

2.1. Participants and treatments

Participants were 309 (79.5% female) self-referred individuals who fulfilled the Rome III-criteria for IBS (Longstreth et al., 2006) and who were recruited via advertisement. Table 1 presents the demographic and clinical characteristics of the sample. Individuals who expressed an interest in the study were excluded in the presence of alarm symptoms that had not been examined by a physician (including blood in stool, persistent diarrhea, rapid weight loss, or recent change in bowel habits if older than 50 years of age), a history of inflammatory bowel disease, lactose or gluten intolerance without proper dietary adjustments, severe
Participants were randomized to either the full treatment protocol (ICBT) or the treatment protocol without exposure (ICBT-WE). The treatment protocols are outlined in their entirety in the original publication. In brief, treatments were delivered over the internet and lasted 10 weeks. The participant had regular contact with an assigned therapist who provided support and guidance via text messages in a closed and password-protected online platform. In both treatments, participants were given homework exercises using the same overall treatment rationale based on the GSA model, i.e., how fear and avoidance of IBS symptoms can contribute to IBS symptom exacerbation and maintenance. Participants read online self-help texts divided into 4 (ICBT-condition) or 3 (ICBT-WE condition) modules and a concluding relapse prevention module. The first two treatments modules focused on the role of fear in exacerbation of IBS-symptoms and the reduction of symptom preoccupation and hypervigilance to symptoms (e.g., through mindfulness training). The third module focused on encouraging acceptance of symptoms and of unwanted negative thoughts and increasing positive behavioral change (e.g., by promoting value-based activities). Participants in ICBT were in addition to the three initial modules, which were identical across conditions, presented with a rationale for performing gradual exposure exercises to IBS-symptoms and situations. Both interoceptive exposure (e.g., eating symptom-provoking foods) and in vivo-exposure (e.g., going to work when in pain) exercises were included in the ICBT condition and patients were encouraged to combine interoceptive and in vivo exposure exercise whenever possible. Participants in this condition were encouraged to reach this final exposure module in week 4, and thus prior to week 4 the ICBT and ICBT-WE were identical. In the ICBT-WE condition, 93 participants (59.6%) started their final module (i.e., module 3), whereas in the ICBT condition, 84 (54.9%) participants started their final module (i.e., module 4). At the end of treatment, patients in both conditions got access to a concluding relapse prevention module.

Previous analyses showed no differences between conditions in the number of messages received by therapist, time spent by therapist on each patient per week, number of completed exercises by patients, missing data at post and follow-up assessments, and patient-rated treatment credibility (Ljótsson et al., 2014).

### 2.2. Measures

#### 2.2.1. Outcome measure

The Gastrointestinal Symptom Rating Scale - IBS version (GSRS-IBS; Wiklund et al., 2003) was the primary outcome in the study. The GSRS-IBS consists of 13 items covering severity of gastrointestinal symptoms (e.g., “Have you been bothered by abdominal pain during the past week?” “Have you been bothered by a feeling of bloating during the past week?”). The items are scored between 1 (no discomfort at all) and 7 (very severe discomfort), resulting in a total score ranging from 13 to 91. Estimates of reliability have been found to be good, with an internal consistency (Chronbach’s α) ranging between 0.74 and 0.85 and test-retest reliability between 0.55 and 0.70 (Wiklund et al., 2003) and the GSRS-IBS adequately captures the different symptom domains of IBS (Ljótsson et al., 2020). Participants completed the GSRS-IBS at four consecutive time points over a prolonged baseline and post-treatment follow-up period and weekly throughout the treatment period (10 weekly assessments). The average GSRS-IBS score of the four weeks over the baseline and post-assessment was used to get reliable estimates of the participants’ symptom levels at pre- and posttreatment assessment.

#### 2.2.2. Moderators

The Visceral Sensitivity Index (VSI; Labus et al., 2004) is a 15-item measure of IBS-related symptom fear that covers symptom worry, symptom awareness, intrusiveness of symptoms (e.g., “I get anxious when I go to a new restaurant”, “I often worry about problems in my belly”). Items are scored between 0 and 5, rendering a total score ranging from 0 (minimum symptom fear) to 75 (maximum symptom fear). Test scores of the VSI have demonstrated high internal consistency (Chronbach’s α = 0.90 - 0.92) and have been shown to be associated with symptom severity and diagnostic status of IBS (Labusch, Mayer, Chang, Bolus, & Baloff, 2007).

The Irritable Bowel Syndrome Behavioral Responses Questionnaire (IBS-BRQ; Reme, Darnley, Kennedy, & Chalder, 2010) measures IBS-related avoidance and control behaviors related primarily to food and eating, toilet habits, and social situations (e.g., “I avoid going out in case I have problems with my IBS”, “I avoid certain foods when I have bowel problems”). The IBS-BRQ consists of 26 items scored between 1 and 7, rendering a total score ranging from 26 (no avoidance or control behavior) to 182 (maximum avoidance or control behavior). Test scores of IBS-BRQ have demonstrated a high internal consistency (Chronbach’s α = 0.86) and strong correlations with dysfunctional IBS-related cognitions, symptomatology, and impairment (Reme et al., 2010).

### 2.3. Statistical analysis

Latent growth curve modeling was used to evaluate moderators of individual difference in change (Bollen & Curran, 2006). Models were fitted with Mplus vs. 8.1 using full information maximum likelihood estimation with non-normality robust standard errors (returned by MLR in Mplus). Models made use of all available data to estimate parameters and their standard errors (without imputation) and missing data was handled under the less restrictive missing at random assumption. The average baseline and post-treatment scores of GSRS-IBS were used along with the 10 weekly assessments of the measure to model change in IBS symptoms over the entire treatment phase. A piecewise growth model was specified to model change and predictors (main effects) and moderators (interaction effects) of change during the distinct phases of the trial, prior to and following the onset of exposure in ICBT. Thus, given our design, we were able to examine predictors and moderates during these distinct phases of the trial. The individual growth trajectory was modeled by a two-piece linear model as expressed by the following formula at level 1,

\[ y_{it} = \alpha_i + \beta_1 x_{it} + \beta_2 x_{it} + \epsilon_{it} \]
where $y_{1i}$ is the observed value of repeated measures GSRS-IBS for individual $i$ at time point $t$, $a_{i}$ is a latent intercept variable (representing initial status), $\beta_{1i}$ is the first latent slope variable for the first phase of the trial (before the onset of exposure in ICBT), $\beta_{2i}$ is the second latent slope variable for second phase of the trial (following the onset of exposure in ICBT), and $e_{1i}$ is an individual- and time-specific residual term.

At level 2, the latent variables (i.e., $\alpha_{i}$, $\beta_{1i}$, $\beta_{2i}$) were regressed on the treatment variable ($tx; 1 =$ ICBT, $0 =$ ICBT-WE), a grand mean centered moderator variable measured at baseline (mod), and the multiplicative interaction between those two variables, $\alpha_{i} = \mu_{a} + \gamma_{1t} + \gamma_{2mod} + \gamma_{3txmod} + \zeta_{m}$. $\beta_{1i} = \mu_{\beta_{1}} + \gamma_{4tx} + \gamma_{5mod} + \gamma_{6txmod} + \zeta_{\beta_{1}}$. $\beta_{2i} = \mu_{\beta_{2}} + \gamma_{7tx} + \gamma_{8mod} + \gamma_{9txmod} + \zeta_{\beta_{2}}$.

The equations at level 2 contain the intercept terms (i.e., $\mu_{a}$, $\mu_{\beta_{1}}$, $\mu_{\beta_{2}}$), the main effects of treatment (i.e., $\gamma_{1t}$, $\gamma_{2}$, $\gamma_{5}$, $\gamma_{6}$), and the interactive effects of treatment and moderator (i.e., $\gamma_{3}$, $\gamma_{7}$, $\gamma_{9}$) on initial level, slope for the first and second phase, respectively. The residual terms (i.e., $\zeta_{m}$, $\zeta_{\beta_{1}}$, $\zeta_{\beta_{2}}$) express individual differences in initial level and slopes unaccounted for by the predictors at level 2. Covariance between random intercept and slopes were freely estimated in the model (i.e., unstructured variance-covariance matrix for random effects), allowing individual differences in initial symptom level to covary with individual differences in change in IBS symptoms during the first and second phase of the study. Of primary interest is $\gamma_{7}$ that represents the interaction term between treatment and moderator variable for linear change during second phase (following the onset of exposure in ICBT). To determine whether there were any non-linear associations between moderators and outcomes we also re-ran the same growth models that also included the main and interactive effects of the squared moderator variable (i.e., $mod^{2}$).

If an interaction was found to be statistically significantly different from zero, we probed the effect by calculating slopes of simple trajectories following recommendations for illustrating interaction effects in latent growth curve analysis (Curran, Bauer, & Willoughby, 2004). We examined the conditional slope of the simple trajectories at different values of the moderator (the mean $\pm 2$ standard deviation) for each condition (ICBT or ICBT-WE) and computed the point estimate along with 95% confidence bands to determine the region of significance. The following equation provides the conditional slope estimate for phase 2 in each condition at specified values of the moderator, $\mu_{\beta_{2}}^{mod,tx} = \left(\mu_{\beta_{2}} + \gamma_{7tx}\right) + \left(\hat{\gamma}_{4} + \hat{\gamma}_{9}\right)_{mod}$.

To further illustrate the interaction, we also calculated the mean difference between conditions based on the slope difference and the estimated trajectories at low, medium, and high-levels of the moderators (i.e., the mean $\pm 1$ standard deviation). A standardized mean difference effect size ($d$) was computed based on estimated slope difference between conditions (Feingold, 2009).

### 3. Results

Table 2 presents means, standard deviations and ns for outcome and moderators as a function of conditions.

<table>
<thead>
<tr>
<th>Time/Measure</th>
<th>ICBT M SD N</th>
<th>ICBT-WE M SD N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome GSRS-IBS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRE</td>
<td>33.13</td>
<td>10.16</td>
</tr>
<tr>
<td>1</td>
<td>33.91</td>
<td>12.28</td>
</tr>
<tr>
<td>2</td>
<td>33.51</td>
<td>12.96</td>
</tr>
<tr>
<td>3</td>
<td>31.00</td>
<td>12.97</td>
</tr>
<tr>
<td>4</td>
<td>29.30</td>
<td>14.60</td>
</tr>
<tr>
<td>5</td>
<td>28.52</td>
<td>12.83</td>
</tr>
<tr>
<td>6</td>
<td>26.47</td>
<td>12.93</td>
</tr>
<tr>
<td>7</td>
<td>25.05</td>
<td>12.48</td>
</tr>
<tr>
<td>8</td>
<td>25.41</td>
<td>11.75</td>
</tr>
<tr>
<td>9</td>
<td>22.13</td>
<td>12.26</td>
</tr>
<tr>
<td>10</td>
<td>23.07</td>
<td>13.35</td>
</tr>
<tr>
<td>POST</td>
<td>19.82</td>
<td>11.35</td>
</tr>
<tr>
<td>Moderator pre-treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS-BRQ</td>
<td>88.16</td>
<td>22.45</td>
</tr>
<tr>
<td>VSI</td>
<td>37.23</td>
<td>17.06</td>
</tr>
</tbody>
</table>

Note. GSRS-IBS = Gastrointestinal Symptom Rating Scale –IBS version. IBS-BRQ = Irritable Bowel Syndrome Behavioral Responses Questionnaire; VSI = Visceral Sensitivity Index.

There was a statistically significant interaction between moderator and treatment for the IBS-BRQ on the slope in the second phase (during the exposure), indicating that the strength of the differential treatment effect during this phase varied as a function of pretreatment scores of IBS-BRQ. Fig. 1 depicts the conditional mean of the simple trajectories slopes (during the exposure phase) at different values of the moderator IBS-BRQ as a function of condition. The estimated slope was negative and statistically significant different from zero in both conditions for all values of the moderator (i.e., both conditions improved for all moderator values). It can be seen that the slope means of GSRS-IBS decreased (improved) with higher pretreatment IBS-BRQ scores in the ICBT, whereas a small positive increase was evident in ICBT-WE with higher pretreatment scores. Subsequently, differences in slope means of GSRS-IBS between conditions increased as a function of higher baseline scores on IBS-BRQ and the slope difference between conditions was statistically significant (non-overlapping confidence intervals) for all values above 13.27 points below the mean (see Fig. 1). Given that IBS-BRQ was centered around the mean, this gives a nonsignificant difference between conditions on GSRS-IBS at 13.37 units (or 0.57 SD) below the mean of IBS-BRQ (see Fig. 1). The estimated endpoint mean difference between conditions at low (1 SD below), medium (sample average), and high-levels (1 SD above) of the IBS-BRQ were $-1.495$, $95\%$ CI $[-3.906, 0.915]$, $-4.693$, $95\%$ CI $[-6.951, -2.435]$, and $-7.891$, $95\%$ CI $[-11.78, -4.002]$, with corresponding effect sizes ($d$) of 0.173, 0.542, and 0.912, respectively (see Fig. 2 for a graphical representation of estimated conditional trajectories). Note that these treatment effects represented change during the phase in which exposure was performed in ICBT (whilst holding constant the effects that had occurred in the previous phase). None of the other main or interactive effects on slope 1 or slope 2 were statistically significant in the IBS-BRQ model. In addition, there were no significant main or interactive effects in the model with VSI included as the moderator.

We also tested models in which non-linear associations between
5

Results from piecewise growth models examining moderated treatment effects on the outcome GSRS-IBS.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Intercept</th>
<th>Slope phase 1</th>
<th>Slope phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>est</td>
<td>SE</td>
<td>p</td>
</tr>
<tr>
<td>BRQ</td>
<td>-0.784</td>
<td>0.991</td>
<td>0.429</td>
</tr>
<tr>
<td>Tx</td>
<td>0.265</td>
<td>0.028</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TxbyMod</td>
<td>-0.019</td>
<td>0.044</td>
<td>0.663</td>
</tr>
<tr>
<td>VSI</td>
<td>-0.877</td>
<td>1.036</td>
<td>0.398</td>
</tr>
<tr>
<td>Mod</td>
<td>0.305</td>
<td>0.049</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TxbyMod</td>
<td>0.029</td>
<td>0.064</td>
<td>0.658</td>
</tr>
</tbody>
</table>

Note. Unstandardized parameter estimates are shown. Intercept represented the pretreatment assessment; slope in phase 1 captured the growth rate between pretreatment assessment and week 4 (3 weeks in treatment); slope in phase 2 captured the growth rate between week 5 (4 weeks in treatment) and postassessment. Tx = treatment variable (1 = ICBT; 0 = ICBT-WE); GSRS-IBS = Gastrointestinal Symptom Rating Scale –IBS version. IBS-BRQ = Irritable Bowel Syndrome Behavioral Responses Questionnaire; VSI = Visceral Sensitivity Index; Mod = moderator.

4. Discussion

Based on the GSA model of IBS, and in line with prediction, IBS-specific avoidance emerged as a moderator of the added effect of exposure on IBS-symptoms. Individuals with higher scores on IBS-BRQ at pretreatment had more favorably outcomes during the exposure phase in ICBT relative to ICBT-WE. The interaction effect was substantial as indicated by large differences in effects for different values of the moderator, ranging from small and non-significant (d = 0.17) to large and significant (d = 0.91) effects for one standard deviation above and below the sample mean of the moderator. The results are noteworthy given that the design and analytic model provided support for that the moderated effect during the specific phase at which exposure was implemented in ICBT. This indicated that the moderator effect was not driven by unspecific factors (e.g., experimental demand, attention) but represented the added effect of exposure therapy on outcomes. The finding also highlights the importance of considering the context when evaluating moderators of psychological treatments. That is, individual differences, the time point of assessment and the specific treatment components all matter and by aggregating across such factors, as normally done in most clinical trials, potentially important modifiers of treatment outcome can be missed.

The finding, if replicated, provides a clear prescriptive recommendation for treatment selection: Individuals who have moderate to high baseline levels of avoidance behaviors of IBS would be suited for a treatment that in addition to promoting general behavioral change and mindfulness skills also includes exposure exercises to IBS-sensations and situations. The finding is consistent with the prediction made by the GSA model of IBS, and with previous examinations that have found changes in avoidance to mediate outcomes following this exposure-based treatment for adults and children with IBS (Bonnert et al., 2018; Hesser et al., 2018). More broadly, the findings highlight that insightful combination of mediators and moderators can be a fruitful avenue in the search of answers to the central question: what works for whom?

Similar to IBS-specific avoidance, IBS-specific anxiety has also been found to mediate outcomes following exposure-based CBT (Ljôttson, Hesser, et al., 2013; Wolitzky-Taylor et al., 2012). Yet, contrary to predictions, IBS-specific anxiety was not found to be a predictor nor moderator of the outcome in this study. This finding aligns with the result of one previous study that used the same measure (i.e., VSI) of IBS-specific anxiety (Ljôttson, Andersson, et al., 2013). A potential explanation for the lack of a moderating effect of the VSI may be that the measure focuses primarily on cognitive and perceptive aspects of GSA (worry about symptoms, symptom awareness, intrusiveness of symptoms) while the ICBT directly targets behavioral aspects of GSA (avoidance and control behaviors). Thus, the exposure-based ICBT may be more suitable for “high avoiders” rather than “high worriers”. In addition, in direct comparisons of several putative mediator variables, across different analytic models, IBS-specific avoidance was found to be

moderators (VSI², IBS-BRQ²) and the changes in outcomes in piecewise growth models. There were no statistically significant interactions between the quadratic term and condition on slope changes prior to (slope 1) and following the onset of exposure in ICBT (slope 2) (ps > .1).
the most clear-cut mediator in our trial (Hesser et al., 2018). Weaker evidence was provided for IBS-specific anxiety, although it outperformed non-IBS specific variables. Thus, taken together, this points to IBS-specific avoidance as a more important process variable than IBS-specific anxiety in exposure-based CBT for IBS. Of course, measurement issues could play a role. Indeed, it has been argued that interaction effects are sensitive to the scale of measurement and that lack of an identified moderator effect may provide grounds for measurement improvement (MacKinnon, 2011).

The results should also be interpreted in the light of other limitations. First, the study was powered to detect small effects between conditions on the outcome, but no a prior power calculation was performed on the higher-order interaction effects that were examined in the current study. Although the study was based on a fairly large sample, identifying interactions normally require larger sample sizes than detecting main effects. On a related note, while these analyses were theoretically justified based on the GSA model, they were not prespecified. Given this, our findings should be viewed as exploratory and are in need of confirmatory replication, preferably using an appropriate experimental design for testing moderation in a rigorous way (e.g., miss-match design). Second, the analysis was based on all individuals who were randomized, irrespective of whether they complied with the treatment (i.e., ITT-analysis). A secondary analysis of the primary outcome, using a complier average causal effect analysis, indicated that the relative effect of exposure on outcomes was substantially larger than those obtained in ITT-analysis (Hesser et al., 2017). The main reason why we did not test moderators based on such an analytic model was that this complicates model specifications (see Jo, 2002). It could also be argued that ITT-analysis is more relevant for policy decisions and, consequently, is potentially the correct data analytic model when examining moderators that have clear clinical implications in terms of treatment selection among all individuals with IBS who are eligible for treatment (rather than just the subgroup of compliers). Third, it should be noted that treatments were delivered over the internet and this may have restricted the generalizability of the findings to other treatment formats, including face-to-face.

Notwithstanding the limitations, the current study provides the first evidence for that exposure for IBS is especially beneficial in reducing IBS symptoms among individuals who have marked levels of avoidance at pretreatment. Reflecting the same association but in the other end of the scale, not all individuals with IBS may benefit from exposure. Our results suggest that individuals with low levels of avoidance (approximately 0.6 Sd below the sample mean) did not significantly improve from the added exposure component in ICBT. For this subgroup exposure exercises may not be warranted in addition to the general behavioral components as implemented in ICBT-WE treatment.

The specific details of avoidance in IBS should be subject to further studies. Avoidance can take on many forms and, of course, not all avoidance is maladaptive. It is critical to understand under which set of conditions different forms of avoidance interact with specific treatment techniques to produce desired outcomes. Laboratory studies with high internal validity have the potential to provide a more detailed analysis on the underlying mechanisms involved in exposure therapy for IBS. Treatment comparisons are also needed in which the design explicitly incorporates moderators based on theory-based predictions. Given the present findings, it would be valuable if such clinical trials single out key treatment components, select candidate variables based on identified mediators of treatment outcome, and evaluate interaction effects at various relevant time points throughout the course of the trial, rather than aggregating across time points and treatment components. Such a theory-driven strategy may be more successful in providing information that can help guide matching of patient characteristics to different psychological therapies for IBS.

Credit author statement

Hugo Hesser: Conceptualization, Methodology, Investigation, Writing – original draft, Visualization, Formal analysis. Erik Hedman-Lagerlöf: Conceptualization, Methodology, Investigation, Writing – review & editing. Per Johän Lindfors: Methodology, Investigation, Writing – review & editing. Erik Andersson: Methodology, Investigation, Writing – review & editing. Björn Ljotsson: Conceptualization, Methodology, Investigation, Software, Supervision, Data curation, Project administration, Writing – review & editing.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors wish to thank all contributors to the IBS-0 project. Data from this clinical trial has been previously published. Findings from the data collection have been reported in separate manuscripts (all cited in the current manuscript). MS 1 (published) focuses the effects on all primary and secondary outcomes; M2 (published) focuses on the effects on the primary outcome among those who adhered to the treatment protocol using complier average causal effect analysis; MS 3 (published) focuses on processes of change using mediation and moderated mediation analysis (i.e., whether the effect on mediators was moderated). MS 4 (the current manuscript) focuses on moderators of the effects on the primary outcome.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2021.103862.

References


