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The role of avoidance behavior in the treatment of adolescents with irritable bowel syndrome: A mediation analysis

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ABSTRACT

Irritable bowel syndrome (IBS) is common in adolescents with a pronounced negative impact on quality of life. A pattern of avoidance behavior is commonly seen in the IBS population, which is associated with more gastrointestinal (GI) symptoms. Exposure-based cognitive behavior therapy (CBT) targets the avoidance behavior to reduce symptoms, but it is unknown whether reduced avoidance is a mediator of symptom improvement in adolescent IBS. Stress has been suggested to play a key role in worsening GI symptoms and is also a potential mediator of the treatment effect in IBS. This study was based on data from a randomized controlled trial (N = 101) that evaluated exposure-based internet-delivered CBT (Internet-CBT) compared with a wait-list for adolescents with IBS. We investigated whether avoidance behavior and perceived stress mediated the improvement in global GI symptoms due to treatment. We found that a change in avoidance behavior, but not perceived stress, mediated the effect of exposure-based Internet-CBT on GI symptoms. The decrease in avoidance behavior explained a large portion (67%) of the total treatment effect. Moreover, a unidirectional relationship over time was observed between avoidance behavior and GI symptoms. Our conclusion is that exposure-based CBT in adolescent IBS reduces avoidance and, consequently, reduces GI symptoms.

1. Introduction

Irritable bowel syndrome (IBS) is the most common of the pediatric pain-predominant functional gastrointestinal disorders (P-FGIDs). According to the diagnostic Rome III criteria, IBS is characterized by at least weekly abdominal pain or discomfort with a disturbed defecation pattern and a duration of at least 2 months (Rasquin et al., 2006). There is a worldwide prevalence of adolescent IBS of 8% (Korterink, Diederen, Benninga, & Tabbers, 2015a). The disorder has a profound negative impact on quality of life and often persists into adulthood (Chitkara, van Tilburg, Blois-Martin, & Whitehead, 2008).

There is weak support for the efficacy of medical or dietary treatment for pediatric IBS (Korterink, Rutten, Venmans, Benninga, & Tabbers, 2015b). Although cognitive behavior therapy (CBT) is generally considered an effective treatment for adolescent P-FGIDs (Chiou & Nurko, 2010), the availability is low (Reed-Knight, Claar, Schurman, & van Tilburg, 2016). There is only one study that has specifically investigated the effect of CBT for adolescent IBS (Bonnert et al., 2017). Previously conducted studies of CBT for chronic pain, where P-FGIDs are often included, have yielded mixed results (Eccleston et al., 2014). There is thus a need to further investigate CBT for pediatric IBS.

One potential reason for the mixed findings, in terms of unstable long-term effects, is that the contents of the CBT protocols that have been evaluated include different interventions that target different putative mechanisms of the disorders. Commonly used interventions are relaxation to reduce stress and stress-induced symptoms, parental behavior change, behavioral activation despite pain, and coping

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techniques such as distraction, thought-stopping and positive self-talk (Groß & Warschburger, 2013; Levy et al., 2010; Palermo et al., 2016; Palermo, Wilson, Peters, Lewandowski, & Somhegyi, 2009; Robins, Smith, Glutting, & Bishop, 2002; Van Der Veek, Derkx, Benninga, Boer, & De Haan, 2013). The term multicomponent CBT has been used to describe these interventions that comprise a variety of strategies (Palermo, Eccleston, Lewandowski, Williams, & Morley, 2010). A potential problem with multicomponent CBT is that the interventions are seldom based on clear hypothesized mechanisms of effect. If the different components are not coherent, the efficacy of the intervention may be reduced. A typical example may be an intervention that stresses the importance of changing maladaptive IBS-related thoughts and simultaneously encourages the patient to use distraction as a coping technique.

To develop effective treatments there is a need to establish which specific components of a treatment that are effective and which are not (Kazdin, 2007). Mediation analysis can be used to identify possible mechanisms that underlie change in the desired outcome and thereby indicate which components are critical to include in the treatment (Kazdin, 2009; MacKinnon et al., 2007). A prior mediation study on IBS in adults showed that the effect of internet-delivered exposure-based CBT (Internet-CBT) on gastrointestinal (GI) symptom severity was mediated by reductions in GI-specific anxiety (Ljótsson et al., 2013). The mediation analysis was based on a study that included 195 participants with IBS who were randomized to either Internet-CBT based on exposure principle or internet-delivered stress management (Ljótsson et al., 2011). The study showed that the exposure-based CBT was superior to the stress management condition. The mediation analyses were based on weekly measurements of mediators and outcome and showed that change in GI-specific anxiety but not change in perceived stress explained the treatment effect on GI symptoms. Furthermore, change in GI-specific anxiety preceded change in symptom severity, but not the other way around (Ljótsson et al., 2013). To the best of our knowledge, no mediation analysis have been published on CBT for pediatric IBS. Previous mediation analyses on pediatric chronic pain, in which children and adolescents with IBS are sometimes included, have found that change in pain has been mediated by changes in coping behaviors (Van der Veek, Nobel, & Derkx, 2012), parental behavior (Levy et al., 2014; Sieberg, Williams, & Simons, 2011), pain catastrophizing (Levy et al., 2014), parental perceived pain threat (Levy et al., 2014), and pain interference together with pain impairment beliefs (Wicksell, Olsson, & Hayes, 2011).

However, the data underlying these mediation analyses have not been optimal to investigate mediational processes. Two of the studies relied on cross-sectional data for which the mediator and outcome were assessed at post-treatment only (Sieberg et al., 2011; Van Der Veek, Derkx, De Haan, Benninga, & Boer, 2012). To causally demonstrate a mediating effect of a proposed treatment mechanism a timeline between change and outcome must be established (Cole & Maxwell, 2003), which necessarily involves repeated measurements. Two of the previously conducted studies used a design in which the mediator was assessed at pre- and post-treatment and the outcome was assessed 3–12 months after treatment termination (Levy et al., 2014; Wicksell et al., 2011). A weakness with this type of design is that it cannot be used to investigate a treatment process where the changes in the mediator and the outcome are correlated and occur gradually during the treatment period. For this reason, it has been suggested that both the mediator and the outcome should be assessed frequently with close intervals during the treatment (Hesser, 2015). This approach enables analysis of whether the change in the mediator occurs before the change in the outcome (Kazdin, 2009).

In summary, only one randomized controlled trial (RCT) has investigated CBT specifically in adolescent IBS; most protocols targeting P-FGIDs have included multiple components; and there are important methodological limitations in previous studies on putative mediators of the treatment effect in CBT for chronic pain disorders.

Our recently published study on the efficacy of Internet-CBT in adolescents with IBS (Bonnert et al., 2017), evaluated an exposure-based treatment. We found significant improvements in both GI symptoms and in secondary outcomes (e.g., quality of life), with stable or further increased improvements at a 6 month follow-up. Exposure-based Internet-CBT has also been successful for adult IBS in reducing symptoms compared with a wait-list control, stress management, and behavior therapy without exposure (Ljótsson et al., 2011; 2010; 2014). Furthermore, it has demonstrated preliminary positive effects in children and adolescents with P-FGID (Bonnert et al., 2014; Lalouni et al., 2016). The exposure-based Internet-CBT differs from previous multicomponent CBT-protocols for P-FGIDs by emphasizing one main treatment strategy, namely exposure to GI symptoms. The treatment is based on the evidence indicating that heightened visceral sensitivity to GI symptoms and fear for symptoms (GI-specific anxiety) are associated with increased levels of GI symptoms (Labus et al., 2004). To avoid situations that might elicit symptoms and try to control symptoms if they arise a pattern of avoidance behavior is commonly seen in the IBS-population, a strategy that is associated with more GI symptoms (Labus, Mayer, Chang, Bolus, & Naliboff, 2007).

1.1. Proposed mediator: avoidance behavior

Although Mowrer's two-factor theory has had a major clinical impact, especially for the use of exposure therapy to reduce fear (Krypotos, 2015), it has been criticized for not being able to explain avoidance in the absence of fear (Krypotos, 2015; LeDoux, Moscarello, Sears, & Campese, 2017). To explain the development and maintenance of excessive avoidance behavior, also in the absence of fear, LeDoux et al. (2017) suggested a three-step model: A neutral stimulus is associated with a threat through classical conditioning which elicits an adaptive response (that may include fear). To escape the now aversive stimulus the individual develops avoidance behavior that is negatively reinforced through operant conditioning. Over time the avoidance behavior becomes habitual and persistent. In the case of IBS avoidance prevents extinction of the threat responses associated with GI symptoms. Fig. 1 illustrates the respondent conditioning of GI symptoms in IBS and how avoidance behavior maintains the association.

Robust findings from experimental research have shown that extinction can be viewed as inhibitory learning of the conditioned response in the presence of the conditioned stimulus (Bouton, 2004). Exposure therapy is probably the most common method used in CBT to achieve extinction of fear. In exposure therapy participants engage in systematic and repeated contact with the fear-provoking stimulus without attempting to avoid or control the fearful stimulus (Barlow, Allen, & Choate, 2004; White & Barlow, 2004). Research on anxiety disorders has demonstrated that exposure leads to large reductions in anxiety (Vervliet et al., 2013). However, relapse of the conditioned response has been observed in humans when the contexts changes (Vervliet et al., 2013). Even if the conditioned stimuli after successful exposure therapy are associated with the inhibitory response, the association with the originally conditioned response still remains (Bouton, 2004). Thus, repeated exposure in many different contexts may strengthen the inhibitory response, and thereby prevent reoccurrence of fear (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014).

Hence, for an exposure treatment to be successful in the long term, it is probably necessary that avoidance behavior in everyday life decreases. Overall reduction in behavioral avoidance provides many opportunities for *in vivo* exposures in different contexts and may thus be an important mediator to successfully target the mechanism of GI-specific anxiety. The role of reduced avoidance behavior has not been previously studied in CBT for adolescents with IBS.

1.2. Stress as competing mediator

To control for specificity of the effect of the proposed mediator it is