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Intolerance of uncertainty as a mediator of reductions in worry in a cognitive behavioral treatment program for generalized anxiety disorder

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Abstract

Growing evidence suggests that intolerance of uncertainty (IU) is a cognitive vulnerability that is a central feature across diverse anxiety disorders, including generalized anxiety disorder (GAD). Although cognitive behavioral therapy (CBT) has been shown to reduce IU, it remains to be established whether or not reductions in IU mediate reductions in worry. This study examined the process of change in IU and worry in a sample of 28 individuals with GAD who completed CBT. Changes in IU and worry, assessed bi-weekly during treatment, were analyzed using multilevel mediation models. Results revealed that change in IU mediated change in worry (ab = -0.20; 95% CI [-.35, -.09]), but change in worry did not mediate change in IU (ab = -0.16; 95% CI [-.06, .12]). Findings indicated that reductions in IU accounted for 59% of the reductions in worry observed over the course of treatment, suggesting that changes in IU are not simply concomitants of changes in worry. Findings support the idea that IU is a critical construct underlying GAD.

Keywords

Intolerance of uncertainty; anxiety; worry; GAD; treatment

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1. Introduction

Intolerance of uncertainty (IU), the dispositional tendency to experience fear of the unknown, is considered to be an important factor in the development and maintenance of anxiety disorders (Carleton, 2012). IU includes beliefs that uncertainty is threatening, stressful, and anxiety provoking, as well as the desire to avoid situations where uncertainty and ambiguity may be present (Buhr & Dugas, 2002; Dugas, Gosselin, & LaDoucuer, 2001). Although IU likely contributes to multiple anxiety disorders (e.g., Carleton, 2012), the most comprehensive conceptual model of the relationships between IU and anxiety psychopathology was designed primarily to account for symptoms of generalized anxiety disorder (GAD; Dugas, Gagnon, Ladouceur, & Freeston, 1998). GAD features worry, defined as “repetitive, uncontrollable thoughts about negative life events” (Segerstrom, Tsao, Alden, & Craske, 2000), as a predominant symptom (American Psychiatric Association, 2013). For those high in IU, the possibility of negative outcomes is proposed to trigger maladaptive behavioral and cognitive reactivity (e.g., biased interpretations of the situation, increased need for information during decision-making) that serve to increase worry and anxiety (Dugas et al., 2005; Dugas & Robichaud, 2007; Ladouceur, Gosselin, & Dugas, 2000). Moreover, IU contributes to other problematic cognitive processes, including poor problem orientation and cognitive avoidance, which conjointly and paradoxically maintain worry and anxiety (Dugas & Robichaud, 2007).

Data from several treatment outcome studies indicate that anxiety interventions impact IU, and suggest that IU may play a role in maintaining anxiety. Dugas and colleagues (e.g., Dugas et al., 2010; Dugas & Ladouceur, 2000; Dugas et al., 2003) have developed a cognitive-behavioral intervention specifically to address IU as part of a comprehensive treatment for GAD, which has been shown to effectively decrease IU and other symptoms (e.g., worry, depression). Other types of CBT interventions that do not feature an explicit focus on IU also appear to reduce IU in GAD (e.g., Boswell, Thompson-Hollands, Farchione, & Barlow, 2013; Hewitt, Egan, & Rees, 2009; van der Heiden, Muris, & van der Molen, 2012). Thus, preliminary evidence suggests that IU is malleable with CBT interventions in individuals with GAD.

Establishing IU as a process relevant to symptom reduction is critical to validate cognitive theories and to identify treatment strategies to optimize therapeutic outcomes (Kazdin, 2007; Smits, Julian, Rosenfield, & Powers, 2012). The aforementioned treatment outcome studies provide evidence that IU changes from pre to post treatment, but the process by which IU changes relative to other symptoms has not been empirically established. For example, it is possible that reducing IU lessens worry, or that IU levels are lower at the end of treatment because worry or general anxiety symptoms have decreased. One case-controlled study suggests that reductions in IU precede reductions in worry in treatment for GAD (Dugas & Ladoceur, 2000). An analogue study of exposure-based treatment components also suggested that reductions in IU predicted subsequent reductions in worry (Goldman, Dugas, Sexton, & Gervais, 2007). Further support for a causal relationship between IU and worry comes from experimental psychopathology studies indicating that manipulating IU appears to impact worry (Ladoucoeur et al., 2000; Meeten, Dash, Scarlet, & Davey, 2012). However, models demonstrating reduction in IU as a mediator of reductions in worry longitudinally

over the course of treatment have yet to be confirmed empirically. Evaluating whether or not changes in IU precede and account for symptom change during treatment provides a more rigorous test of the hypothesis that IU is a core construct that perpetuates worry and anxiety (Kazdin, 2007).

The present study examined the process of change in IU and worry in a sample of individuals with GAD who completed a CBT program. The goal of the analyses was to test the proposed mediational relationship outlined in models of GAD and worry - specifically that reductions in IU would account for reductions in worry over the course of treatment. Using data from an open trial of a transdiagnostic CBT treatment protocol for anxiety, changes in IU and worry assessed at pre-treatment and bi-weekly during treatment were analyzed using multilevel mediation procedures. We hypothesized that reductions in IU would mediate subsequent reductions in worry across sessions.

2. Method

2.1. Design

Data were drawn from a trial examining neural differences between healthy and anxious individuals and the relationship between neural activity and treatment response to 10 sessions of cognitive behavioral therapy (clinicaltrials.gov Identifier NCT00947570). Analyses utilized symptom measures collected from participants over the course of CBT. Each assessment in the mediation models was collected at baseline and sessions 2, 4, 6, 8, and 10. The institutional review board of the University of California San Diego approved all procedures, and all participants provided written informed consent.

2.2. Participants

Participants were 28 individuals aged 18-55 recruited from the San Diego community, who met current diagnostic criteria for primary GAD and had at least a high school level education. Because of the specific theoretical link between IU and GAD, individuals were selected based on GAD diagnosis from a larger sample of individuals with anxiety disorders who were enrolled in the clinical trial. Exclusion criteria included a diagnostic history of a psychotic disorder, bipolar I disorder, organic mental disorder, substance dependence (past 12 months) or abuse (past month), use of psychotropic or anti-epileptic medication (past 6 weeks), consumption of more than 6 caffeinated beverages daily or cigarette use, and unwillingness or contraindications to completing fMRI scanning (e.g., potential pregnancy, history of claustrophobia, metal in body). Individuals with comorbid depression were eligible provided the level of depression was not in the severe range (operationalized as Quick Inventory of Depression Symptomology-6 ≤ 18 and neither of depressed mood or anhedonia most of the day nearly every day during the past two weeks; Rush et al., 2006). Eligibility for the study was determined with structured diagnostic interviewing using the MINI Neuropsychiatric Interview (MINI) conducted by masters- and doctoral-level interviewers. Potential participants were referred to the study from the University of California San Diego (UCSD) and UCSD-affiliated outpatient clinics, other local clinical facilities, and through community-based advertisements.

2.3. Intervention

The CBT program consisted of 10 one-hour individual in-person sessions delivered over 10-12 weeks. The intervention was adapted from the protocol developed as part of a multi-site trial of evidence-based treatment for anxiety in primary care (Coordinated Anxiety Learning and Management program [CALM]; for a detailed review of treatment components see Craske et al., 2009). The intervention included generic modules of anxiety treatment (self-monitoring, psychoeducation, breathing retraining, and relapse prevention). The intervention also included disorder-specific modules addressing exposure to internal and external cues (e.g., imaginal exposure to worry themes) and cognitive restructuring (e.g., generating alternative thoughts in response to catastrophic negative predictions). Modules did not specifically aim to target IU; however, in the course of therapy participants completed activities or discussed thoughts that may have addressed concerns about uncertainty (see Mahoney & McEvoy, 2012, and van der Heiden et al., 2012 for examples of general CBT's effects on IU). Modules were presented in a computer-assisted, interactive module format that directed the clinician and patient. Clinicians for the study were Ph.D.-level psychologists with specialized training in cognitive behavioral treatment of anxiety. To assure treatment fidelity, all sessions were audiotaped (with patients' permission), and for each patient one session was randomly chosen to be rated on protocol adherence and clinician competence by a licensed clinical supervisor (AJL). The highest adherence rating, a 2 on a 0-2 scale, indicated that the therapist "Presented all materials per CALM Tools program;" the highest competence rating, also a 2 on a 0-2 scale, indicated that the therapist "Facilitated application of the materials. Appropriately fielded patients' questions and elicited relevant examples." In all cases, therapists received ratings of "2", indicating they adhered to the treatment protocol, and appropriately delivered the components of the CALM intervention.

2.4. Assessments

2.4.1. Demographic variables—Demographic information was collected via a self-report assessment administered at the time of the in-person screening for study eligibility. This assessment included questions regarding ethnicity, gender, and socioeconomic status.

2.4.2. Diagnostic status—To determine diagnostic status and other initial eligibility criteria, a study clinician administered the MINI (Sheehan et al., 1998). Interviewers were individuals with prior clinical diagnostic experience (e.g., psychologists, marriage and family counselors), and underwent training to develop proficiency in the MINI assessment. Quality assurance procedures were in place to assure diagnostic accuracy (e.g., taping and re-rating of assessments by expert interviewers).

2.4.3. Worry—Worry was assessed using the abbreviated Penn State Worry Questionnaire (PSWQ-A; Hopko et al., 2003). The PSWQ-A is an 8-item assessment of the tendency to worry. It possesses adequate psychometric properties (i.e., high internal consistency, test-retest reliability, convergent-divergent validity) and correlates highly with the full-length PSWQ (Crittendon & Hopko, 2006; Hopko et al., 2003). Cronbach's αs ranged from 0.84 to 0.92.

2.4.4. Intolerance of uncertainty—Intolerance of uncertainty was assessed using the Intolerance of Uncertainty Scale (IUS; Buhr & Dugas, 2002). The IUS consists of 27 items that assess the degree to which the individual has negative beliefs about and reactions to uncertainty. This measure possesses adequate psychometric properties (Buhr & Dugas, 2002, 2006; Carleton, Sharpe, & Asmundson, 2007; Norton, 2005). Based on evidence that the 12-item version of this measure demonstrates reduced redundancy in items while maintaining sound psychometric properties relative to the full 27-item version (Carleton, Norton, & Asmundson, 2007; Carleton, Thibodeau, Osborne, & Asmundson, 2012; Gentes & Ruscio, 2011; Khawaja & Yu, 2010), we analyzed the 12-item IUS derived from this questionnaire[i]. Cronbach's αs ranged from 0.92 to 0.94.

2.5 Analytic strategy

Data formed a multilevel structure with repeated measures collected over time (i.e., across 10 treatment sessions) nested within participants. For all models, the lower level (Level 1) data included the repeated measures of worry and IU collected bi-weekly at the treatment sessions. Individual participants were the upper level units (Level 2). All participants in the study were analyzed using an intent-to-treat approach. A multilevel modeling framework, which effectively handles missing data and varied numbers of observations across individuals, was thus appropriate for the data structure. All analyses were completed using SPSS version 18.0 software.

To determine the presence of mediation, we examined whether or not the potentially mediating variable (i.e., IU) partially or fully accounted for the relationship between the independent variable (i.e., time, operationalized by session) and the outcome of interest (i.e., worry). Originally described by Baron and Kenny (1986), mediation traditionally involves demonstration that the relationship between a given independent variable and the outcome of interest is reduced when the mediator and independent variable are modeled simultaneously (see also Mackinnon, Fairchild, & Fritz, 2007 for an updated description of mediated effects). Mediated effects can also be explored in the context of longitudinal, multilevel data using a multilevel modeling approach (lower level mediation; Bauer, Preacher, & Gil, 2006; Kenny, Korchmaros, & Bolger, 2003).

We tested two models accounting for the relationship between IU and worry following guidelines established by Kenny et al. (2003) and Bauer et al. (2006). We first modeled mediation in the predicted direction, such that changes in IU preceded and statistically mediated changes in worry over time. We subsequently tested a reverse mediation model, where changes in worry predicted changes in IU over time. Repeated assessments allowed us to include the mediator as a "lagged" variable with temporal precedence; that is, we examined whether changes in the mediator at time point *t* influenced the outcome variable at time point *t* + 1 (see for example Aderka, Foa, Applebaum, Shafran, & Gilboa-Schechtman, 2011; Donegan & Dugas, 2012). For each model we also indexed the significance of potential mediated effects using the Prodclin program (MacKinnon et al., 2007), which

[i]Analyses were also conducted with the full-length version of the IUS. These analyses produced the same pattern of results, and thus only the IUS-12 analyses are reported here. Results from analyses with the full IUS are available from the first author upon request.

provides confidence intervals for the indirect effect, and calculated the percent mediation for each model using the procedures described by Kenny and colleagues (2003).

3. Results

3.1. Demographic and clinical variables

Table 1 presents data on participant demographic and socioeconomic characteristics. Descriptive information on clinical variables, including PSWQ-A and IUS scores, is also presented in this table. Examination of change over sessions indicated that symptom measures ameliorated with treatment (PSWQ-A: $F(1, 122) = 8.23$, $p < .01$, $\eta_p^2 = .12$; IUS: $F(1, 114) = 51.69$, $p < .001$, $\eta_p^2 = .41$).

3.2. Intolerance of uncertainty reduction as a mediator of worry reduction

First, we tested the hypothesized mediation model; namely that reductions in IU preceded and mediated subsequent reductions in worry. The results of mediation models are presented in Tables 2 and 3. We examined whether reductions in IU resulted in reduced worry as proposed in our hypothesized model (Table 2). As noted in the table, the Level 1 model regressing worry on time indicated that worry symptoms significantly reduced during treatment ($B = -.34$, $p < .001$, path c). Regressing IU on time also indicated that IUS scores decreased over the course of treatment ($B = -1.68$, $p < .001$; path a). When entering time and IU simultaneously to predict worry, IU predicted worry ($B = .12$, $p < .001$; path b), but time was no longer a significant predictor ($B = -.14$, $p = .23$; path c′). Tests of the indirect effect using the Prodclin program indicated the presence of a significant mediated effect, as the confidence intervals for the indirect effect did not cross zero (ab = -0.20; 95% CI [-.35, -0.09]). Moreover, change in IU accounted for 59% of the effect of time on worry reduction.

Second, the reverse mediation model was examined (Table 3). When regressing IU on time and worry, the effect of time on IU remained significant and was minimally attenuated ($B = -2.20$, $p < .001$; path c′). There was no evidence of statistically significant mediation (ab = -0.16; 95% CI [-0.06, 0.12]) and change in worry accounted for less than 1% of the effect of time on IU reduction.

4. Conclusions

Cognitive models suggest a causal relationship between IU and worry, and reduction of IU has been proposed as a potential process by which psychological treatments may reduce worry. We sought to examine the relationship between reduction in worry and IU over the course of CBT for individuals with GAD. Consistent with our hypothesis, results revealed that IU and worry ameliorated over time, and that reductions in IU significantly mediated subsequent reductions in worry over the course of treatment. The reverse mediation model indicated that the converse patterns of mediation did not hold; change in IU was not significantly mediated by change in worry over time.

Theoretical models and empirical data suggest that IU is a cognitive vulnerability to anxiety (Carleton, 2012). IU plays a central role in the model of GAD outlined by Dugas and colleagues (e.g., Dugas & Robichaud, 2007), which proposes that individuals with high

levels of IU exhibit negative psychological reactions to uncertain situations, and tend to respond to uncertain situations with worry. Findings indicating mediation of reduction in worry by reduction in IU add to a growing body of literature suggesting that IU is not only associated with worry but may be causally linked to it (e.g., Ladouceur et al., 2000; Meeten et al., 2012). Consistent with trials of CBT for anxiety (e.g., Boswell et al., 2013; Dugas et al., 2003, 2010; Ladouceur et al., 2000; Mahoney & McEvoy, 2012), our data suggests that CBT-based interventions effectively reduce IU for individuals with GAD. While reductions in IU have been shown to precede reductions in worry in short-term exposure exercises with high worriers (Goldman et al., 2007), our analysis of treatment data extends examination of change over time to a sample of clinically anxious individuals completing CBT. Data not only suggest a reduction in IU with treatment, but longitudinal observation of changes across constructs establishes temporal precedence of change in a group of individuals completing treatment.

Reducing IU during treatment might promote subsequent reductions in worry in a number of ways. First, cognitive behavioral treatments aimed at decreasing anxiety promote behavioral exposure to uncertain situations, which would likely decrease reactivity to uncertainty. If anxiety surrounding uncertain situations decreases (corresponding to an increased tolerance for uncertainty), a concomitant decrease in avoidance behaviors (i.e., worry) could be reasonably expected to follow. Treatment components might also alter beliefs about uncertainty. For example, following treatment individuals may be less likely to believe that worry is an effective or necessary way to plan for uncertain outcomes, or may no longer believe that uncertainty is inherently bad. However empirical evidence is needed to evaluate the potential of these explanations to account for the mediation findings observed in the present study.

Given that IU accounts for reductions in worry over time, incorporating an emphasis on IU may be helpful within treatment protocols for disorders characterized by worry. In the present treatment protocol, IU was not an explicit intervention target. Individuals were encouraged to complete exposure exercises wherein they confronted situations that invoked anxiety generally. However, exposure to uncertainty was undoubtedly present during anxiety exposures and associated cognitive restructuring may have touched upon negative beliefs about uncertainty more broadly. Indeed, prior studies found that CBT programs do reduce IU (e.g., Mahoney & McEvoy, 2012), and in some cases IU may change more during interventions that are not IU specific as compared to those that directly aim to target IU (van der Heiden, et al., 2012). Nonetheless, deliberately including situations with high levels of uncertainty within an exposure hierarchy framework while addressing negative beliefs about the uncertain potential for negative outcomes (e.g., treatment as described by Dugas et al., 2010) may be even more successful in producing IU reductions. To date, no studies have compared the process of change between intervention approaches with respect to reductions in IU. In addition, it remains to be established if individual-level characteristics, such as an individual's level of IU or other factors, would make him/her a more ideal candidate for a specific type of approach. Future research is needed to address ways to maximize treatment effectiveness while also personalizing treatments (Kazdin, 2007; Smits et al., 2012).

Several study limitations should be noted. First, selection of participants based on neuroimaging inclusion and exclusion criteria limits generalizability (e.g., participants utilizing certain medications or substances were excluded). The effect size observed for reductions in the PSWQ-A were also modest. It is possible that aspects of the transdiagnostic CALM program (as opposed to GAD-specific CBT programs) did not optimally target worry-related symptoms. Alternatively, the particular sample treated may have possessed features that negatively influenced treatment response as compared to prior studies, or the abbreviated PSWQ may have been less sensitive to change than the full version. Future studies would ideally include a broader range of participants with a larger sample and incorporate different treatment types to address whether or not such patterns of change are consistent for other individuals in other intervention modalities. In addition, recent evidence supports the role of both IU and worry across diverse anxiety disorders (e.g., OCD, panic disorder; Boswell et al., 2013; Carleton, 2012), and suggests that reductions in IU have the potential to mediate change in worry and other anxiety-related constructs across different conditions. Further research is warranted to examine how IU changes over time in different disorders, and how IU reductions may influence change in worry or other disorder-specific constructs (e.g., obsessions or compulsions in OCD). The design did not allow for comparison of mediation processes to a control group. Thus, one cannot conclude that the changes in worry and IU were directly attributable to the treatment components per se, as opposed to non-specific factors or the passage of time. Finally, assessments were conducted every other session only within the acute phase of treatment. Patterns of change within the measured sessions or beyond the acute phase of treatment thus cannot be determined.

In summary, reductions in IU mediated subsequent reductions in worry over the course of CBT in a sample of individuals diagnosed with GAD. Results are consistent with theoretical models outlining the importance of IU as a cognitive vulnerability to GAD that operates via its effect on worry. Thus, IU is malleable with treatment and targeting IU during treatment may be one effective strategy to reduce worry.

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Highlights

- Intolerance of uncertainty (IU) is theorized to be a key factor pathological worry
- The effect of CBT on IU and worry was examined over the course of CBT
- Changes in IU mediated subsequent changes in worry

Table 1

Demographic and Clinical Variables

Variable	
Mean Age (*SD*)	34.4 (10.8)
Gender (% female)	71.4
Race (N per category)	
Hispanic	1
Asian	3
White	22
Black	0
Native American	1
Other or mixed race	1
Mean Years Education (*SD*)	15.5 (2.1)
Mean IUS score	
Baseline	37.96 (10.4)
Session 2	39.36 (10.5)
Session 4	37.08 (11.0)
Session 6	32.72 (12.0)
Session 8	32.50 (9.8)
Session 10	31.60 (10.5)
Mean PSWQ-A score	
Baseline score	18.0 (2.6)
Session 2	18.2 (2.4)
Session 4	18.3 (2.3)
Session 6	17.3 (2.1)
Session 8	17.7 (2.6)
Session 10	16.7 (2.7)

Note: IUS: 12-item Intolerance of uncertainty scale; PSWQ-A: 8-item Penn State Worry Questionnaire

Table 2

Summary of Multilevel Regression Analyses for Mediational Model (IU mediating worry)

Step	Path	Predictor variable	Outcome variable	*B*	SE *B*	T	p
1	c	Time	Worry	-0.34	0.10	-3.36	< .01
2	a	Time	IU	-1.68	0.37	-4.57	< .001
3	b	IU	Worry	0.12	0.03	4.56	< .001
	c′	Time	Worry	-0.14	0.11	-1.22	.23

Table 3

Summary of Multilevel Regression Analyses for Reverse Mediational Model (worry mediating IU)

Step	Path	Predictor variable	Outcom variable	*B*	SE *B*	T	p
1	c	Time	IU	-2.17	.40	-5.35	< .001
2	a	Time	Worry	-0.16	0.13	-0.92	.37
3	b	Worry	IU	-0.11	0.25	-0.46	.65
	c′	Time	IU	-2.20	0.41	-5.32	< .001