

**THE ROLE OF INTOLERANCE OF UNCERTAINTY IN THE TREATMENT OF
ANXIOUS YOUTH**

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ABSTRACT

Background: Intolerance of uncertainty (IU) is a cognitive vulnerability implicated in the etiology and maintenance of pathological anxiety. Research has yet to examine IU during the course of treatment for anxious youth to inform whether IU may be an important construct to target to improve the effectiveness of available interventions. The current study evaluated whether IU mediates the relationship between anxiety severity pre- to post-treatment while controlling for levels of IU at pre-treatment.

Methods: Participants were 69 youth aged 7 to 17 who participated in cognitive behavioral therapy (CBT) for anxiety. Youth and their caregiver(s) completed a diagnostic interview administered by an Independent Evaluator (IE) and self- and parent-report measures pre- and post-treatment. Multiple regression mediation analyses examined the degree to which mid-treatment IU mediates the relationship between anxiety severity pre- to post-treatment while controlling for pre-treatment IU. Multiple regression mediation analyses also examined the degree to which post-treatment IU mediates the relationship between anxiety severity pre- to post-treatment while controlling for pre-treatment IU. For both analyses, three separate models were estimated to measure anxiety severity (a) by IE-report, (b) by youth self-report and (c) by parent-report.

Results: There were no significant indirect effects for IE-, youth-, or parent-report models when mid-treatment IU or post-treatment IU were tested as potential mediators.

Discussion: Additional work is needed to explore other potential mediators of CBT outcomes as well as the role of IU before attempts are made to target IU directly to improve current interventions. Study limitations and future directions are discussed.

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CHAPTER 1

INTRODUCTION

Anxiety disorders are the most prevalent mental health condition and approximately one third of the population will experience an anxiety disorder in their lifetime (Bandelow & Michaelis, 2015). Anxiety disorders tend to onset early with estimated prevalence rates between 10% and 32% among children and adolescents (Costello et al., 2003; Merikangas et al., 2010). If left untreated, anxiety disorders follow a chronic course resulting in meaningful functional impairment (Bandelow & Michaelis, 2015) and negative sequelae including depression, other anxiety disorders, substance abuse and suicidality (Costello et al., 2003; Cummings et al., 2014; Sareen et al., 2005; Swan & Kendall, 2016). Cognitive-behavioral therapy (CBT) is an empirically supported treatment for anxiety disorders with approximately 60% of individuals classified as treatment responders (James et al., 2015; Norton & Barrera, 2012) and evidence of reductions in negative sequelae at follow-up (Keeton et al., 2019; Puleo et al., 2011; Wolk et al., 2015). However, 30% to 40% of individuals do not achieve symptom remission post-treatment (James et al., 2015; Norton & Barrera, 2012). It is important to understand mediators through which CBT leads to symptom reduction to enhance treatment and improve outcomes for anxious youth.

Intolerance of uncertainty (IU) has been identified as an important cognitive vulnerability for pathological anxiety (Carleton, 2016b; Dugas et al., 1998; Holaway et al., 2006; Norton et al., 2005). Anxiety inherently requires a degree of uncertainty given that it is a product of anticipation about a future negative event that has yet to transpire. Researchers have therefore proposed IU to be a foundational aspect of maladaptive anxiety (Carleton, 2016a; Holaway et al., 2006). IU has most recently been defined as “an individual’s dispositional incapacity to endure

the aversive response triggered by the perceived absence of salient, key, or sufficient information, and sustained by the associated perception of uncertainty” (Carleton, 2016b). This definition allows one to differentiate between the feared stimulus (i.e., the unknown), emotional, cognitive, and behavioral responses to the feared stimulus (e.g., fear, avoidance, worry) and the inability to tolerate the fear response to uncertainty which is maintained by the individual’s perception of uncertainty (i.e., IU).

Research indicates that IU is a transdiagnostic vulnerability across anxiety disorders (e.g., (Carleton, 2016b; Gentes & Ruscio, 2011; McEvoy et al., 2019; Osmanağaoğlu et al., 2018). IU in youth is associated with diagnoses and symptoms of generalized anxiety disorder (Cowie et al., 2016; Donovan et al., 2016; Hearn, Donovan, Spence, & March, 2017; Read et al., 2013; Rifkin & Kendall, 2020) and social phobia (SP; Boelen et al., 2010; Cornacchio et al., 2018; Hearn, Donovan, Spence, & March, 2017; Hearn, Donovan, Spence, March, et al., 2017; Wright et al., 2016) as well as symptoms of separation anxiety disorder (SAD; Cornacchio et al., 2018; Wright et al., 2016), panic disorder (Wright et al., 2016), OCD (Wright et al., 2016) and health anxiety (Wright et al., 2016). In addition, a meta-analysis found that IU accounted for 36% and 39.69% of variance in anxiety and worry, respectively (Osmanağaoğlu et al., 2018), providing further evidence that it is an important transdiagnostic vulnerability for youth anxiety.

IU may be an important mediator in CBT. The cognitive component of CBT involves identifying negative automatic thoughts and associated maladaptive thinking patterns and challenging these thoughts. Individuals are taught to challenge negative automatic thoughts that arise in the face of uncertainty, thereby increasing their ability to cope with and tolerate uncertainty. The behavioral component of CBT consists of exposing individuals to feared situations to facilitate learning that stimuli and/or situations are not as frightening as they may

have originally thought and that they can tolerate the associated distress. There is a high degree of uncertainty involved in exposure tasks as individuals are asked to engage with feared stimuli and accept the possibility of a negative outcome (i.e., often testing whether the negative outcome will occur). In this way, CBT may be exposing individuals to uncertainty and facilitating acceptance of uncertainty (e.g., something bad could happen but I am going to do this anyways). In addition, CBT exposure tasks may culminate in a version of the feared outcome occurring (e.g., people laugh at you when you walk into a room) to help individuals learn that they can tolerate the worst case scenario. Exposure tasks may be “inoculating” individuals to uncertainty as they learn that they can tolerate the worst case scenario. IU may therefore be an important mediator of treatment outcome for anxious youth.

Despite the potential to enhance the efficacy of CBT, mediation in youth treatment outcome remains largely understudied (Carper et al., 2018). Initial research examining mediators of treatment outcome for anxious youth identified several constructs of interest including anxious self-talk (Kendall & Treadwell, 2007; Lau et al., 2010; Treadwell & Kendall, 1996), negative self-talk (Kendall & Treadwell, 2007), coping efficacy (Lau et al., 2010; Ollendick et al., 2017) and catastrophic cognitions (Ollendick et al., 2017) but did not establish temporal precedence which is necessary to identify a mechanism of change. More recent work implementing longitudinal designs has found evidence that perceived control (Pereira et al., 2018), interpretation bias (Pereira et al., 2018), positive self-talk (Hogendoorn et al., 2014), and coping efficacy (Kendall et al., 2016) mediate treatment outcome for anxious youth. Researchers have called to expand this nascent area of research and have emphasized the importance of making theory driven predictions and establishing temporal precedence in future work (Carper et al., 2018; Kendall et al., 2017).

Previous research supports examination of IU as a mediator in CBT for anxious youth. Research indicates that IU decreases over the course of individual and group treatment aimed at reducing anxiety in both adults (Bomyea et al., 2015; Boswell et al., 2013; Dugas et al., 2003; Hebert & Dugas, 2019; Hewitt et al., 2009; Katz et al., 2017; Ladouceur et al., 2000; Mahoney & McEvoy, 2012; Stevens et al., 2018; Talkovsky & Norton, 2016; van der Heiden et al., 2012) and youth (Holmes et al., 2014; Palitz et al., 2019; Wahlund et al., 2019) . Two studies implementing longitudinal designs with adults receiving treatment for GAD indicate that reductions in IU precede reductions in worry while reductions in worry do not precede reductions in IU (Bomyea et al., 2015; Dugas & Ladouceur, 2000), providing further evidence IU may be an active ingredient. Early work has also begun to target IU in the treatment of anxious youth (Holmes et al., 2014; Léger et al., 2003; Payne et al., 2011; Wahlund et al., 2019); however, these studies have small sample sizes ranging from $N = 7$ to $N = 42$, limiting the ability to draw conclusions, and foundational research examining the role of IU over the course of treatment is still needed.

Only one study to date has examined IU in the context of CBT for youth anxiety. Palitz et al. (2019) examined IU in youth ($N = 73$) aged 7 to 17 with principal anxiety diagnoses pre- and post- treatment. Results indicated that IU decreased significantly from pre- to post-treatment and that decreases in IU as measured by self- and parent-report predicted decreases in functional impairment as measured by an IE rating, decreases in anxiety severity as measured by self- and parent-report, and increases in coping efficacy as measured by self- and parent-report. However, this study did not measure IU during the course of treatment and it remains unclear whether reductions in IU temporally precede changes in anxiety symptom severity for youth. Temporal precedence is necessary to determine the degree to which IU is an active mediator of change.

The present study evaluated the degree to which IU measured at mid-treatment mediates the relationship between anxiety severity pre- to post-treatment as measured by (a) independent evaluator (IE) report, (b) youth self-report and (c) parent-report, while controlling for levels of IU at pre-treatment. It is hypothesized that IU will significantly mediate anxiety symptom reduction for IE-report, youth self-report and parent-report.

CHAPTER 2

METHODS

Participants

All study procedures were approved by the Temple University Institutional Review Board. Participants ($N = 69$) were youth aged 7-17 ($M_{age} = 12.06$, $SD = 3.17$) who received treatment at the Child and Adolescent Anxiety Disorders Clinic (CAADC) at Temple University. Youth were self-referred or referred by school personnel or health providers in the greater Philadelphia (tri-state) area. Youth were eligible to participate if they met diagnostic criteria for one or more DSM-5 principal anxiety disorders (e.g., GAD, SP, SAD, specific phobia, etc.) and had not participated in a course of CBT for at least two years. Diagnoses were determined by IEs using the Anxiety Disorders Interview Schedule for DSM-5—Child and Parent Versions (ADIS-5-C/P; Albano & Silverman, *in press*). Participants were included in the current analysis if they had complete data on measures of IU at pre-treatment and mid-treatment. Youth in the current sample met criteria for a principal diagnosis of GAD (39.1%), Social Phobia (15.9%), Separation Anxiety Disorder (5.8%), Specific Phobia (2.9%), Illness Anxiety Disorder (1.5%), Panic Disorder (1.5%), or more than one principal diagnosis (i.e., co-principal diagnoses; 33.33%). Comorbidity was high and the majority of youth met diagnostic criteria for more than one DSM-5 diagnosis (76.81%). Slightly over half of youth identified as female (52.2%) and none identified as other. The majority identified as White (75.4%), followed by Hispanic (7.2%), other (7.2%), African American (5.8%), and Asian (4.3%). Over half of participants had a household income level of \$80,000 or greater (53.6%), followed by \$70,000 – \$80,000 (11.6%), \$40,000 – \$49,999 (8.7%), not reported (7.2%), \$60,000 – \$69,999 (5.8%), \$30,000 - \$39,999 (4.3%),

\$20,000 - \$29,999 (4.3%), \$50,000 - \$59,999 (2.9%), and \$10,000 - \$19,999 (1.6%). Exclusion criteria included psychotic symptoms and current active suicidality.

Therapy

Youth were assigned to receive 16 weekly sessions of CBT using the developmentally appropriate *Coping Cat* (Kendall & Hedtke, 2006; developed for youth aged 7-12) or *C.A.T. Project* (Kendall et al., 2002; developed for youth aged 13-17) protocols or using the *Coping Cat – Accommodation Reduction Intervention* (CC-ARI; Kagan et al., under review) protocol, an adaptation of the *Coping Cat* protocol targeting parental accommodation (i.e., ways parents behave to reduce their child’s anxiety). All protocols included identical psychoeducational content for youth that was presented in different formats and different orders. The first nine sessions of all protocols are comprised of psychoeducation and skill building. In this first phase of treatment, youth are taught to identify emotions and somatic responses to anxiety, apply relaxation techniques, identify and challenge negative automatic thoughts, engage in problem solving and self-evaluate and reward their own efforts. These skills are taught in context of the F.E.A.R. plan (**F**eeling Frightened?, **E**xpecting bad things to happen?, **A**ttitudes and Actions that can help, **R**esults and Rewards) to help youth recall and implement these skills when feeling anxious. All parent sessions take place during the first nine sessions. The second phase of treatment consists of gradual individualized exposure tasks (e.g., in vivo, imaginal, interoceptive) in which the youth practices approaching rather than avoiding feared situations. *Coping Cat/C.A.T. Project* and *CC-ARI* require the same number of exposure tasks and produced comparable outcomes (Kagan et al., under review). Analyses were performed collapsing across participants.

Measures

Anxiety Disorder Interview Schedule for DSM-5 – Child and Parent Versions (ADIS-5-C/P; Albano & Silverman, *in press*). The ADIS-5-C/P is a semi-structured diagnostic interview that assesses for DSM-5 psychopathology based on parent- and child-report. Parents and children were interviewed separately by reliable IEs who were doctoral students in clinical psychology. IEs were required to reach and maintain interrater reliability of .85 and above (Cohen's Kappa). Each diagnosis was assigned a clinical severity rating (CSR) ranging from 0 to 8, with a score of 4 or higher indicating that an individual meets diagnostic criteria for the disorder. An integrated composite diagnosis was generated such that a diagnosis was considered present if endorsed by the child *or* the parent, in accordance with Silverman and Albano (1996). Principal diagnosis was determined by a CSR at least one point above the CSRs for other diagnoses, and if two disorders had the same CSR they were considered co-principal diagnoses. The ADIS-5-C/P has been updated from the ADIS-IV to reflect changes in the diagnostic system. The ADIS-IV-C/P evidences strong psychometric properties including interrater reliability, convergent validity and retest reliability (Silverman et al., 2001; Wood et al., 2002). Diagnosticians in the current study evidenced inter-rater reliability on the ADIS-5-C/P $k > .90$.

Clinical Global Impression – Severity Scale (CGI-S; Guy, 1976). The CGI-S is a 1-item IE-rated measure designed to assess anxiety symptom severity. IEs are asked to provide a rating on a 7-point Likert scale ranging from 1, *normal, not at all ill* to 7, *extremely ill* following the ADIS-5 pre- and post-assessment. The CGI-S is widely used as an outcome measure (Peris et al., 2015). It is significantly associated with the Pediatric Anxiety Rating Scale (PARS; Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002) and with clinician and client-rated symptom severity in adults with social anxiety (Zaider et al., 2003).

Multidimensional Anxiety Scale for Children – Parent and Child Report (MASC-P/C; March, Parker, Sullivan, Stallings, & Conners, 1997). The MASC is a 39-item measure with corresponding parent- and child-report forms designed to assess youth anxiety. Parents and youth are asked to rate each item on a 4-point Likert type scale ranging from 0, *never* to 3, *often*. Total scores range from 0 to 117 with higher scores indicating more severe anxiety. The MASC evidences strong psychometric properties including internal consistency $\alpha = .89-.90$ (Baldwin & Dadds, 2007; March et al., 1997; March, Sullivan, & Parker, 1999; Villabø, Gere, Torgersen, March, & Kendall, 2012), convergent validity with another youth self-report measure of anxiety (March et al., 1997), divergent validity with a youth self-report measure of depression, and retest reliability over a three-week (ICCs = .79 and .88; March et al., 1997, 1999) and three-month period (ICC = .93; March et al., 1997). The MASC can be used to predict treatment response and overall remission in anxious youth (Palitz et al., 2018). Internal consistency was $\alpha = .87$ and $\alpha = .90$ for parent- and child-report, respectively, in the current sample.

The Intolerance of Uncertainty Index – A – Child (IUI-A-C; Rifkin & Kendall, 2020) is a 15-item self-report measure designed to assess the extent to which a youth considers uncertainty to be unacceptable and unbearable. Youth are asked to rate how well each item describes them on a 5-point Likert-type scale ranging from 1, *not at all like me* to 5, *totally like me*. The IUI-A-C evidences strong psychometric properties including internal consistency of $\alpha = .94$, convergent validity with self-report measures of anxiety and functional impairment, divergent validity with ADHD symptom severity, and retest reliability with a mean interval of over four weeks ($r = .67$; Rifkin & Kendall, 2020). Internal consistency was $\alpha = .93$ in the current sample.

Procedure

Informed consent and assent for study procedures were obtained from all parents and youth. Following an initial phone screen for exclusionary criteria with the clinic coordinator, youth and their parents presented to the clinic for an initial diagnostic evaluation using the ADIS-5-C/P. Parents and youth were interviewed separately by IEs who were doctoral students in clinical psychology. Parents and youth completed a battery of self-report questionnaires on the day of the initial evaluation. IEs completed the CGI-S following the ADIS. Eligible youth completed 16 one-hour weekly sessions of CBT using the *Coping Cat*, *C.A.T Project* or *CC-ARI* treatment protocols. Participants completed a battery of questionnaires mid-way through treatment (i.e., session 8). Participants completed a post-treatment evaluation following session 16 which included a diagnostic re-assessment and another battery of questionnaires. IEs also completed the CGI-S following the diagnostic reassessment.

Data Analytic Plan

Power Analysis. Sample size necessary to achieve 80% power was determined according to guidelines provided by Pan et al. (2018) given that simple formulas for mediational analyses using longitudinal data do not exist. Pan et al. (2018) conducted simulations to determine the sample size needed to achieve 80% power depending on the size of the estimated effect, the strength of interclass correlation coefficients (ICCs) and number of repeated observations. For purposes of the current study, the size of estimated effects were specified as “medium” as previous work has identified medium effects for mediators of youth anxiety treatment outcome (Kendall et al., 2016). The within-subject correlation was estimated at 0.9 given that MASC retest reliability over a three-week period has previously been reported as ICC = .93 (March et al., 1997). There were 3 repeated observations and use of bootstrapping was specified.

Examination of Table 5 (Pan et al., 2018) revealed that $N = 65$ participants would be required to achieve 80% power in the current study.

Preliminary Analyses. First, bivariate correlations among main study variables were calculated. Linear regression analyses examined the degree to which demographic variables including age, gender, socio-economic status (SES) and race were associated with post-treatment anxiety severity as measured by IE-, youth- and parent-report. Subsequent analyses controlled for demographic variables that were significantly related to post-treatment anxiety severity.

Primary Analyses. Multiple regression mediation analyses examined the degree to which *mid-treatment* IU mediates the relationship between anxiety severity at pre- and post-treatment while controlling for pre-treatment IU. Three separate models examining indirect effects were estimated to measure anxiety severity (a) by IE-report using the CGI-S, (b) by youth self-report using the MASC-C and (c) by parent-report using the MASC-P. Bias-corrected 95% confidence intervals (CIs) using 10,000 boot-strapped samples were calculated and indirect effects were interpreted as significant when bootstrapped CIs did not overlap with zero. Full Information Maximum Likelihood (FIML) estimation was used to estimate missing data in the analytic sample.

Secondary Analyses. Multiple regression mediation analyses examined the degree to which *post-treatment* IU mediates the relationship between anxiety severity at pre- and post-treatment while controlling for pre-treatment IU. Again, three separate models examining indirect effects were estimated to measure anxiety severity (a) by IE-report using the CGI-S, (b) by youth self-report using the MASC-C and (c) by parent-report using the MASC-P. Indirect effects were again estimated by calculating bias-corrected 95% CIs using 10,000 boot-strapped samples. Results were interpreted as significant when CIs do not overlap with zero and FIML

estimation was used to estimate missing data in the analytic sample. Finally, paired samples t-tests examined whether change in IU scores from pre- to mid-treatment differed significantly from change in IU scores from mid- to post-treatment as well as whether IU decreased significantly from pre- to post-treatment.

CHAPTER 3

RESULTS

Preliminary Analyses

Means, standard deviations and correlations between all main study variables are shown in Table 1. Demographic variables including age, gender, SES and race were not significantly associated with post-treatment anxiety severity as measured by IE- (all $ps > .22$), youth- (all $ps > .10$) or parent-report (all $ps > .11$).

Table 1.

Descriptive statistics and bivariate correlations for main study variables.

	IU Pre	IU Mid	IU Post	MASC-P Pre	MASC-P Post	MASC-C Pre	MASC-C Post	CGI-S Pre	CGIS- Post
IU Pre		.64***	.49***	.22	.05	.36**	0.24	.04	.11
IU Mid			.55***	.14	.07	.40**	.35*	.19	.23
IU Post				.08	.25	.38**	.57***	.09	.45**
MASC-P Pre					.52***	.40**	.20	.08	.21
MASC-P Post						.07	.52***	.13	.37**
MASC-C Pre							.50**	.21	.15
MASC-C Post								.19	.52***
CGI-S Pre									-.03
CGIS-Post									
Mean	41.64	39.49	31.56	54.57	40.92	57.03	39.22	4.42	3.21
SD	14.37	14.81	14.71	16.15	19.21	19.27	21.64	0.55	1.07

* $p < .05$, ** $p < .01$, *** $p < .001$

Note. IU = Intolerance of Uncertainty Index – A – Child; MASC-P/C = Multidimensional Anxiety Scale for Children – Parent/ Child Report; CGI-S = Clinical Global Impression – Severity Scale.

Primary Analyses

Three separate mediation models were estimated to measure anxiety symptom severity (a) by IE-report using the CGI-S, (b) by youth self-report using the MASC-C, and (c) by parent-report using the MASC-P. In each of the three models, anxiety symptom severity at pre-treatment was entered as the predictor, IU at mid-treatment was entered as the mediator and anxiety symptom severity at post-treatment was entered as the outcome. All models controlled for IU pre-treatment. Results indicated that there were no significant indirect effects for IE-, youth-, or parent-report models (i.e., all confidence intervals estimating indirect effects contained 0; see Table 2 and Table 3).

Table 2

Indices of Mediation

Index of Mediation	<i>B</i>	95% CI
Child Report, Mediator: IU Mid	0.048	(-.015 - .191)
Parent Report, Mediator: IU Mid	0.000	(-.033 - .069)
IE Report, Mediator: IU Mid	0.051	(-.017 - .152)
Child Report, Mediator: IU Post	0.085	(-.132 - .293)
Parent Report, Mediator: IU Post	-0.033	(-.155 - .044)
IE Report, Mediator: IU Post	0.380	(-.106 - .220)

Table 3

IU at mid-treatment does not mediate the relationship between anxiety at pre- and post-treatment while controlling for IU at pre-treatment

	Child Report	Parent Report	IE Report
	<i>B (SE)</i>		
<i>a' path: predicting to IU Mid</i>			
Anxiety Pre	.181 (.102)	.006 (.113)	.162 (.088)
IU Pre	.572 (.109)***	.638 (.077)***	.633 (.081)***
<i>b' path: predicting to Anxiety Post</i>			
IU Mid	.238 (.173)	.052 (.192)	.316 (.195)
Anxiety Pre	.407 (.159)*	.533 (.147)***	-.079 (.162)
IU Pre	-.037 (.172)	-.034 (.192)	-.096 (.199)
Association between IU Pre and Anxiety Pre	.371 (.137)**	.212 (.128)	.038 (.125)

* $p > .05$, ** $p > .01$, *** $p < .001$

Secondary Analyses.

Three separate mediation models were repeated measuring anxiety symptom severity (a) by IE-report using the CGI-S, (b) by youth self-report using the MASC-C and (c) by parent-report using the MASC-P. In each of the three models, anxiety symptom severity at pre-treatment was entered as the predictor, IU at post-treatment was entered as the mediator and anxiety symptom severity at post-treatment was entered as the outcome. All models controlled for IU at pre-treatment. Results indicated that there were no significant indirect effects for IE-,

youth-, or parent-report models (i.e., all confidence intervals estimating indirect effects contained 0; see Table 2 and Table 4). Of note, change in IU from pre-treatment to mid-treatment ($M = -1.36, SD = 11.67$) differed significantly from change in IU from mid-treatment to post-treatment ($M = -8.75, SD = 13.71$), $t(54) = 2.59, p < .02$. IU decreased significantly from pre- to post-treatment, $t(54) = 5.27, p < .001$.

Table 4.

IU at post-treatment does not mediate the relationship between anxiety at pre- and post-treatment while controlling for IU at pre-treatment.

	Child Report	Parent Report	IE Report
	<i>B (SE)</i>		
<i>a' path: predicting to IU Post</i>			
Anxiety Pre	.147 (.161)	-0.078 (0.102)	.070 (.146)
IU Pre	.454 (.154)**	.552 (.113)***	.514 (.119)***
<i>b' path: predicting to Anxiety Post</i>			
IU Post	.512 (.107)***	.425 (.135)**	.534 (.137)***
Anxiety Pre	.355 (.186)	.585 (.128)***	-.067 (.142)
IU Pre	-.148 (.137)	-.238 (.145)	-.159 (.140)
Association between IU Pre and Anxiety Pre	.352 (.138)*	.203 (.127)	.038 (.125)

* $p > .05$, ** $p > .01$, *** $p < .001$

CHAPTER 4

DISCUSSION

IU is a cognitive vulnerability implicated in the etiology and maintenance of pathological anxiety; however, the role of IU in the treatment of anxious youth remains unclear. The findings from the current study, contrary to study hypotheses, indicate that IU measured midway through treatment (i.e., session 8 of a 16-week protocol) did not mediate reduction of anxiety symptoms from pre- to post-treatment as measured by child-, parent-, or IE-report. In addition, IU measured at post-treatment also did not mediate reduction of anxiety symptoms from pre- to post-treatment as measured by child-, parent-, and IE-report.

The finding that IU does not mediate treatment outcome for anxious youth is in contrast to the two previous studies of adults that examined IU as a mediator with temporal precedence and found that decreases in IU mediate subsequent decreases in worry (Bomyea et al., 2015; Dugas & Ladouceur, 2000). Importantly, these studies (a) included only adults with a principal diagnosis of GAD rather than youth with a range of principal anxiety diagnoses, (b) examined worry severity rather than symptom severity more broadly and (c) had small sample sizes (Bomyea et al., 2015, N = 28; Dugas & Ladouceur, 2000, N = 4). It is possible that IU mediates treatment outcome only for individuals with GAD but not for individuals with other principal anxiety diagnoses. Although IU is not specific to GAD and is associated with a variety of other anxiety disorders (Gentes & Ruscio, 2011; McEvoy et al., 2019; Read et al., 2013; Rifkin & Kendall, 2020), a recent meta-analysis found that the strength of the association between IU and GAD was significantly higher than that of IU and SP, OCD and panic/agoraphobia (McEvoy et al., 2019), suggesting IU could have a unique relationship with GAD. It is important to note that these differences were small and it remains unclear whether they have meaningful clinical

implications. In addition, other work indicates that IU is important in predicting outcome for transdiagnostic anxiety severity in anxious youth (Palitz et al., 2019). The degree to which there is specificity of IU to GAD remains unresolved.

The one previous study to examine IU during treatment for anxious youth found that decreases in IU from pre- to post-treatment predicted decreases in transdiagnostic anxiety severity as measured by self- and parent-report (Palitz et al., 2019). Importantly, IU was assessed at two time points rather than three and authors were therefore unable to examine whether reductions in IU temporally precede reductions in anxiety as the current study did. Of note, the current study found that a significantly greater reduction in IU occurs from mid- to post-treatment during exposures than from pre- to mid-treatment during psychoeducation. During the exposure phase of treatment youth are afforded opportunities to confront uncertainty which may lead to learning that one can tolerate uncertainty without attempting to manage it. In contrast, the psychoeducation phase of treatment includes activities such as cognitive restructuring and relaxation which may serve to reduce uncertainty and associated somatic responses rather than increase one's tolerance for it more broadly. The introduction of strategies that are effective in coping with uncertainty may lead to the slight decreases on measures of IU observed following the first half of treatment.

The current study did not find significant results in mediation analyses without temporal precedence examining whether IU measured at post-treatment mediates the relationship between anxiety at pre- and post-treatment, which is unexpected given that Palitz et al. (2019) found that decreases in IU from pre- to post-treatment predicted decreases in anxiety severity. Measurement differences may be explanatory. The current study used a measure of IU which assesses the general inability to tolerate uncertainty whereas Palitz et al. (2019) used a measure of IU which

examines various behavior, cognitive and emotional reactions to IU (e.g., “I do not sleep well if I do not know what will happen”), some of which are symptoms of anxiety disorders. Thus, measures of IU that overlap with anxiety symptoms are more likely to predict reductions in anxiety symptom severity than measures of IU that do not overlap with anxiety symptoms. It is possible that CBT may boost coping efficacy in the face of uncertainty rather than truly increase tolerance for uncertainty even in the exposure phase of treatment and increased coping efficacy in the face of uncertainty rather than habituation to uncertainty may be responsible for symptom reduction. This view is in line with previous research which has indicated that coping efficacy mediates treatment outcome for anxious youth (Kendall et al., 2016; Lau et al., 2010; Ollendick et al., 2017). Although IU decreased significantly from pre- to post-treatment, it is unclear whether this decrease is clinically meaningful and possible that larger decreases in IU are needed to mediate outcome, which can only be achieved by targeting IU directly.

Several studies have already attempted to modify existing treatments to target IU in anxious youth directly in hopes of improving outcomes (Holmes et al., 2014; Léger et al., 2003; Payne et al., 2011; Wahlund et al., 2019); however, these studies suffer from small sample sizes ranging from $N = 7$ to $N = 42$, limiting the power/ability to conduct proper statistical tests and draw conclusions. Recently, Wahlund (2019; $N = 12$) implemented exposures designed as opportunities to explore the connections between IU and worry and to allow oneself to experience uncertainty fully (e.g., without use of safety behaviors) in order to increase the ability to endure uncertainty and decrease the perceived need to worry. Results indicated that IU decreased from pre- to post-treatment; however, 58.3% of participants were classified as responders at post-treatment on measures of clinical global improvement suggesting that this intervention was *not* more effective than other forms of CBT for anxiety. Research is needed

conducting tightly controlled experimental manipulations examining the impact of exposures designed to target IU versus traditional exposures on both IU and anxiety symptoms.

The current study has several strengths. A prospective longitudinal study design with pre-, mid- and post-treatment measures was used which provided temporal precedence for mediation analyses. Youth were assessed by IEs using a diagnostic interview (i.e., ADIS-5) pre- and post-engaging in an empirically supported treatment in an outpatient anxiety clinic. In addition, anxiety symptoms were assessed using multi-methods including youth, parents and IEs. Finally, the current study had few exclusionary criteria and included youth with a broad range of anxiety diagnoses and co-morbidities. Limitations also merit consideration. First, the current sample was not racially and economically diverse which limits generalizability. Second, IU was measured by child-report only. Future work should include parent- and clinician-report measures of IU. Last, IU was assessed during treatment at a single time point (midway) and before exposure therapy had begun. Future work should assess IU at numerous points throughout the course of treatment to inform the trajectory of IU during the course of treatment and relationship to anxiety symptomology.

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APPENDIX A
EXPANDED LITERATURE REVIEW

The Role of Intolerance of Uncertainty in Anxiety Disorders

Preliminary Examination, May 2017

Anxiety disorders are the most prevalent mental health condition and approximately one third of the population will experience an anxiety disorder in their lifetime (Bandelow & Michaelis, 2015). If left untreated, anxiety disorders follow a chronic course resulting in meaningful functional impairment (Bandelow & Michaelis, 2015) and negative sequelae including depression, other anxiety disorders, substance abuse and suicidality (Costello et al., 2003; Cummings et al., 2014; Sareen et al., 2005). Cognitive-behavioral therapy (CBT) is an empirically supported treatment for anxiety disorders with approximately 60% of individuals classified as treatment responders (James et al., 2015; Norton & Barrera, 2012) and evidence of reductions in the negative sequelae at follow-up (Puleo et al., 2011; Wolk et al., 2015). However, 30% to 40% of individuals do not achieve symptom remission post-treatment (James et al., 2015; Norton & Barrera, 2012). It is important to understand why these disorders develop and maintain in order to increase the effectiveness of interventions.

In the 1980s and 1990s, research sought to better understand anxiety and specifically why individuals worry. This work indicated that individuals who worry excessively are hypervigilant for and preferentially attend to threatening information (Mathews, 1990), are more likely to interpret ambiguous information as threatening (Butler & Mathews, 1983, 1987; Russell & Davey, 1993) and generate higher estimates of risk (Butler & Mathews, 1983, 1987; Vasey &

Borkovec, 1992) compared to those who do not worry excessively. In addition, early evidence suggested that individuals who engage in significant worry take longer to make decisions when presented with ambiguous information that does not indicate a clear correct response (Metzger et al., 1990; Tallis et al., 1991). This literature suggests that individuals who worry require more information than those who do not and struggle to effectively handle life situations high in ambiguity because of a necessity to have more information and less uncertainty. In 1994, Freeston et al. proposed the construct of intolerance of uncertainty (IU) and found that IU could distinguish individuals who met diagnostic criteria for Generalized Anxiety Disorder (GAD), characterized by worry, from university students who did not meet criteria for GAD based on self-report measures.

According to some, IU is a foundational aspect of maladaptive anxiety (Carleton, 2016a; Holaway et al., 2006). Specifically, anxiety inherently requires a degree of uncertainty given that it is a product of anticipation about a future negative event that has yet to transpire. Initially, IU was defined as “a relatively broad construct representing cognitive, emotional, and behavioral reactions to uncertainty in everyday life situations” (Freeston et al., 1994). The definition of IU has evolved to differentiate between the feared stimulus (i.e., the unknown), emotional, cognitive, and behavioral responses to the feared stimulus (e.g., fear, avoidance, worry) and the inability to tolerate the fear response to uncertainty which is maintained by the individual’s perception of uncertainty (i.e., IU). As such, IU has most recently been defined as “an individual’s dispositional incapacity to endure the aversive response triggered by the perceived absence of salient, key, or sufficient information, and sustained by the associated perception of uncertainty” (Carleton, 2016b). This definition enables one to parse apart fear of the unknown,

IU and different cognitive (e.g., worry, cognitive avoidance) and behavioral (e.g., trouble sleeping, checking) reactions which characterize the inability to tolerate uncertainty.

Theoretical Models of IU

Several theoretical models have been proposed to describe the role of IU in pathological anxiety. The initial intolerance of uncertainty model (IUM) was developed to explain the etiology and maintenance of GAD (Dugas et al., 1995, 1998, 2004; Freeston et al., 1994). Specifically, the IUM suggested that high levels of IU increase an individual's predisposition to pose 'what if' questions. Individuals with high levels of IU hold positive beliefs about worry regarding its abilities assist in problem solving, avoid disappointment and avoid negative outcomes. Worry and anxiety then trigger negative problem orientation in which individuals construct negatively biased evaluations of a problem and their ability to handle it, thereby further increasing anxiety and worry. In addition, the IUM suggests that individuals with GAD use worry as a means of cognitive avoidance. Specifically, because worry is primarily a linguistic process, it has been conceptualized as a way of avoiding more distressing mental imagery.

Research offers some support for the IUM. IU, positive beliefs about worry, cognitive avoidance and negative problem orientation all discriminate between individuals with GAD and healthy controls that do not meet diagnostic criteria for DSM-IV diagnoses as determined by diagnostic interview, with IU providing the strongest discrimination (Dugas et al., 1998). In addition, studies examining whether these four factors can distinguish between individuals with GAD and individuals with other anxiety disorders suggest that IU alone is specific to GAD (Dugas et al., 2005; Ladouceur et al., 1999). IU also appears to be more strongly related to worry, characteristic of GAD, than other anxiety symptoms including panic and obsessions (Dugas et al., 2001). Support for the IUM has also been found in youth aged 13 and older.

Specifically, Fialko et al. (2012) conducted path analyses that indicated IU is a higher order vulnerability for positive beliefs about worry and cognitive avoidance. In addition, Fialko et al. (2012) found significant associations between IU, positive beliefs about worry, cognitive avoidance, and worry, with IU evidencing the strongest relationships with all variables. All originally hypothesized cognitive variables remained in the model and the findings can be interpreted as evidence that the IUM can be applied to adolescents. Overall, IU, positive beliefs about worry and cognitive avoidance accounted for 46% of the variance in worry. These results did not hold for youth younger than age 13. Specifically, positive beliefs about worry were not associated with worry or anxiety when accounting for IU and cognitive avoidance. In addition, there was a stronger relationship between IU and worry in youth aged 7-12 than in youth aged 13-17 ($r = .55$ versus $r = .31$). These findings indicate that IU is strongly associated with worry in youth but that this relationship may become weaker as youth age and develop positive beliefs about worry.

Hebert and Dugas, (2019) developed a new model of IU. This model parses apart the state of being uncertain, perceptions of uncertainty, and symptoms of anxiety. Specifically, this model indicates that negative and catastrophic perceptions of uncertainty result in maladaptive emotional, cognitive and behavioral responses. The model further specifies that environmental triggers of “novelty, ambiguity and unpredictability” result in a state of being unsure. The model distinguishes between uncertain situations and the internal experience of being unsure as not all environmental ambiguity may trigger a state of being uncertain in a given individual. When this state of uncertainty is interpreted as negative and catastrophic an individual experiences anxiety and engages maladaptive behaviors such as worry and safety behaviors. The model specifies that this behavioral manifestation of IU can vary widely depending on the individuals, the situations

and the specific negative beliefs about uncertainty which have been activated. The model suggests that IU is constantly present and effecting each component of the model. Specifically, individuals high in IU are more likely to detect ambiguity and once they have detected this ambiguity, they are more likely to transition to a state of uncertainty. The model specifies that the dispositional characteristic to detect ambiguity and to transition to a state of uncertainty upon detection of ambiguity results from “catastrophically negative” beliefs about uncertainty. Activation of these beliefs result in anxiety, worry and safety behaviors. In addition, emotional state and life circumstances are taken into account and impact all components of the model. There is some support for this model with research indicating experimental manipulation of IU results in increased worry (Ladouceur, Gosselin, et al., 2000) and information seeking behavior (Rosen & Knäuper, 2009). In addition, high levels of IU are associated with the number of cues an individual requires before providing a response on an ambiguous task (Ladouceur et al., 1997).

State versus Trait IU

Anxiety has long benefitted from distinguishing between an anxious emotional state (how one feels right now) and an anxiety trait (how one usually feels; Spielberger et al., 1968). Indeed, studies of measures that separate state and trait anxiety (e.g., Kendall et al., 1976; Kendall, 1978; Southam-Gerow et al., 2003) support the distinction. Although IU has primarily been studied as a dispositional trait, researchers have distinguished between trait IU and state IU, also described as disorder-specific IU (Thibodeau et al., 2015), situational uncertainty (SU; Rosen & Knäuper, 2009) or situation-specific IU (Mahoney & McEvoy, 2012b) in the literature. The state-trait distinction stemmed from the idea that the nature of uncertainty may differ across situations and disorders. Specifically, researchers theorized that the uncertainty related to social

evaluation situations may be different from uncertainty related to obsessive thoughts about contamination. State IU is thought of as the inability to endure uncertainty that results from lack of information about stimuli in the environment and is evidenced in individuals with and without high trait IU and with and without specific anxiety disorders.

In an early study of IU as a state variable, Rosen and Knäuper (2009) manipulated both trait IU and state IU. To manipulate state IU, researchers provided participants with two different sheets of information about an infection, one of which was designed to induce uncertainty about whether they may have the infection and the other of which was designed to reduce uncertainty about whether they may have the infection. The authors also manipulated trait IU given variability in how individuals express particular traits throughout the course of a given day. Trait IU was manipulated by providing participants with a self-report measure of IU and altering the probability of an individual endorsing each item (i.e., in the high IU condition questionnaire items were paired with the qualifier “occasionally” while in the low IU condition questionnaire items were paired with the qualifier “almost always”). As such, participants in the high trait IU condition were more likely to agree with IU statements and therefore view themselves as being more intolerant of uncertainty. Participants were also provided with fabricated feedback about their own IU based on questionnaire responses. Results indicated a significant interaction between trait IU and state IU such that those in the high trait IU and high state IU condition evidenced significantly more worry and sought out significantly more information than those in the low trait IU and low state IU condition. This suggests that both state and trait IU impact behavior and play important roles in disorders characterized by worry and reassurance seeking (e.g., GAD).

Mahoney and McEvoy (2012b) examined IU as both a trait and state variable in a group of individuals (N = 218) meeting diagnostic criteria for a principal anxiety or depressive disorder (94% and 6%, respectively). Specifically, Mahoney and McEvoy (2012b) developed a situation specific measure of state IU and found that it was significantly associated with trait IU. In addition, participants evidenced significantly higher state IU than trait IU indicating that individuals with anxiety disorder struggle to tolerate uncertainty more when relevant to a particular feared situation (e.g., individuals with Social Phobia are more intolerant of uncertainty surrounding social interaction). State IU was a transdiagnostic construct that was present across anxiety disorders as evidenced by significant associations with symptoms of GAD, Social Phobia (SP), Obsessive-Compulsive Disorder (OCD), Panic Disorder (PD) and Agoraphobia. Interestingly, state IU did not significantly predict worry after accounting for trait IU in the model. State IU did predict symptoms of panic disorder and agoraphobia after accounting for trait IU but not symptoms of GAD, SP, or OCD. These findings suggest that although IU appears to be transdiagnostic, there may be differences in the extent to which IU is a general trait vulnerability or specific to a feared situation across disorders.

Jensen and Heimberg (2015) examined the relative contribution of disorder specific state IU and trait IU to anxiety symptoms in three groups: (a) elevated symptoms of social anxiety, (b) elevated symptoms of OCD, and (c) a control group comprised of university students who scored below the median on self-report measures of social anxiety and OCD. Results indicated that individuals with elevated symptoms of social anxiety reported higher IU in social situations compared to IU regarding cleanliness or trait IU. Individuals with elevated symptoms of OCD reported higher IU regarding cleanliness compared to IU in social situations or trait IU. In addition, IU in social situations predicted social anxiety symptoms above and beyond trait IU

and IU about cleanliness predicted OCD symptoms above and beyond trait IU. Findings suggest that there is a strong context dependent component of IU which may be more closely related to symptoms of disorders than to trait IU.

Thibodeau et al. (2015) found that disorder-specific state IU accounted for unique variance in all disorder congruent domains when accounting for trait IU. Interestingly, more variance in GAD and OCD symptoms was accounted for by trait IU than disorder-specific state IU while more variance in social anxiety and panic symptoms was accounted for by disorder-specific state IU than trait IU. Disorder-specific state IU and trait IU contributed relatively equally to symptoms of health anxiety, PTSD and specific phobia. Overall this line of research suggests that there is a clear distinction between state and trait IU. In addition, some disorders may be better accounted for by trait IU whereas others may be better accounted for by disorder specific state IU.

Sex Differences in IU

Are there sex differences in IU? The evidence is quite mixed. Two studies found that typically developing adolescent females reported significantly higher IU compared to males (Fialko et al., 2012; Thielsch et al., 2015). However, another study found that typically developing adolescent males reported significantly higher IU than females (Barahmand, 2008). In addition, another study found no significant differences in IU between typically developing adolescent males and females self-reporting comparable levels of social anxiety (Boelen et al., 2010). A recent meta-analysis indicated that the association between IU and anxiety was not moderated by gender in youth (Osmanağaoğlu et al., 2018). Another recent meta-analysis indicated that the association between IU and anxiety in youth and adults was moderated by the proportion of females included in each study (McEvoy et al., 2019). Specifically, a greater

proportion of females included in each study was significantly and positively associated with the strength of the relationship between IU and symptom severity and accounted for 10% of the variance in this relationship. The authors also examined this association in the context of individual diagnoses and found that sex accounted for 42% of the variance in the association between IU and OCD symptom severity, 19% of the variance in the association between IU and SP symptom severity and 15% of the variance in the association between IU and GAD symptom severity. Sex did not account for significant variance in the relationship between IU and panic and/or agoraphobia. In sum, as noted at the outset, evidence for sex differences in IU is mixed.

IU as a Distinct Cognitive Vulnerability

Theoretical differences between IU and closely related constructs have been identified and discussed. For example, researchers have argued that the primary distinction between IU and intolerance of ambiguity (IA) is time-orientation (Grenier et al., 2005), with IA being present-moment oriented and referring to an inability to tolerate environmental ambiguity in the present. In contrast, IU is future oriented and conceptualized as an inability to tolerate the possibility that a future negative event may transpire. IU is specifically focused on the idea that the future is not certain and therefore may include negative events. Buhr and Dugas, (2006) examined whether IU accounts for unique variance in worry beyond that of IA, perfectionism, and perceived control or ones belief of their ability to impact the outcome of a situation. Results indicated that IU was most strongly related to worry compared to IA, perfectionism and perceived control and that the association between IU and worry was significantly larger than that between worry and IA, perfectionism and perceived control. In addition, IU accounted for an additional 14% of variance in worry beyond that of age, gender, IA, perfectionism and perceived control. Additional

research supports the unique association between IU and worry and well as IU and GAD when accounting for IA and perfectionism (Koerner et al., 2017).

Norr et al. (2013) examined whether IU accounts for unique variance beyond that of other cognitive vulnerabilities in SP symptoms, OCD symptoms and worry. Specifically, authors examined the relative contributions of anxiety sensitivity (AS) or the fear of physical sensations that accompany anxiety due to perceived consequences (Reiss, 1991), distress tolerance (DT) or the ability to tolerate negative emotions (Simons et al., 2005), and discomfort intolerance (DI) or the extent to which one can tolerate physical discomfort (Schmidt et al., 2006) and IU. Results indicated that IU accounted for unique variance in SP symptoms, OCD symptoms and worry beyond that of AS, DT, or DI. Additional research supports the unique association between IU and anxiety when accounting for AS (Boelen & Reijntjes, 2009; Carleton et al., 2007; Carleton, Collimore, et al., 2010; Dugas et al., 2001; Norton et al., 2005; Norton & Mehta, 2007; Sexton et al., 2003).

A body of research provides evidence that IU explains unique variance in anxiety when accounting for a wide variety of other closely related cognitive vulnerabilities including negative affect (Norton et al., 2005; Norton & Mehta, 2007), negative meta-cognitive beliefs (Shihata et al., 2017), fear of negative evaluation (Shihata et al., 2017), inflated responsibility (Shihata et al., 2017), agoraphobic cognitions (Shihata et al., 2017), negative risk orientation (Koerner et al., 2017), low trait curiosity (Koerner et al., 2017), indecisiveness (Koerner et al., 2017), perception of personal constraints (Koerner et al., 2017), a need for predictability (Koerner et al., 2017), a need for order and structure (Koerner et al., 2017) and neuroticism (Sexton et al., 2003). Given these findings, it appears reasonable to consider IU to be a distinct cognitive vulnerability.

Measurement of IU

IU is a construct of interest, but how best to measure the construct? The following section reviews measurement tools used to assess IU in adults and in youth.

Measurement of IU in Adults

The Intolerance of Uncertainty Scale (IUS; Freeston et al., 1994) has been the most widely used measure of IU to date. The IUS assesses cognitive, behavioral, and emotional reactions to uncertainty and was initially proposed to have five factors (i.e., unacceptability and avoidance of uncertainty, negative social evaluation caused by uncertainty, uncertainty-related frustration, uncertainty causes stress, and uncertainty preventing action). Buhr and Dugas (2002) translated the IUS from French to English and reported a four factor structure (i.e., uncertainty is stressful and upsetting, uncertainty leads to the inability to act, uncertain events are negative and should be avoided, and being uncertain is unfair). Other research has reported both five- and six-factor solutions with items that load onto multiple factors (Norton, 2005). The IUS has demonstrated psychometric properties including internal consistency of $\alpha = .91$, retest reliability of $r = .74$ over a period of five weeks and convergent validity with self-report measures of worry and anxiety (Buhr & Dugas, 2002).

Carleton et al. (2007) revised the IUS which resulted in a 12-item measure (IUS-12) that evidences internal consistency of $\alpha = .91$ and convergent validity with the IUS as well as self-report measures of anxiety and worry. Carleton et al. (2007) identified a two-factor structure in the IUS-12 comprised of prospective anxiety and inhibitory anxiety. The prospective anxiety factor assesses emotional, cognitive and behavioral responses to future uncertain events whereas the inhibitory anxiety factor assesses ways in which uncertainty might hinder action. Subsequent work identified that a bifactor model evidenced superior fit to the data with a general IU factor in addition to prospective and inhibitory factors (Hale et al., 2016). This study found that loading of

IUS-12 items on a general factor of IU was stronger (ranged from .68-.80) than loading of items on their respective factors (ranged from .17-.56 for inhibitory IU with only two items loading $> .50$; ranged from -.17-.66 for prospective IU with only one item loading $> .50$). Given that four items loading $> .50$ are needed to compute factor scores (Reise et al., 2010), empirical support for computing prospective and inhibitory subscale scores is weak. In addition, the IU general factor accounted for 47.40% and 80.30% of total and shared variance among items, respectively, while inhibitory IU accounted for 6.60% and 11.20% of total and shared variance, respectively and prospective IU accounted for 5.00% and 8.50% of total and shared variance, respectively. Finally, estimates of reliability indicated high reliability for the general IU factor ($\omega_h = .88$) and weak reliability for the inhibitory ($\omega_s = .20$) and prospective IU factors ($\omega_s = .03$). This research indicates that the IUS-12 is best used as a unidimensional measure.

Given that both the IUS and the IUS-12 assess cognitive, emotional and behavioral reactions to anxiety, it is important to consider how these reactions overlap with symptoms of particular anxiety disorders. Some of the reactions assessed include “always look[ing] ahead to avoid surprises” (worry), “get[ing] away from all uncertain situations” (avoidance) and “organize[ing] everything in advance” (organization). This potential overlap is particularly important given that previous research has found differential levels of IU across different anxiety disorders and has suggested that there may in fact be differential levels of IU associated with different anxiety disorders (e.g., Carleton et al., 2007; Carleton et al., 2010; see IU and Anxiety Disorders section below).

In 2008, Gosselin et al. developed the Intolerance of Uncertainty Index (IUI; Carleton et al., 2010) to limit overlap between items and symptoms of particular disorders. The IUI allows for the distinction between an individual’s perception of uncertainty and an individual’s

emotional, cognitive, and behavioral responses to the feared stimuli (e.g., fear, avoidance, worry). The IUI has part A, 15 items that assess an individual's perception of uncertainty and part B, 30 items that assesses an individual's range of emotional, cognitive and behavioral reactions to uncertainty. The IUI-A has demonstrated a stable, one-factor solution and strong psychometric properties including internal consistency of $\alpha = .94$ and convergent validity with self-report measures of worry, anxiety, negative problem orientation and depression (Carleton, Gosselin, et al., 2010). Internal consistency for the IUI-B evaluated in two different samples was $\alpha = .97/.98$ and the IUI-B evidenced incremental validity with self-report measures of worry, anxiety, negative problem orientation and depression beyond that of the IUI-A.

Situation and disorder specific measures of IU have also been developed. Mahoney and McEvoy (2012b) modified the IUS-12 to create the Intolerance of Uncertainty Scale- Situation-Specific Version (IUS-SS) to parse apart assessment of state and trait IU. This measure asks participants to identify a common anxiety provoking situation they encounter which is categorized into one of four domains: social evaluative, intrusive thoughts/repetitive behaviors, worry and panic. Participants are then asked to complete the IUS-12 about the identified situation. The IUS-SS evidences a single factor structure, internal consistency of $\alpha = .96$, convergent validity with trait IU and neuroticism, and discriminant validity with measures of extraversion and alcohol use.

In a continued attempt to specify the uncertainty that participants find intolerable a disorder specific measure of IU (DSIU) was developed (Thibodeau et al., 2015). The DSIU assesses IU with three items in eight different subscales relevant to GAD, SP, OCD, health anxiety, posttraumatic stress disorder, PD, specific phobia and major depressive disorder. This measure specifies aspects of uncertain situations that are distressing to individuals with various

anxiety disorders (e.g., “I’m anxious because I can’t be certain about when my next panic attack will be”; “I am anxious in social situations because I don’t know for sure what people think of me”). Each IU subscale was strongly associated with a general IU factor. Each subscale also predicted unique variance in domain congruent disorder symptoms beyond that accounted for by the general IU factor. Interestingly, some subscales, including that for SP and PD, were stronger predictors of relevant symptoms in comparison to general IU whereas other subscales including GAD and OCD were weaker predictors of relevant symptoms in comparison to general IU.

Another self-report measure of IU, the Uncertainty Response Scale (URS), was developed by Greco and Roger (2001) to assess a variety of responses individuals have to uncertainty. The URS evidences three factors: emotional uncertainty (i.e., emotional responses to uncertainty such as anxiety and sadness), desire for change and cognitive uncertainty. Although this scale has demonstrated acceptable psychometric properties, it has 76 items and its length likely contributes to it not being widely used.

There have been efforts to measure IU behaviorally. Jacoby et al. (2016) adapted the Beads Task to serve as a behavioral analog for how individuals with anxiety navigate uncertainty. This modified Beads Task asks participants to observe two jars presented on a computer screen, each containing 100 beads of two colors in equal ratio (e.g., 50:50 yellow to green; 50:50 green to yellow). Beads are drawn individually with replacement and participants are told that their task is to guess which jar the beads are being drawn from. Participants are instructed to request as many beads as they would like in order to correctly decide which jar the beads are being drawn from. In addition, participants are asked to complete the Cold Pressor Task (CPT; place their hand in ice water for as long as they can) before the Beads Task and are told they will have to repeat the CPT if they guess incorrectly. Results identified a significant

association between self-reported distress during the Beads Task and inhibitory IU (as measured by the IUS-12) but not prospective IU, perfectionism, or general psychological distress. The authors contend that the Beads Task is capturing behavioral responses and specifically inhibition of action during uncertainty (e.g., “The smallest doubt stops me from acting”). Interestingly, behavioral measures including the number of beads requested before a response is provided and the amount of time taken to make a decision were not associated with self-report IU. These findings are in line with those of Jensen et al. (2014) who found that individuals with high IUS-12 scores became less confident over trials on a decision making task while those with low IUS-12 scores became more confident. These authors also found that there were no differences in response times between those with high and low IUS-12 scores. This may imply that IU as measured by the IUS-12 is associated with distress and reduced confidence in the face of uncertainty rather than actual behavioral responses that impede task completion in the face of uncertainty.

Measurement of IU in youth

The capacity to be intolerant of uncertainty requires the maturation of particular cognitive capacities. Specifically, meta-cognition enables one to reflect on various courses of action, feelings about possible outcomes and feelings about the uncertainty itself. Therefore, some degree of meta-cognitive ability is necessary for a youth to both experience and self-report on IU. Meta-cognitive abilities continue to progress through late adolescence and stabilize entering adulthood (Weil et al., 2013), however, the exact age at which youth first develop the ability to experience and report on IU is unknown. Beginning at age 7, children begin to develop an understanding that multiple outcomes are possible in a given situation and develop the capacity to consider them (Schneider, 2008; Vasey et al., 1994). Research examining developmentally

normative children aged 3-14 indicates increases in age and associated increases in cognitive development predict increases in ability to generate potential negative outcomes for a particular situation (worry elaboration) which is in turn associated with children worrying about situations in their own life; (Muris et al., 2002). Ages 7-11 is a time when children begin to generate and consider numerous outcomes to a situation in Piaget's theory of cognitive development. One study found that eight-year-old children evidence meta-cognitive capacities and can self-report uncertainty when not confident about the correct response to a question (Roebbers et al., 2007). Results also indicated that children were just as likely as adults to withhold an answer to a question that they are uncertain about, suggesting that they are able to metacognitively reflect on their uncertainty and use this to inform their behavior. This work indicates that youth as young as seven may have the cognitive capacity to engage in worry and therefore suggests there is utility in designing self-report measures to assess IU in youth beginning at this age.

Comer et al. (2009) adapted the adult IUS for use with youth aged 7-17 (Intolerance of Uncertainty Scale for Children; IUSC), creating the first measure designed to assess IU in youth. The IUSC is comprised of a youth-self report form and parent-report form, which include 27 corresponding items assessing a variety of cognitive, behavioral and emotional reactions that youth evidence in response to uncertainty. The IUSC youth-report form evidences internal consistency of $\alpha = 0.92$ and convergent validity with measures of anxiety, worry and reassurance seeking and can distinguish between anxiety disorder and non-referred community youth (area under the curve [AUC] = .75). However, the IUSC youth-report form displays poorer discriminating utility between anxiety disorder and non-referred community youth at tail ends of the age spectrum (AUC for youth aged 7-8 = .65; AUC for youth aged 16-17 = .60). The IUSC parent-report form also evidences strong internal consistency of $\alpha = 0.96$ and convergent validity

with measures of anxiety and worry in the overall sample, however, it was worse at discriminating between anxiety disorder and non-referred community youth ($AUC = .64$).

Convergent validity on the parent-report form was found to be poor for youth at either end of the age spectrum (i.e., aged 7-8 and aged 16-17); this difference was not present in the youth-report form. These findings suggest that the IUSC parent-report form should be used for youth 8 to 16 (not used for youth aged 7-8 and 16-17). Parent-child agreement was only $r = .16$; however, disagreement on parent and child report, particularly for unobservable symptoms, is common for youth experiencing anxiety (e.g., Comer & Kendall, 2004; De Los Reyes et al., 2012).

Research has examined the factor structure of the IUSC. Cornacchio et al. (2018) reported a confirmatory factor analyses that indicated the best fit for the data was a general IU factor, an inhibitory IU factor and a prospective IU factor. The youth-report form displayed good model fit while the parent-report form displayed mixed model fit. In the youth-report form, the general factor evidenced high reliability ($\omega_h = .89$) whereas the inhibitory and prospective IU factors evidenced weak reliability ($\omega_s = .07$ and $\omega_s = <.001$, respectively). The general factor accounted for 88% of common variance in the youth-report form. In parent-report, the general factor also evidenced high reliability ($\omega_h = .91$) while the inhibitory and prospective IU factors again evidenced weak reliability ($\omega_s = .21$ and $\omega_s = .04$, respectively). The general factor accounted for 84% of common variance in parent-report form. Similar to the adult IUS-12 report form, the loading of IUSC-12-youth report items on a general factor of IU was stronger (ranged from .49-.77) than loading of items onto their respective factors (ranged from .06-.32 for inhibitory IU; ranged from -.45-.28 for prospective IU). The loading of IUSC-12-parent report items on a general factor of IU was also stronger (ranged from .62-.90) than loading of items onto their respective factors (ranged from .24-.51 for inhibitory IU; ranged from -.18-.45 for

prospective IU). Given the practice of requiring four items loading $>.50$ to compute factor scores (Reise et al., 2010), computing prospective and inhibitory subscale scores using the IUSC-12 youth- and parent-report forms is not supported. Factor analytic results also indicated that a two-factor model comprised of inhibitory IU and prospective IU evidenced good fit for the youth-report form. Factor loadings for the two factor model on inhibitory and prospective subscales were high, ranging from .49-.75 and .65-.72 on the IUSC-12 youth-report, respectively. These findings support the use of the inhibitory and prospective IU subscales on the IUSC-12 child-report form.

There are three other lesser used self- and/or parent-report measures of IU in youth. Przeworski (2006) created a 34-item measure with corresponding parent and child-report forms designed to assess the extent to which uncertainty is unacceptable and aversive. This measure has internal consistency of $\alpha = 0.94$ and $\alpha = 0.95$ in youth- and parent-report forms, respectively, convergent validity with measures of anxiety and divergent validity with measures of externalizing behaviors (Przeworski, 2006). The 15-item IUI-A has been adapted for use with youth (IUI-A-C) and asks youth to report on their general inability to tolerance uncertainty rather than reactions to uncertainty (Rifkin & Kendall, 2020). The IUI-A-C evidences internal consistency of $\alpha = .94$, convergent validity with self-report measures of anxiety and worry, divergent validity with Attention-Deficit/Hyperactivity Disorder diagnosis severity and retest reliability over a mean interval of over 30 days. A 12-item parent-report form was developed to attempt to assess young children's (aged 3-10) behavioral responses to uncertainty and low environmental structure (rather than cognitive beliefs about uncertainty) titled Responses to Uncertainty and Low Environmental Structure (RULES; Sanchez et al., 2017). The RULES evidences a single factor structure, internal consistency of $\alpha = .94$, convergent validity with the

IUSC parent-report form and parent-report of anxiety symptoms and divergent validity with parent-report of externalizing behaviors.

Rifkin and Kendall (2020) also developed an IU clinician rating (IUCR) which allows an independent evaluator (IE) or therapist to rate a youth's tendency to consider uncertainty as unacceptable or intolerable on a 5-point Likert type scale ranging from 1, *not at all characteristic of the child* to 5, *entirely characteristic of the child*. The IUCR states that the youth's inability to tolerate uncertainty may be broad or specific to one or more domains (e.g., social, separation, specific stimuli, sleeping, panic, health). IUCR evidences strong psychometric properties including convergent validity with the IUI-A-C and self-report measures of anxiety and functional impairment and divergent validity with ADHD severity.

In sum, there are six measures that have utility in assessing IU in youth, three of which have corresponding parent and child report forms, one of which assesses only child report, one of which assesses behavioral reactions in young children using only parent report and one of which allows a clinician to provide a rating. Correspondence between child- and parent-report on the most widely used form with published psychometrics is poor.

Research is needed to clarify how the different measures of IU in adults and youth influence the associations with different anxiety diagnoses. McEvoy et al. (2019) conducted a meta-analysis examining associations between IU and diagnoses based on measure in adults. Results indicated that disorder association did not differ by measure, however, only two general measures of IU designed for adults (the IUS; the IUS-12) were included. As such, it remains unclear how disorder specific associations differ based on which scale is used. Additional research comparing the various measures directly in a single large sample study is needed in both adult and youth populations.

IU and Anxiety Disorders

The following section evaluates and summarizes the results of research examining the relationship between IU and various anxiety disorders in both adult and youth populations. Evidence for a specific relationship between IU and GAD and evidence for IU as a transdiagnostic vulnerability across anxiety disorders are discussed.

IU and Anxiety Disorders in Adults

IU was originally proposed as a construct to explain the function of worry and the etiology and maintenance of GAD. Extensive research has indicated that elevated levels of IU are found in adults meeting diagnostic criteria for GAD (e.g., Boswell et al., 2013; Counsell et al., 2017; Dugas et al., 2004; Dugas & Ladouceur, 2000; Gentes & Ruscio, 2011; Koerner & Dugas, 2006; Ladouceur, Gosselin, et al., 2000; Mahoney & McEvoy, 2012c; Talkovsky & Norton, 2016). In addition, some work examining the relationship between IU and anxiety disorders has provided support for a specific relationship with GAD. One study found that IU is significantly higher for individuals with GAD in comparison to individuals with panic disorder without agoraphobia (Dugas, Marchand, & Ladouceur, 2005). Another study found that IU to be more strongly related to worry, characteristic of GAD, than other anxiety symptoms including panic and obsessions (Dugas, Gosselin, & Ladouceur, 2001). An additional study found that levels of IU distinguished individuals with GAD from those with other anxiety disorders (Ladouceur et al., 1999).

Despite research indicating IU may have a specific relationship to GAD, IU has been found to be strongly associated with a variety of anxiety disorders. Research has indicated that elevated levels of IU are found in adults meeting diagnostic criteria for SP (Counsell et al., 2017), PD (Carleton et al., 2014), OCD (Jacoby et al., 2013; Lind & Boschen, 2009; Tolin et al.,

2003) and Post-Traumatic Stress Disorder (White & Gumley, 2009). In addition, elevated IU is associated with increased self-report symptoms of SP (Boelen & Reijntjes, 2009; Carleton, Collimore, et al., 2010; Counsell et al., 2017; Katz et al., 2017; Khawaja & McMahon, 2011; McEvoy & Mahoney, 2012; Teale Sapach et al., 2015), Separation Anxiety Disorder (SAD; Boelen et al., 2014), health anxiety (Fergus, 2013; Fergus & Bardeen, 2013; Fergus & Valentiner, 2011) OCD (McEvoy & Mahoney, 2012c) and panic disorder and/or agoraphobia (McEvoy & Mahoney, 2012c).

The idea that IU is a transdiagnostic cognitive vulnerability (across the anxiety disorders) has been supported by two meta-analyses. The first meta-analysis investigated the relationship between IU, GAD and OCD , and included 58 studies conducted before September of 2010 (Gentes & Ruscio, 2011). Results indicated that the strength of the association between IU and GAD was 0.57 (95% CI: 0.52-0.62) whereas the strength of the association between IU and OCD was 0.50 (95% CI: .44-.55). Analyses also indicated that the relationship observed between IU and GAD was significantly greater than that observed between IU and OCD. However, these findings do not provide support for the specificity of IU to GAD based on guidelines for etiological specificity (Garber & Hollon, 1991) given the significant association with OCD. A more recent meta-analysis including 181 studies conducted between August of 2010 through December of 2018 also concluded that IU is a transdiagnostic vulnerability associated with a variety of anxiety disorders (McEvoy et al., 2019). The strength of the association between IU and anxiety-related disorders was 0.50 (95% CI: 0.46-0.55) for SP, 0.42 (95% CI: 0.40-0.45) for OCD, 0.47 (95% CI: 0.43-0.52) for PD and/or agoraphobia, and 0.57 (95% CI: 0.56-0.59) for GAD. Results also indicated that the strength of the association between IU and GAD was significantly higher than that of SP, OCD and panic/agoraphobia, however, the differences are

small and may not have meaningful clinical implications. In addition this work again indicates that IU is not specific to GAD based on established guidelines for specificity (Garber & Hollon, 1991) and provides support for IU as a transdiagnostic vulnerability across anxiety disorders in adults.

The Relationship Between IU and Anxiety Disorders in Youth

Research indicates that IU is associated with GAD in youth (Cowie et al., 2016; Donovan et al., 2016; Hearn, Donovan, Spence, & March, 2017; Read et al., 2013) and some work has investigated the specificity of IU to GAD in youth. Read et al. (2013) administered the IUSC to treatment seeking anxious youth aged 7-17 and found that the IUSC predicted a group of youth with a composite primary diagnosis of GAD compared a group of youth with composite primary diagnoses of either SAD or SP. However, the IUSC also predicted child-report principal diagnosis symptom severity and diagnosis did not moderate this relationship indicating that IU may be associated with anxiety symptom severity rather than specifically with GAD.

Cowie et al. (2016) independently simplified language on the IUS for use with a community sample of youth aged 6-11 and found that the highest IU scores were present in youth meeting diagnostic criteria for GAD comorbid with at least one additional disorder (SP, SAD, specific phobia, ADHD, ODD and/or MDD) compared to youth meeting diagnostic criteria for pure GAD or healthy controls assessed to have no current DSM-IV psychiatric diagnoses. Youth meeting diagnostic criteria for comorbid GAD evidenced significantly higher anxiety severity as reported by parent and child indicating that IU may be associated with anxiety symptom severity rather than GAD specifically. Finally, Rifkin and Kendall (2020) administered the IUI-A-C to treatment seeking youth aged 7-17 and found that IU significantly predicted composite principal diagnosis severity but not composite GAD diagnosis severity.

Anxiety severity was significantly higher in the composite principal diagnosis group compared to the composite GAD diagnosis group indicating that findings are consistent with the notion that IU is a transdiagnostic vulnerability associated with anxiety severity rather than a specific anxiety diagnosis. The IUI-A-C also predicted both child-report principal diagnosis severity and child-report GAD diagnosis severity (Rifkin & Kendall, 2020).

In line with the idea that IU is a transdiagnostic vulnerability for anxiety associated with anxiety severity more than GAD specifically, research indicates that IU in youth is also associated with diagnosis and symptoms of SP (Boelen et al., 2010; Cornacchio et al., 2018; Hearn, Donovan, Spence, & March, 2017; Hearn, Donovan, Spence, March, et al., 2017; Wright et al., 2016) as well as symptoms of SAD (Cornacchio et al., 2018; Wright et al., 2016), panic disorder (Wright et al., 2016), OCD (Wright et al., 2016) and health anxiety (Wright et al., 2016). A meta-analysis indicated that IU accounted for 36% and 39.69% of variance in anxiety and worry, respectively (Osmanağaoğlu et al., 2018). In sum, it appears that IU is a transdiagnostic vulnerability for anxiety in youth.

Critical Remarks on IU and Anxiety Disorders

Overall, research with adults and youth suggests that IU is not specific to GAD based on established guidelines for specificity (Garber & Hollon, 1991) as IU is associated with a variety of other anxiety disorders (Gentes & Ruscio, 2011; McEvoy et al., 2019; Read et al., 2013; Rifkin & Kendall, 2020). However, it remains unclear as to whether IU has a unique relationship with GAD. A recent metaanalysis found that the strength of the association between IU and GAD was significantly higher than that of SP, OCD and panic/agoraphobia (McEvoy et al., 2019), however, the differences are small and may not have meaningful clinical implications. In addition, a variety of self-report measures were used to assess IU in studies included in the meta-

analysis and it remains unclear how measurement of IU impacts the ability to answer this question. Shared method variance may also result in inflated associations in these studies, as analyses where the same individual reports on IU and symptom severity are interpreted (e.g., Boelen & Reijntjes, 2009; Carleton, Collimore, et al., 2010; Counsell et al., 2017; Cowie et al., 2016; Donovan et al., 2016; Hearn, Donovan, Spence, & March, 2017; Katz et al., 2017; Khawaja & McMahon, 2011; McEvoy & Mahoney, 2012; Read et al., 2013; Rifkin & Kendall, 2020; Teale Sapach et al., 2015). Future work should clarify whether IU has a unique association with GAD by (a) examining whether measure selection impacts the strength of the association between IU and GAD, (b) using a combination of self-report measures and IE ratings of IU (i.e., IUCR; Rifkin & Kendall, 2020) and anxiety severity and relying on the composite diagnosis in work with youth to limit inflated associations due to shared method variance.

IU and Treatment

Cognitive behavioral therapy (CBT) is considered the gold standard (David et al., 2018) empirically supported treatment for anxiety disorders in adults (see Hofmann et al., 2012; Norton & Price, 2007) and youth (see Kendall et al., 2008; Silverman et al., 2008; Walkup et al., 2008). The cognitive component of treatment involves identifying negative automatic thoughts and associated maladaptive thinking patterns and challenging these thoughts. The behavioral component of treatment consists of exposing individuals to feared situations to facilitate learning that stimuli and/or situations are not as frightening as they may have originally thought and that they can tolerate the associated distress (not allowing avoidance). There is a high degree of uncertainty involved in exposure tasks as individuals are asked to engage with feared stimuli and accept the possibility of a negative outcome (i.e., often testing whether the negative outcome will occur). In this way, CBT may actually be exposing individuals to uncertainty and facilitating

acceptance of uncertainty (e.g., something bad could happen but I am going to do this anyways). In addition, CBT exposure tasks may culminate in a version of the feared outcome occurring (e.g., people laugh at you when you walk into a room) to help individuals learn that they can tolerate the worst case scenario. Exposure tasks may be “inoculating” individuals to uncertainty as they learn that they can tolerate the worst case scenario. Although CBT is an effective treatment for anxiety disorders in youth and adults with approximately 60% classified as positive treatment responders, around 40% of individuals do not experience full symptom remission post-treatment (James et al., 2015; Norton & Barrera, 2012). What is the mechanism of action in CBT? Knowing the mechanisms of action would facilitate direct targeting of these mechanisms and potentially improve treatment outcomes. IU may be one such mechanism to target.

IU and Treatment in Adults

Two studies have investigated how individual CBT for anxiety impacts IU and whether reductions in IU are associated with symptom reduction. One study administered 18 individual sessions of CBT to adults (N = 37) with a range of primary anxiety diagnoses comorbid with depression and found a significant reduction in IUS scores from pre- to post-treatment compared to waitlist controls (Boswell et al., 2013). The magnitude of change in IUS score over treatment was similar across diagnoses. In addition, when controlling for pre-treatment anxiety severity, change in IUS scores predicted post-treatment symptom severity across diagnoses as measured by independent evaluator (IE) ratings. Another study recruited a community sample of adults meeting diagnostic criteria for GAD (N = 28) and examined whether reductions in IU preceded and accounted for reductions in worry following 10 individual sessions of CBT (Bomyea et al., 2015). Results indicated that IUS-12 scores decreased significantly from pre- to post-treatment and that decreases in IUS-12 scores mediated subsequent decreases in worry. Decreases in worry

during the course of treatment did not mediate subsequent decreases in IUS-12 scores. These results suggest that IU may be an important construct to target directly in treatment.

Research has examined how group CBT impacts IU and whether reductions in IU are associated with anxiety symptom reduction at post-treatment. One study found significant reductions in IUS scores occurred over the course of treatment for all principal diagnosis groups (SP, PD; GAD; N = 151) and that larger reductions in IU were associated with larger reductions in symptom severity at post-treatment (Talkovsky & Norton, 2016). Another study found that higher IUS-12 scores at pre-treatment predicted higher levels of social anxiety symptom severity during the course of treatment (i.e., at weeks 4 and 8) and at post-treatment (Katz et al., 2017). However, the rate of symptom change over the course of treatment was not moderated by the individual's level of IU, indicating that higher scores of IU at pre-treatment did not result in slower symptom reduction during the course of treatment. This finding suggests that treatment was effective in reducing symptoms for all individuals but that those who reported high levels of IU post-treatment continued to report high levels of social anxiety symptoms post-treatment (Katz et al., 2017). This finding is again consistent with the notion that IU may be a particularly important mechanism to target in treatment.

Stevens et al (2018) administered the IUS-12 to a heterogeneous patient group participating in treatment at a partial hospital program (N = 272) and examined the prospective and inhibitory anxiety subscales separately (Stevens et al., 2018). Results indicated that both prospective and inhibitory IU decreased significantly from pre- to post-treatment regardless of diagnostic group membership (MDD, GAD, Social, PTSD, PD and OCD) and there were no significant differences in levels of IU at post-treatment based on diagnostic group membership. In addition, reductions in inhibitory (but not prospective) anxiety from pre- to post-treatment

significantly predicted reductions in self-report anxiety symptoms from pre- to post-treatment. The finding suggests that addressing avoidance or inhibition of action due to IU may be a worthy target for improving anxiety outcomes.

Some studies target IU directly in treatments developed for adults with GAD. Ladouceur, Dugas, et al. (2000) randomized participants with a principal diagnosis of GAD to a 16-week individual intolerance of uncertainty treatment (IUT) condition (n = 14) or waitlist control (n = 12). Components of IUT included an overview of treatment rationale, awareness training, targeting positive beliefs about worry, problem-orientation training and cognitive exposure. Participants were first told that IU can fuel worry and anxiety and that because uncertainty is inherent to life the goal of treatment is to learn to recognize, accept and develop strategies to cope with uncertainty. Next participants were asked to record their worries at several pre-determined points throughout the day and to record whether these worries were appropriate for problem solving. Participants were also asked to identify their positive beliefs about worry which were targeted using cognitive restructuring and behavioral experiments. For worries appropriate for problem solving participants were coached in remaining focused on important aspects of the problem instead of small related details and in carrying out problem solving. Finally, for worries that were not appropriate for problem solving, participants were asked to describe the image they had in mind which was then recorded for them to listen to repeatedly while suspending any activities that might reduce distress.

Results indicated that 77% of participants no longer met diagnostic criteria for GAD at post-treatment (Ladouceur, Dugas, et al., 2000). Symptoms of GAD and IUS scores decreased significantly from pre- to post-treatment and treatment gains was maintained at 6- and 12-month follow-ups. Authors also examined the impact of treatment on the presence of comorbid

diagnoses, which included specific phobia ($n = 16$), SP ($n = 12$), PD ($n = 6$), MDD ($n = 1$), OCD ($n = 1$), and trichotillomania ($n = 1$). Results indicated a significant decrease in the number of comorbid diagnoses from pre- ($M = 1.50$) to post-treatment ($M = 0.65$) suggesting there is merit in examining the effectiveness of IUT for anxiety disorders other than GAD. Although IUT, which has since been detailed in a treatment manual for GAD (Dugas & Robichaud, 2007), was designed to target IU, authors did not examine mechanisms of action and whether reductions in IU precede anxiety symptom improvement.

Dugas and Ladouceur (2000) anticipated and addressed this in a report on baseline data of the IUT described above ($N = 4$). Specifically, the authors conducted a time-series analyses which indicated that change in IU preceded change in time spent worrying for three of the four participants. Change in time spent worrying did not precede change in IU for any of the participants. This indicates that targeting IU in treatment may be important for reducing worry, a hallmark symptom of GAD. However, examination of IU as a mediator requires replication in a larger sample and with assessment of the full range of symptoms that characterize GAD.

Dugas et al. (2003) modified the IUT described above to a group format in efforts to increase cost effectiveness. Participants ($N = 52$) with a primary diagnosis of GAD were randomized to 14 two-hour treatment sessions in groups of four to six or to a waitlist control. Results indicated that participants evidenced significant improvement in symptoms of GAD as measured by IE ratings as well as in IUS scores and self-report symptoms of anxiety and worry. In addition, these treatment gains were maintained at follow-up assessments conducted 6-, 12- and 24-months post-treatment. This suggests that treatment targeting IU directly in group format may be comparable in effectiveness to an individual format.

Two other studies examined the effectiveness of group treatments modified to directly target IU. Mahoney and McEvoy (2012a) explored the relationship between IU as measured by the IUS-SS and symptoms of social phobia and depression following a seven session course of group CBT aimed at targeting SP (N = 32). The authors sought to incorporate components of IU specific treatment into existing group CBT treatment for social anxiety disorder (McEvoy, 2007). Specifically, treatment was modified to emphasize the importance of practicing to accept uncertainty before, during and after social exposures. Exposures were framed as behavioral experiments in which one can not only empirically test whether feared outcomes will occur but also accept the uncertainty surrounding negative evaluations of others. Results indicated that decreased IUS-SS scores from pre- to post-treatment were associated with decreased scores on self-report measures of social anxiety but not depression (Mahoney & McEvoy, 2012a). Another study provided 12 sessions of group CBT to individuals with a principal diagnosis of GAD (N = 81) and modified one session to directly target IU including psychoeducation and discussion of how IU could be incorporated into their exposure hierarchy (Torbit & Laposa, 2016). Results indicated that IUS scores decreased significantly from pre- to post-treatment and that decreases in IUS scores were significantly associated with decreases in stress, worry and depression. Results also indicated that IU mediated change in worry from pre- to post-treatment, however, data was collected at only two time points and therefore does not afford temporal precedence to indicate that change in IU preceded change in worry. Overall, results from these studies suggest that group CBT modified to target IU directly results in decreases in IU and associated decreases in stress, worry and symptoms of social anxiety from pre- to post-treatment.

Dugas et al. (2010) expanded on this work by comparing the effectiveness of individual IUT (Ladouceur, Dugas, et al., 2000) described above to an active treatment condition, although

this study did not examine effects on IU specifically. Participants (N = 65) with a principal diagnosis of GAD were randomized to 12 sessions of individual IUT, 12 sessions of applied relaxation, or a waitlist control condition. Results indicated that IUT significantly outperformed the waitlist control condition on four of the six outcomes examined including self-report measures of worry and somatic symptoms of GAD and IE ratings of GAD severity and clinical global improvement (CGI) but not general self-report anxiety and depression symptoms. IUT outperformed applied relaxation only on IE CGI rating. In addition, 70% of participants achieved remission post-treatment in the IUT condition while 55% achieved remission in the applied relaxation condition. There were no significant differences at 6-, 12-, or 24-month follow-ups between the IUT and applied relaxation conditions, however, the IUT condition did evidence continued gains over follow-up on self-report measures of worry and anxiety as well as on IE CGI ratings (i.e., slope significantly differed from zero) while the AR group did not. This may indicate that change in IU begins in treatment and continues as an individual encounters more uncertainty in the environment post-treatment.

One additional study compared IUT to an active treatment condition. Specifically, van der Heiden et al. (2012) conducted an RCT comparing the effectiveness of IUT to another therapy developed to specifically target GAD, metacognitive therapy (MCT). Participants (N = 126) were randomly assigned to 14 sessions of IUT, MCT or waitlist control. Participants assigned to MCT were asked to identify and examine positive and negative beliefs about worry in addition to participating in exposure and response prevention. IUT was modified in two ways from previous descriptions (e.g., Ladouceur, Dugas, et al., 2000). Specifically, re-evaluation of positive beliefs about worry was included as the final module of treatment rather than being introduced after worry awareness training. In addition, rather than listening to recordings of

worry images participants were asked to engage in worry exposures (van der Heiden & ten Broeke, 2009) in which they were instructed to picture a feared outcome in as vivid detail as possible, hold this imagine in their mind for a minimum of 25 minutes without any attempts to reduce anxiety and then immediately write down as many alternative outcomes as they can think of. Results indicated that participants improved significantly in both active treatment conditions compared to waitlist controls on all outcome measures which included self-report of worry, anxiety, depression and general psychopathology. Further, 91% of participants in the MCT no longer met diagnostic criteria for GAD while 80% of participants no longer met diagnostic criteria for GAD in the IUT group. Overall, results indicated MCT had larger effect sizes than IUT on all outcome measures. Interestingly, results indicated that IUS scores decreased significantly pre- to post-treatment in both active conditions but that IUS scores were significantly lower in the MCT group compared to the IUT group post-treatment (there were no significant differences in IUS scores between groups pre-treatment). This is in line with the idea that treatment response may be associated with decreases in IU and that it is therefore important to effectively target IU in treatment.

Hewitt et al. (2009) conducted a single case study examining the impact of a six-session modified IUT on a young adult with diagnoses of SP, PD, GAD, MDD and dysthymia. Results indicated that there was significant improvement in IUS scores and social anxiety symptoms but not general anxiety symptoms (as measured by the Beck Anxiety Inventory; BAI; Beck et al., 1988) from pre- to post-treatment. Improvement on the BAI may not have been observed because it primarily assesses physical symptoms and therefore may be a better proxy of PD symptoms rather than GAD symptoms (the patient described was also having multiple panic

attacks a day). This indicates that IUT may have limited utility in treating PD, however, given that this was a single case study findings should be interpreted with caution.

Finally, Hebert and Dugas (2019) most recently developed an alternative 12-session treatment for GAD that is designed to target IU via behavioral experiments. This treatment consists of three components. First, patients are presented with psychoeducation about IU and undergo awareness training in which they are instructed to keep worry and uncertainty diaries. In the second phase, patients complete behavioral experiments designed to target and loosen negative beliefs about uncertainty while creating and solidifying neutral or positive beliefs about uncertainty. The final component of treatment consists of relapse prevention which includes reflecting on impactful behavioral experiments, discussing old and new beliefs and behaviors surrounding uncertainty and creating an ongoing plan for future behavioral experiments. Preliminary analyses indicated that participants with primary diagnoses of GAD ($N = 7$) experienced significant decreases in IUS scores and self-reported symptoms of GAD pre- to post-treatment and that six out of seven participants no longer met diagnostic criteria for GAD post-treatment. These gains were maintained at 6-month follow-up.

Critical Remarks on IU and Treatment in Adults

In sum, research indicates that decreases in IU are observed pre- to post- transdiagnostic treatment for anxiety disorders and that reductions in IU are significantly associated with decreases in symptom severity as measured by self-report and IE ratings. In addition, targeting IU directly in treatment leads to decreases in IU, decreases in self-report symptoms of worry, GAD, social anxiety and general psychopathology, decreases in GAD symptoms as evaluated by an IE and higher IE CGI ratings. However, the majority of studies examining IU in treatment have small sample sizes and require replication. One noteworthy RCT randomized participants

(N = 126) to two therapies designed specifically to target GAD and found that MCT resulted in significantly lower IU post-treatment compared to IUT (there were no significant differences in groups pre-treatment (van der Heiden et al., 2012). In addition, more individuals achieved symptom remission (80% for IUT vs. 91% for MCT) and effect sizes were larger for all outcome variables for MCT compared to IUT. This suggests that additional foundational research is needed. First, research should examine whether changes in IU precede changes in symptom reduction. Two studies have examined IU as a mediator with temporal precedence and have found that decreases in IU mediate subsequent decreases in worry, however, these studies had small sample sizes (Bomyea et al., 2015; Dugas & Ladouceur, 2000; N = 28 and N = 4, respectively) and require replication with general symptom severity for GAD and other anxiety disorders. Next, research conducting experimental manipulations to target and decrease IU over the course of treatment is needed. Specifically, given that MCT was more successful at reducing IU than IUT, researchers should investigate which components of treatment are most effective at reducing IU.

IU and Treatment in Youth

Only one study to date has examined IU in the context of general CBT for youth anxiety. Palitz et al. (2019) examined IU in youth (N = 73) aged 7 to 17 with principal anxiety diagnoses pre- and post- treatment (i.e. 16 sessions of *Coping Cat*; Kendall, 1994; Kendall & Hedtke, 2006a, 2006b; *C.A.T. Project* Kendall et al., 2002a, 2002b). Results indicated that IU, (as measured by the IUS-C/P (Przeworski, 2006) decreased significantly from pre- to post-treatment and that decreases in IU as measured by self- and parent-report predicted decreases in functional impairment as measured by an IE rating, decreases in anxiety severity as measured by self- and parent-report, and increases coping efficacy as measured by self- and parent-report. Treatment

reduced IU; future work should measure IU during the course of treatment and examine whether reductions in IU temporally precede changes in anxiety reduction.

Several studies have targeted IU directly in treatment of youth anxiety. Initially, these studies were designed to target worry in youth with a principal diagnosis of GAD based on the IU model of GAD. The first study to do this examined the effectiveness of individual treatment (with no parent component) for adolescents ($N = 7$) aged 16-18 with a principal diagnosis of GAD (Léger et al., 2003). Treatment duration was an average of 13.2 sessions and included worry awareness training, followed by directly targeting worry in several ways. Adolescents were asked to identify IU that they experience in daily life and to engage in behaviors that further generate uncertainty (e.g., ask a teacher a question when unsure about their response). Adolescents were also asked to challenge positive beliefs about worry via cognitive restructuring and underwent problem solving training where they were encouraged to view problems as opportunities to learn or gain something from a situation before engaging in systematic problem solving. Finally, adolescents were asked to engage in imaginal exposures by audio recording and repeatedly listening to a feared scenario they worry about. Although this treatment directly targeted IU, a measure of IU was not administered in this study. Results indicated that three participants no longer met diagnostic criteria for GAD post-treatment while two participants evidenced a moderate reduction in GAD symptoms, one participant did not evidence a reduction in GAD symptoms and one participant dropped out. Conclusions are limited based on small sample size employed in this study.

In another pilot study, this treatment was adapted for use with younger youth. Specifically, Payne et al. (2011) examined outcome for youth ($N = 16$) aged 7-17 with a principal diagnosis of GAD. Treatment duration was an average of 9.7 sessions and consisted of individual

cognitive therapy and optional parent check-ins. Treatment was based on that developed by Ladouceur, Dugas, et al. (2000) but was implemented flexibly to increase youth engagement with a reduced focus on didactics and an increased focus on experiential exercises. These included a review of current worries during which the therapist illustrated IU and cognitive avoidance, distinction between worries and serious problems, behavioral experiments to evaluate the utility of beliefs about worry, cognitive suppression and rumination followed by both imaginal and in vivo exposures to worry topics. Although IU was directly targeted, IU again was not directly measured in this study. Results indicated that all participants completed treatment and that 13 (81%) no longer met diagnostic criteria for GAD post-treatment, while two participants experienced symptom improvement but still met diagnostic criteria for GAD and one participant did not experience symptom reduction (of note, these outcomes were not assessed by an IE). In addition, youth evidenced significant reductions in self-report worry (Cohen's $d = 2.0$) and anxiety (Cohen's $d = 1.4$).

Holmes et al. (2014) conducted an RCT to evaluate a group treatment program designed to target GAD and perfectionism in youth based on the IU model of GAD. Youth ($N = 42$) aged 7-12 with a principal diagnosis of GAD and high comorbidity (9.5% had GAD only; $M = 3.69$ clinical diagnoses, $SD = 1.70$) were randomized to a waitlist control or a 10-session group intervention comprised of 5-7 youth with a 9-session complimentary parent group and one combined session. Treatment included psychoeducation about anxiety and worry, relaxation training, problem solving training and cognitive restructuring focused on IU, cognitive avoidance, positive beliefs about worry and negative problem orientation. Of the participants randomized to the active treatment condition ($N = 20$), 17 were assessed at post-treatment (two dropped out and one did not complete the diagnostic interview due to geographical limitations)

and 15 were assessed at the 3-month follow-up (two were lost to follow-up). Results indicated that 52.9% of participants who completed the active treatment no longer met diagnostic criteria for GAD post-treatment compared to 0% assigned to the waitlist control. In addition, at the 3-month follow-up, 100% of treatment completers no longer met diagnostic criteria for GAD and 50% of participants no longer met diagnostic criteria for any diagnosis while 50% of participants retained diagnoses of SP or a specific phobia. Effects may be enhanced at the 3-month follow-up due to opportunities to practice and consolidate principals discussed in treatment in real life and it should be noted that there were two booster sessions between session 10 and the 3-month follow up which likely contributed to these effects. Interestingly, there were no significant differences in decreases in IUSC scores pre- to post-treatment for the active treatment condition compared to the waitlist control condition.

Wahlund et al. (2019) conducted a pilot study to evaluate feasibility, acceptability and effectiveness of a 12-session IU-focused CBT (IU-CBT) for adolescents ($N = 12$) aged 13-17 reporting high levels of worry. Parents were provided with online supplemental psychoeducation about worry and IU which included information as to how they can best be helpful to their child. IU-CBT was based on the IUT developed for adults (i.e., Ladouceur, Dugas, et al., 2000) and included worry awareness training, establishing the connection between IU and worry, and the use of exposure to increase tolerance of uncertainty. Exposures were not designed to serve as a behavioral experiment or to facilitate habituation but rather were described as opportunities to explore the connections between IU and worry and to allow oneself to experience uncertainty fully (e.g., without use of safety behaviors) in order to increase the ability to endure uncertainty and decrease the perceived need to worry. Results indicated no families dropped out of the treatment and families reported high satisfaction with treatment. In addition, there were

significant changes in adolescents' self-reported levels of worry pre- to post-treatment. There were also significant decreases on self-report measures of anxiety, depression, IU (as measured by a five-items adapted from IUS) and on parent-report measures of worry. Measures of clinical global improvement indicated that 58.3% of participants were classified as responders post-treatment and 66% were classified as responders at a 3-month follow-up.

Concluding Remarks on IU and Treatment in Youth

Research findings indicate that reductions in IU are observed in youth receiving transdiagnostic CBT for anxiety and are associated with decreases in functional impairment and anxiety severity and increases in coping efficacy. However, no studies to date have examined whether changes in IU temporally precede symptom reduction in anxious youth. Evaluating the degree to which IU mediates treatment gains is important to guide the targeting of IU to maximize treatment for anxious youth. Studies that have already targeted IU directly in treatment indicate that youth exhibit significant reductions in GAD symptom severity as measured by self- and IE-report and decreases in presence of comorbid diagnoses as measured by IE report pre- to post-treatment. However, with one exception, this body of work is comprised of pilot studies with sample sizes ranging from $N = 7$ to $N = 16$, severely limiting the ability to draw conclusions. The only RCT investigating an IU specific intervention in youth with a principal diagnosis of GAD ($N = 42$) found that 52.9% of participants in the active treatment no longer met diagnostic criteria for GAD compared to 0% assigned to the waitlist control post-treatment and that 100% no longer met diagnostic criteria for GAD at the 3-month follow-up. It should be noted that only 15 individuals were assessed at follow-up and findings again require replication in a larger sample. If research establishes that IU mediates treatment outcome, studies should next examine how best to target IU during the course of treatment in anxious youth.

Conclusion

IU appears to be a transdiagnostic cognitive vulnerability that is associated with a variety of anxiety disorders in adults and youth. Numerous measures have been developed to assess IU in both adults and youth, but some measures assess reactions to uncertainty that overlap with symptoms of individual disorders. Future work would benefit from direct comparisons of measures to determine the degree to which the strength of associations with particular disorders differs by measure. Existing findings with adult and youth samples indicate that decreases in IU from pre- to post-treatment are associated with symptom reduction and disorder remission. Research examining whether reductions in IU temporally precede reductions in anxiety is needed, as is research that evaluates the degree to which IU is a mechanism of action and a target for treatment. This foundational research is a necessary step before examining how best to target IU during the course of treatment.