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Targeting intolerance of uncertainty in treatment: A meta-analysis of therapeutic effects, treatment moderators, and underlying mechanisms

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ABSTRACT

Objective: Anxiety-related disorders are among the most prevalent psychiatric conditions and cause significant impairment. Intolerance of uncertainty (IU) contributes to the emergence, maintenance, and symptom severity of anxiety-related disorders, yet information regarding treatment-related changes in IU is limited. This systematic review and meta-analysis examined the efficacy of evidence-based treatments for anxiety-related disorders on IU, explored factors moderating treatment effects of IU, and examined whether therapeutic improvement in IU corresponded with improvements in anxiety symptom severity.

Methods: PubMED and PsycINFO were searched for randomized controlled trials (RCTs) using the terms "intolerance of uncertainty" AND "treatment" OR "therapy." Data for pre and post-treatment measures and patient, intervention, and trial-level characteristics were extracted from 28 RCTs. Separate random effects models examined the treatment efficacy of interventions on IU and symptom severity. Moderators of therapeutic effects were analyzed via method-of-moments meta-regression or an analog to the analysis of variance.

Results: Across RCTs, interventions exhibited a large therapeutic effect on IU compared to control conditions ($g = 0.89$). Treatment effects on IU positively corresponded with improved symptom severity and accounted for 36 % of the variance. Interestingly, comorbid depression and certain treatment approaches were associated with larger improvements in IU.

Conclusion: Evidence-based treatments are effective in improving IU, highlighting the importance of IU in the treatment of anxiety-related disorders. Moderator analyses identified patient and intervention-level factors to inform approaches to improve therapeutic effects on IU. Future research is needed to optimize interventions targeting IU and evaluate long-term efficacy of interventions on IU for anxiety-related disorders.

1. Introduction

Anxiety-related disorders (e.g., generalized anxiety disorder, social anxiety disorder, obsessive compulsive disorder) are among the most prevalent mental health conditions (Kessler et al., 2005b; Ruscio et al., 2010). Estimates suggest that anxiety disorders affect 18 % of the population within a 12-month period (Kessler et al., 2005b), with up to 29–34 % of people affected at some point during their lifetime (Bandelow and Michaelis, 2015; Kessler et al., 2005a). Concerningly, there has been a marked increase in the overall incidence of anxiety disorders over the past few years (Bitsko et al., 2018; Kessler et al., 2005a; Santomauro et al., 2021). Anxiety-related conditions cause significant impairment in academic, occupational, family, and social functioning across the lifespan (Leon et al., 1995; McKnight et al., 2016). In the absence of evidence-based treatment, anxiety-related disorders often persist for many years and contribute to the development of chronic physical conditions (Bhattacharya et al., 2014), long-term disability (Hendriks et al., 2016; Jellestad et al., 2021; Karno, 1988; Yang et al., 2021), comorbid mental health conditions (Buckley et al., 2023; Jacobson and Newman, 2017), suicidal thoughts and behaviors (Bentley et al., 2016), and an increased risk of all causes of mortality (Meier et al., 2016). Thus, the effective treatment of anxiety-related disorders represents a pressing public health concern (Allen et al., 2020).

While anxiety-related disorders present differently across patients, these conditions are characterized by the presence of cognitive symptoms (e.g., difficulty concentrating, obsessive thoughts, irrational appraisals, anticipatory thinking), behavioral symptoms (e.g. avoidance of stimuli/situations that elicit anxiety, reassurance seeking, engagement

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in safety behaviors), emotional symptoms (e.g., strong feelings of fear, dread, panic, and helplessness), and physical symptoms (e.g., sleep disruption, headaches, nausea, fatigue, muscle tension). There are several key processes underlying the emergence and maintenance of these symptoms. One such underlying process is an individual's ability to tolerate uncertainty to situations and/or stimuli (Carleton, 2012). Broadly, intolerance of uncertainty (IU) is characterized as the inability to "*endure the aversive response triggered by the perceived absence of salient, key, or sufficient information*" (Carleton, 2016). In these moments, individuals can exhibit an increased tendency to interpret uncertain stimuli and/or situations as threatening and to respond accordingly (Carleton, 2012). For example, consider the case of a young adult with generalized anxiety disorder (GAD) that experiences worries about their academic and social performance. When confronted with an upcoming academic presentation, the young adult might experience many intrusive thoughts and/or negative cognitive misappraisals (e.g., "I'm going to do such a bad job" or "Everyone will think that I'm a loser") that make it difficult to focus on writing the presentation. These distressing thoughts and difficulty concentrating might lead to avoidance behaviors (e.g., procrastination in writing presentation), reassurance seeking behaviors (e.g., repeatedly asking classmates to listen to practice presentations, emailing instructor to ask about grade), and/or safety behaviors (e.g., superstitions about lucky outfits that will help the presentation to go well). As the presentation looms closer, the uncertainty surrounding the young adult's performance could increase, leading to feelings of dread and/or panic. The night before the event, the young adult might have difficulty sleeping, experience muscle tension, and even have a headache. Thus, while the young adult experiences numerous cognitive, behavioral, emotional, and/or somatic symptoms—the underlying cause is intolerance of uncertainty regarding the outcome. Indeed, evidence suggests that IU prospectively predicts transdiagnostic severity of emotional psychopathology over six months (Hunt et al., 2022), with changes in IU over one-year corresponding with increased social anxiety, worry, depression, and negative affect (Shapiro et al., 2020). Consistent with these findings, initial studies suggest that greater improvement in IU corresponds with improved clinical outcomes (Boswell et al., 2013; Talkovsky and Norton, 2016). Taken together, this suggests that IU is a theoretically-relevant and clinically important transdiagnostic construct—serving as a key therapeutic target for anxiety-related disorders.

Current evidence-based treatments for anxiety-related disorders include cognitive behavioral therapy (CBT), exposure therapy (ET), mindfulness-based interventions (MBI), and pharmacotherapy (Bandelow et al., 2017; Hofmann et al., 2010). These therapeutic interventions have demonstrated clinical benefit across randomized clinical trials (RCTs; Carl et al., 2019; Carpenter et al., 2018; Haller et al., 2021; Slee et al., 2019). Despite significant reduction in anxiety and OCD symptom severity, many patients remain partially symptomatic or non-responsive to these evidence-based interventions (C. Brown et al., 1996; Springer et al., 2018). While most evidence-based interventions have focused on anxiety and/or OCD symptom severity as primary treatment targets, few studies have specifically focused on measuring and/or targeting IU in treatment. CBT for intolerance of uncertainty (CBT-IU) includes core therapeutic strategies to address cognitions, feelings, and behaviors for anxiety and related symptoms. However, it also incorporates the reevaluation of the usefulness of worry, behavioral exposure to uncertainty, problem-solving training, and imaginal exposure (Robichaud et al., 2019). Although a few initial studies show promise (Beheshti et al., 2018; Hui and Zhihui, 2017; Zemestani et al., 2021), there has been relatively limited research on CBT-IU. Notably, other therapeutic interventions may also confer some benefit to improve tolerance of uncertainty. For example, mindfulness-based interventions have also been found to improve IU and result in positive clinical outcomes (Kim et al., 2016; Mathur et al., 2021). However, given the modest sample sizes and inconsistent reporting of IU across clinical trials, the extent to which current interventions effectively target and improve IU remains largely unknown. Given that IU is a key process underlying anxiety and related disorders, it is essential to understand the therapeutic effect of different therapeutic interventions on IU—which will theoretically produce corresponding improvements in anxiety-related clinical outcomes.

When examining the effects of therapeutic interventions on IU, it is important to understand factors that may influence treatment effects in order to optimize clinical outcomes. These factors include participant-level characteristics (e.g., comorbid psychopathology, demographic characteristics, concurrent pharmacotherapy), intervention-level characteristics (e.g., therapeutic approach, treatment duration), and/or trial-level characteristics (e.g., comparison condition, attrition). In regard to participant-level characteristics, evidence suggests that greater levels of IU correspond with greater symptom severity across multiple mental health conditions (e.g., anxiety, OCD, depression; Boswell et al., 2013; Gentes and Ruscio, 2011; Penney et al., 2020). Consequently, in the setting of greater co-occurrence of these psychiatric conditions, IU may represent a more prominent target, thus providing greater opportunity for therapeutic improvement. Similarly, intervention characteristics such as the type of therapeutic intervention and/or its duration may influence treatment effects on IU (e.g., more treatment sessions would be anticipated to be a greater treatment "dose" and produce greater change in IU). Indeed, specific types of therapeutic interventions (Bandelow et al., 2017; Piacentini et al., 2011) and/or intervention durations (Chong et al., 2022; Herbert et al., 2004; McGuire et al., 2014, 2015) have been found to correspond with greater treatment effects in clinical trials and meta-analyses. Finally, trial design characteristics may also influence treatment effects on IU. For instance, specific types of outcome measures may be more (or less) sensitive to changes in IU. Thus, the decision to use one measure of IU relative to another could unintentionally result in an attenuated improvement in IU. Through better understanding of the factors that influence IU outcomes, clinicians and researchers can optimize interventions to effectively target IU—which represents an important underlying process that can improve symptom severity outcomes.

While some prior reports have examined the initial effect of therapeutic interventions on IU (Beheshti et al., 2018; Hebert and Dugas, 2019; Talkovsky and Norton, 2016; Wahlund et al., 2020), these studies have been limited by uncontrolled trials, modest sample sizes, and/or limited generalizability beyond a single site. Given the theoretical and clinical relevance of IU, we examined the intervention effects on IU in patients with clinically meaningful anxiety. Additionally, we explored potential moderators of treatment effects (e.g., participant-level characteristics, intervention-level characteristics, and trial-level characteristics) to understand the factors that influence IU outcomes. Finally, we conducted a preliminary mechanism test to determine whether improvements in IU corresponded with improvements in symptom severity.

2. Methods

2.1. Design, search strategy, and eligibility criteria

This meta-analysis was conducted in accordance with the PRISMA guidelines. PubMED and PsycInfo were searched using the following key search terms: "intolerance of uncertainty" AND "treatment" OR "therapy" (1997–October 2022). Identified abstracts were reviewed independently by two raters for appropriateness (MLM and JFM). The references of eligible RCTs and review articles were also searched until no new reports were identified. Identified abstracts and/or citations were evaluated for the following inclusion criteria: (1) randomized controlled trials (RCT); (2) available in English; (3) the therapeutic intervention targeted anxiety-related disorders; (4) administered a quantitative measure of IU before and after the therapeutic intervention; and (5) included the provision of sufficient data to calculate treatment effects on IU. When insufficient data were present, study investigators

were contacted to obtain specific values. Reports were excluded if: (1) data were inaccessible even after outreach to study investigators; (2) it involved duplicate samples from other studies; (3) included fewer than 10 participants; and/or (4) included youth with autism spectrum disorders (ASD) or intellectual disability (ID) due to differences in intervention implementation. For each study, the risk of bias (ROB) was assessed using the revised Cochrane risk of bias tool (ROB2) for RCTs. Fig. 1 details RCTs that were included and excluded.

2.2. Data collection and extraction

Data were extracted and reviewed by both authors to minimize errors in reporting. Any discrepancies identified between authors were resolved through discussion and consensus. Studies were coded for the following information: *Patient Characteristics* – (1) mean age, (2) percentage of sample that was female, (3) participant diagnostic characteristics (e.g., GAD, mix of anxiety disorders, community sample with clinically significant anxiety), (4) percentage of sample with OCD, (5) percentage of sample with a depressive disorder, (6) percentage of sample on a stable dose of selective serotonin reuptake inhibitors or clomipramine; *Intervention Characteristics* – (1) type of intervention type (e.g., behavioral, mindfulness, cognitive, cognitive bias modification, unified protocol, spiritual), (2) total treatment duration, (3) total hours of treatment, and (4) treatment delivery format (i.e., group versus individual); *Trial Design Characteristics* – (1) overall sample size, (2) publication year, (3) participant attrition, (4) risk of bias, (5) trial type (i.e., waitlist, placebo/control condition, active treatment condition), (6) IU measure, (7) primary study target, and (8) primary outcome measure.

Several scales were used to extract treatment effects for IU: the Intolerance of Uncertainty Scale-27 item scale (IUS-27; Freeston et al., 1994), the Intolerance of Uncertainty Scale-12 item scale (IUS-12; Carleton et al., 2007), the IUS-5 (Fialko et al., 2012), the Intolerance of Uncertainty Scale for Children (IUS-C; Comer et al., 2009), and the Obsessive Beliefs Questionnaire Perfectionism and Intolerance of Uncertainty subscale (OBQ-44; Myers et al., 2008). Meanwhile to characterize treatment effects on symptom severity outcomes, multiple scales were used based on the primary study target. These scales included: the Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990) the Penn State Worry Questionnaire-Child (PSWQ-C; Chorpita et al., 1997), the Yale Brown Obsessive Compulsive Scale (Y-BOCS; Goodman, 1989), the Beck Anxiety Inventory (BAI; Beck et al., 1988), the Padua Inventory Washington State University Revision (PI-WSUR; Sanavio, 1988), the State Trait Anxiety Inventory (STAI; Spielberger et al., 1983), the Anxiety Scale of the Depression Anxiety Stress Scales (DASS; Lovibond & Lovibond, 1995). If multiple scales were reported for the primary study target in a RCT, the clinician-rated scales administered by an independent evaluator were prioritized (e.g., Y-BOCS Total Score for OCD severity). However, if multiple self-report clinical scales were present without clinician-rated scales, then the PSWQ was prioritized due to its common use among studies and to facilitate comparability across studies.

2.3. Effect size (ES) calculation and statistical analyses

Given the range in sample sizes across clinical trials (22 to 140 participants), Hedges' *g* was selected to quantify treatment effects and was calculated in Comprehensive Meta-Analysis Version 4 (CMA; Biostat, Inc.; Borenstein, 2022). Effect sizes were calculated using change scores to increase the precision of ES estimators by controlling for pre-treatment group differences in IU. Pre-and-post treatment means and standard deviations from IU rating scales were entered into CMA, and were divided by the pooled post-treatment standard deviation. Effect sizes were standardized so that a positive result indicated that the active treatment performed better than the control condition.

2.4. Statistical analyses

A random effects model using inverse variance weights examined the ES of identified interventions to influence IU outcomes. A random effects model was selected because the true ES was expected to vary across

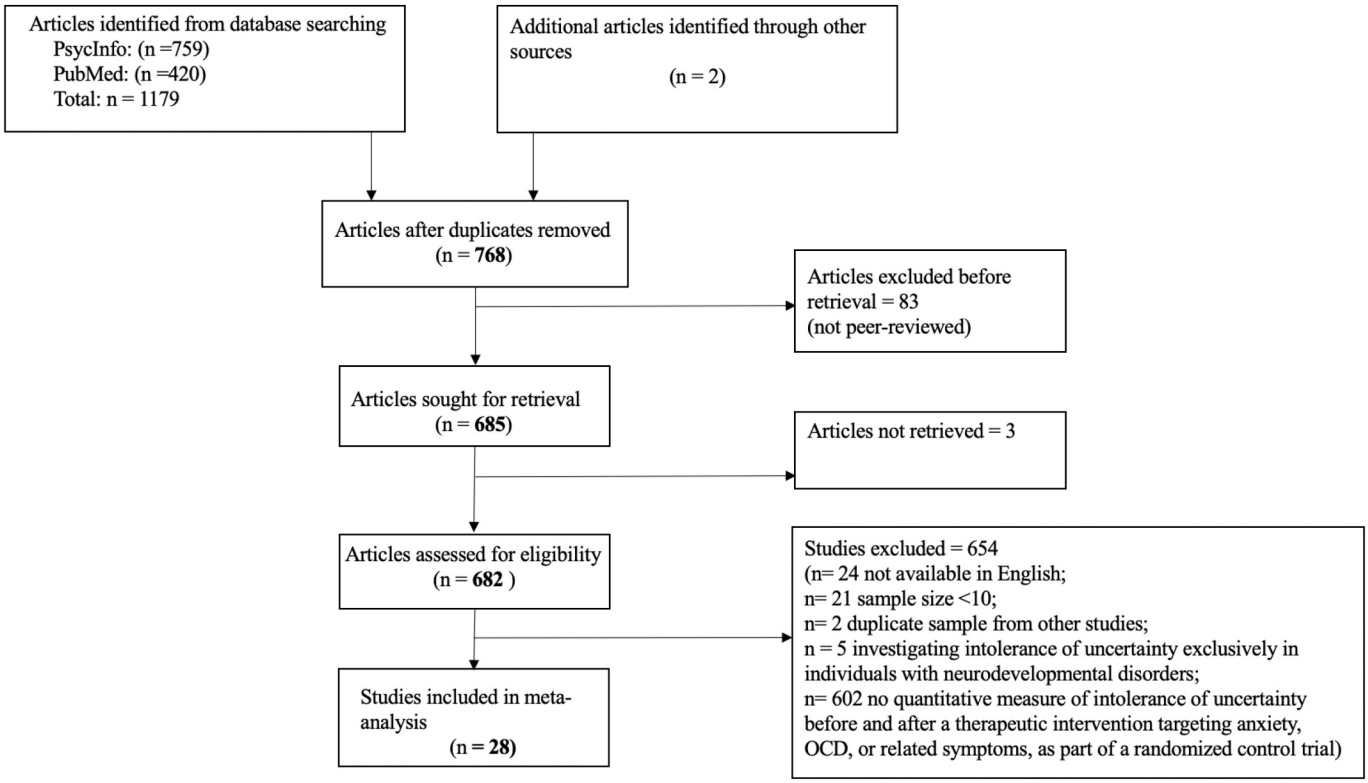

Fig. 1. PRISMA flow chart.

clinical trials due to different study characteristics (Borenstein, 2009a; Borenstein, 2009b). Heterogeneity of ES was assessed using forest plots, the *Q* statistic, and the I^2 statistic. Publication bias was assessed by visual inspection of the funnel plot and Egger's test for bias. Finally, moderator variables were analyzed using either method-of-moments meta-regression or an analog to the analysis of variance (ANOVA). For studies with multiple intervention arms, the same control condition was used as the comparator to calculate treatment effect size (Higgins et al., 2011). Finally, to explore IU effects as a potential mechanism of change underlying improvements in symptom severity, a separate random effects model examined the relationship between the ES of IU in each RCT and its accompanying symptom severity outcomes (e.g., anxiety severity, worry, and/or obsessive-compulsive severity).

3. Results

3.1. Search results and included RCTs

Fig. 1 details outcomes from the literature search that produced 28 RCTs meeting all inclusion criteria. Eight trials had multiple active treatment conditions, which provided an additional eight treatment comparison conditions. Therefore, a total of 36 treatment comparisons were included in this meta-analysis. Table 1 provides the participant-level characteristics for RCTs, and Table 2 provides the intervention-level and trial-level characteristics. Table 3 provides regression analyses and analog to ANOVA results examining moderators of IU treatment effects.

3.2. Treatment effects of identified interventions on IU

A random effects meta-analysis found a large therapeutic effect of identified interventions on IU compared to control conditions ($g = 0.89$; 95 % CI, 0.66 to 1.13; $z = 7.53$; $p < .001$, see Fig. 2). The prediction interval of treatment effects for this model ranged between −0.41 and 2.20, which suggests that the true ES in 95 % of all comparable populations falls within this interval.

Visual inspection of the forest plot, *Q* statistic, and I^2 statistic identified significant heterogeneity [$Q(35) = 198.99$, $p < .001$, $I^2 = 82$ %) and suggested the presence of treatment moderators. While visual inspection of the funnel plot did not suggest publication bias to be present, Egger test for bias was significant ($t = 2.33$, $p = .03$). Accordingly, Duval and Tweedie's trim-and-fill method was applied to account for potential publication bias. This method resulted in seven additional studies to be "filled" to the right of the summary treatment effect, and produced a slightly larger estimated summary treatment effect of identified interventions ($g = 1.14$, 95 % CI, 0.88 to 1.40).

3.3. Participant characteristics as a moderator of treatment effects on IU

Interestingly, a greater presence of comorbid depressive disorders was associated with larger therapeutic effects on IU across interventions (see Table 3). This treatment moderator accounted for 42 % of the variance in identified treatment effects across RCTs. As one RCT reported 100 % of participants exhibited a comorbid depressive disorder (Nasiri et al., 2020), these two treatment comparisons were removed and analyses re-examined as a precautionary step. However, a greater presence of comorbid depressive disorders remained associated with larger therapeutic effects on IU across RCTs ($B = 0.02$, $SE = 0.01$, $z = 2.14$, $p = .03$, $n = 22$).

When examining participant diagnostic characteristics in RCTs, there was no significant difference in effect sizes between clinical trials that had participants with only primary GAD diagnoses ($n = 22$, $g = 0.96$, $t = 5.84$, $p < .001$), a mixed clinical presentation of anxiety-related disorders ($n = 8$, $g = 0.64$, $t = 3.54$, $p < .001$), and those with participants from the community with elevated symptoms ($n = 4$, $g = 1.29$, $t = 3.05$, $p < .002$, see Table 3). Finally, participants' average age, biological sex, concurrent SRI pharmacotherapy, and presence of comorbid OCD was not found to have a significant relationship with treatment effects for IU (see Table 3).

Table 1
Participant characteristics for included studies.

	Participant characteristics					
	Age (M)	% Female	Diagnostic characteristics	% OCD	% Depression	% On SRI
Andersson et al., 2017	32.5	84.3	Primary GAD	4	0	13.6
Avdagic et al., 2014	36.2	66.7	Primary GAD	0	NR	60
Beheshti et al., 2018	25.2	100	Primary GAD	16.7	23.3	50
Black & Grisham, 2018	30.3	76.7	Mixed Anxiety Disorders	100	0.4	NR
Boswell et al., 2013	29.8	94.6	Mixed Anxiety Disorders	24.3	32.4	NR
Chen et al., 2013	39.3	77.6	Community	NR	NR	6.12
Dugas et al., 2004	41.2	71.2	Primary GAD	0	NR	21
Dugas et al., 2022	34.6	85.0	Primary GAD	0	11.7	40
Fracalanza et al., 2014	33.7	79	Primary GAD	0	22.8	NR
Goldman et al., 2007	26.0	66.7	Community	NR	0	0
Holmes et al., 2014	9.6	66.7	Primary GAD	0	4.8	NR
Hui and Zhihui, 2017	65.7	42.9	Primary GAD	0	NR	0
Khakpoor et al., 2019	25.5	78.3	Mixed Anxiety Disorders	13.0	43.5	0
Koszycki et al., 2010	43.5	59.1	Primary GAD	0	0	NR
Koszycki et al., 2014	42.2	65.2	Primary GAD	0	21.7	NR
LeBouthillier & Asmundson, 2017	32.3	76.8	Mixed Anxiety Disorders	0	NR	23
Li et al., 2021	23.9	72.5	NR	NR	NR	0
Mathur et al., 2021	28.3	33.3	Mixed Anxiety Disorders	100	28.3	76.67
Mousavi et al., 2020	35.2	100	NR	NR	NR	0
Nasiri et al., 2020	21.0	74.4	Primary GAD	0	100	0
Ovanessian et al., 2019	27.3	82.2	Community	0	6	NR
Perrin et al., 2019	13.4	62.5	Mixed Anxiety Disorders	0	15	NR
Rosmarin et al., 2010	41.8	76.5	Community	NR	NR	NR
Simpson et al., 2013	33.9	48	Mixed Anxiety Disorders	100	31	100
Treanor et al., 2011	33.6	71.0	Primary GAD	0	29	29
van der Heiden et al., 2012	35.0	73.0	Primary GAD	0	NR	NR
Wilson et al., 2020	36.7	75	Primary GAD	0	27.3	NR
Zemestani et al., 2021	25.2	100	Primary GAD	0	23.3	50

F: Female; M: Mean; GAD: Generalized Anxiety Disorder; OCD: Obsessive Compulsive Disorder; SRI: Selective Serotonin Reuptake Inhibitor; NR: Not reported.

Table 2
Intervention and trial characteristics of included studies.

	Trial characteristics and effect sizes										Intervention characteristics			
	Sample size	Year published	% Active group attrition	Risk of bias	Trial type (control condition)	IU measure	IU effect size	Primary study target	Primary outcome measure	Primary outcome effect size	Intervention type (active condition)	Total treatment duration	Total hours of treatment	Treatment format (group vs individual etc.)
Andersson et al., 2017	140	2017	5.71	Low	Wait list	IUS	0.52	Worry	PSWQ	1.43	Behavioral (Internet-Based Extinction Therapy for Worry)	10 weeks	5 h	Individual
Avdagic et al., 2014	51	2014	24	Low	Active (CBT)	IUS	0.23	Anxiety	PSWQ	0.70	Mindfulness (ACT)	6 weeks	12 h	Group
Beheshti et al., 2018	24	2018	13.33	Some Concerns	Active (pharmacotherapy)	IUS	1.05	Anxiety	PSWQ	NR	Cognitive (CBT-IU)	12 weeks	12 h	Individual
Black & Grisham, 2018	30	2014	0	Low	Placebo/ control (neutral CBMI-I)	OBQ*	6.69	OCD	PI-WSUR	7.46	CBM (Positive CBM-I)	1 week	3.5 h	Individual
Boswell et al., 2013	37	2013	13.5	Low	Wait list	IUS	0.64	Anxiety	PSWQ	NR	Unified Protocol	8 weeks minimum	8 h minimum	Individual
Chen et al., 2013	49	2013	0	Some Concerns	Wait list	IUS	3.09	Anxiety	PSWQ	4.18	Behavioral (Behavioral Activation Treatment for Worry)	8 weeks	16 h	Group
Dugas et al., 2004	52	2003	8	Some Concerns	Wait list	IUS	0.63	Anxiety	PSWQ	NR	Cognitive (CBT)	14 weeks	28 h	Group
Dugas et al., 2022	60	2022	23.3	Low	Wait list	IUS	1.86	Anxiety	PSWQ	2.41	Cognitive (Behavioral Experiments for IU)	12 weeks	12 h	Individual
Fracalanza et al., 2014 A	65	2014	9.5	Low	Placebo/ control (neutral topic writing)	IUS	0.32	Anxiety	PSWQ	0.62	Behavioral (Consistent Written Exposure)	3 days	1 h	Individual
Fracalanza et al., 2014 B	65	2014	17.4	Low	Placebo/ control (neutral topic writing)	IUS	−0.20	Anxiety	PSWQ	−0.22	Behavioral (Varied Written Exposure)	3 days	1 h	Individual
Goldman et al., 2007	30	2007	0	Low	Placebo/ control (control writing condition)	IUS	9.68	Anxiety	PSWQ	−3.23	Behavioral (Written Exposure)	4 days	2.5 h	NR
Holmes et al., 2014	42	2014	15	Low	Wait list	IUS-C	0.49	Anxiety	PSWQ-C	0.74	Cognitive (No Worries! Program)	10 weeks	15 h	Group
Hui and Zhihui, 2017	63	2017	NR	Low	Wait list	IUS Chinese Version	0.98	Anxiety	PSWQ Chinese Version	2.16	Cognitive (CBT-IU)	12 weeks	24 h	Group
Khakpoor et al., 2019	26	2019	15.3	Low	Wait list	IUS-12	1.56	Anxiety	Beck Anxiety Inventory	1.13	UP	NR	20 h	Individual
Koszycki et al., 2010	22	2010	18.2	Some Concerns	Active (SBI)	21 item IUS	0.89	Anxiety	PSWQ	0.71	Cognitive (CBT)	12 weeks	10 h	Individual
Koszycki et al., 2014	23	2014	0	Low	Placebo/ control (supportive therapy)	21 item IUS	1.13	Anxiety	PSWQ	1.36	Spiritual Intervention (SBI)	12 weeks	10 h	Individual

(*continued on next page*)

Table 2 (*continued*)

	Trial characteristics and effect sizes										Intervention characteristics			
	Sample size	Year published	% Active group attrition	Risk of bias	Trial type (control condition)	IU measure	IU effect size	Primary study target	Primary outcome measure	Primary outcome effect size	Intervention type (active condition)	Total treatment duration	Total hours of treatment	Treatment format (group vs individual etc.)
LeBouthillier & Asmundson, 2017 A	56	2017	34.8	Some Concerns	Wait list	IUS-12	0.22	Anxiety	PSWQ	NR	Behavioral (Aerobic Exercise)	4 weeks	8 h	Individual
LeBouthillier & Asmundson, 2017 B	56	2017	22.2	Some Concerns	Wait list	IUS-12	1.19	Anxiety	PSWQ	NR	Behavioral (Resistance Exercise)	4 weeks	8 h	Individual
Li et al., 2021	40	2021	9.1	Low	Active (CBM-I)	IUS-12	0.38	Anxiety	STAI	0.38	CBM (IU CBM-I)	4 weeks	1.67 h	Individual
Mathur et al., 2021	60	2021	10	Low	Placebo/ control (stress management training)	OBQ*	0.50	OCD	Y-BOCS	3.00	Mindfulness (MBCT)	12 weeks	8 h	Individual
Mousavi et al., 2020	30	2020	0	Some Concerns	Waitlist	IUS	0.52	Depression, Anxiety, Stress, and IU	DASS	3.07	Mindfulness (MBSR)	8 weeks	16 h	Group
Nasiri et al., 2020	43	2020	13.33	Low	Wait list	IUS	3.51	Anxiety	PSWQ	3.48	UP + tDCS	12 weeks	17 h	Individual
Nasiri et al., 2020	43	2020	0	Low	Wait list	IUS	3.30	Anxiety	PSWQ	2.48	UP only	12 weeks	12 h	Individual
Ovanessian et al., 2019 A	79	2019	16.1	Some Concerns	Placebo/ control (neutral topic writing)	IUS	−0.15	Anxiety	PSWQ	8.55	Behavioral (Written Exposure with Rescripting)	3 days	1.5 h	Individual
Ovanessian et al., 2019 B	79	2019	15.6	Some Concerns	Placebo/ control (neutral topic writing)	IUS	3.91	Anxiety	PSWQ	0.12	Behavioral Therapy (Written Exposure, No Rescripting)	3 days	1.5 h	Individual
Perrin et al., 2019	40	2019	10	Low	Wait list	IUS-5	1.68	Anxiety	PSWQ-C	2.21	Cognitive (CBT)	10 weeks	NR	Individual
Rosmarin et al., 2010 A	125	2010	56.7	Low	Wait list	IUS-12	1.37	Worry	PSWQ	6.37	SIT	2 weeks	NR	Individual
Rosmarin et al., 2010 B	125	2010	60.3	Low	Wait list	IUS-12	0.78	Worry	PSWQ	6.04	PMR	2 weeks	NR	Individual
Simpson et al., 2013	100	2013	7.5	Low	Placebo/ control (pill placebo)	QBQ*	0.93	OCD	Y-BOCS	2.01	Behavioral (EX/RP)	1530 h	8 weeks	Individual
Simpson et al., 2013	100	2013	7.5	Low	Active (risperidone)	QBQ*	0.74	OCD	Y-BOCS	1.61	Behavioral (EX/RP)	1530 h	8 weeks	Individual
Treanor et al., 2011	31	2011	0	Low	Wait list	IUS	3.45	Anxiety	ACQ-R	6.15	Mindfulness (Acceptance-based behavioral therapy)	18 h	18 weeks	Individual
van der Heiden et al., 2012	126	2012	23.3	Low	Wait list	IUS	0.55	Anxiety	PSWQ	0.97	Cognitive (IUT)	10.5 h	14 weeks	Individual
van der Heiden et al., 2012 B	126	2012	18	Low	Wait list	IUS	0.96	Anxiety	PSWQ	1.44	Cognitive (MCT)	10.5 h	14 weeks	Individual
Wilson et al., 2020 A	82	2020	NR	Low	Wait list	IUS-12	0.50	Anxiety	PSWQ	NR	Cognitive (CBT)	NR	12 weeks	Individual
Wilson et al., 2020 B	82	2020	NR	Low	Wait list	IUS-12	0.79	Anxiety	PSWQ	NR	Mindfulness (Mindfulness Therapy)	NR	12 weeks	Group
Zemestani et al., 2021	30	2021	0	Low	Active (SRI)	IUS	1.06	Anxiety	PSWQ	1.61	Cognitive (CBT-IU)	12 h	12 weeks	Individual

ACT: Acceptance and Commitment Therapy; ACQ-R: The Anxiety Control Questionnaire Revised; CBM−I: Interpretive Cognitive Bias Modification; CBT: Cognitive Behavioral Therapy; CBT-IU: Cognitive Behavioral Therapy focused on Intolerance of Uncertainty; CBM: Cognitive Bias Modification; DASS: Depression Anxiety Stress Scale; EX/RP: Exposure and Response Prevention; IU: Intolerance of Uncertainty; IUS: Intolerance of Uncertainty Scale; IUS-C: Intolerance of Uncertainty Scale for Children; IUT: Intolerance of Uncertainty Therapy; IUS-12: 12-item version of IUS; MBCT: Mindfulness-Based Cognitive Therapy; MBSR-Mindfulness-Based Stress Reduction; MCT: Metacognitive Therapy; NR: Not Reported; OBQ*: Obsessive Beliefs Questionnaire-Perfectionism and Intolerance of Uncertainty Subscale; PANAS: Positive and Negative Affect Scale; PI-WSUR: Padua Inventory—Washington State University Revision; PMR: Progressive Muscle Relaxation; PSWQ: Penn State Worry Questionnaire; PSWQ-C: Penn State Worry Questionnaire for Children; SBI: Spiritually Based Intervention; STT: Spiritually Integrated Treatment; SRI: Serotonin Reuptake Inhibitor; STAI: State-Trait Anxiety Inventory; t-DCS: Transcranial Direct Current Stimulation; UP: Unified Protocol for Transdiagnostic Treatment of Emotional Disorders; UP-Caregiver: Unified Protocol for Transdiagnostic Treatment of Emotional Disorders for Caregivers.

Table 3
Regression analyses and analog to ANOVA Examining moderators of treatment effects for intolerance of uncertaintY.

Study characteristic	Treatment effects					
	B	*SE*	*z*	*p*	R^2 analogue	*n*
Participant characteristics						
Mean participant age	<−0.01	0.01	−0.30	0.76	<0.01	36
Gender (% female)	<0.01	<0.01	0.11	0.91	<0.01	36
SRI Medication (% on)	−0.01	0.01	−1.27	0.20	<0.01	20
Percent OCD	<−0.01	<0.01	−0.75	0.45	<0.01	30
Percent depression	0.03	0.01	5.03	<0.001	0.42	24
Intervention characteristics						
Intervention duration	0.08	0.02	3.63	<0.001	0.12	36
Intervention hours	0.03	0.01	2.01	0.04	0.08	33
Trial design characteristics						
Sample size	<−0.01	<0.01	−1.23	0.22	<0.01	36
Active treatment attrition	<−0.01	0.01	−0.93	0.35	<0.01	33
Publication year	0.02	0.03	0.61	0.54	<0.01	36
		Q	*(df)*	*p*		
Participant characteristics						
Anxiety/clin mix/ community		2.87	2	0.24		34
Intervention characteristics						
Intervention types		22.61	6	0.001		36
Intervention delivery approach		0.10	1	0.75		36
Trial design characteristics						
Intervention comparison group		18.98	2	<0.001		36
IUS outcome measure		8.27	3	0.04		36
Risk of bias (ROB)		0.35	1	0.56		36

3.4. Intervention characteristics as a moderator of treatment effects on IU

Interestingly, RCTs that had a longer treatment duration ($p < .001$) and/or more intervention hours ($p < .04$) exhibited greater treatment effects on IU (see Table 3). These two treatment moderators respectively accounted for 12 % and 8 % of the variance in identified treatment effects across RCTs. Additionally, there were significant differences in treatment effects across interventions in RCTs (Table 3). There were descriptive difference among RCTs that used the Unified Protocol ($n = 4$, $g = 2.20$, $t = 11.72$, $p < .001$), Spiritual-Based Interventions ($n = 2$, $g = 1.34$, $t = 8.10$, $p < .001$), Mindfulness-Based Interventions ($n = 5$, $g = 0.98$, $t = 6.82$, $p = .01$), and Cognitive-Based Interventions ($n = 11$, $g = 0.95$, $t = 1.22$, $p < .001$) relative to RCTs that used Relaxation-Based Interventions ($n = 1$, $g = 0.78$, $t = 4.94$, $p < .001$), Behavioral Interventions ($n = 11$, $g = 0.54$, $t = 2.49$, $p = .01$), and/or Cognitive Bias Modification Interventions ($n = 2$, $g = 0.23$, $t = 0.99$, $p = .32$).

Follow-up pairwise comparisons revealed that both the Unified Protocol [$Q(1) = 5.12$, $p < .02$] and Spiritual-Based Interventions [$Q(1) = 8.48$, $p < .004$] produced greater treatment effects on IU relative to Behavioral Interventions. Further comparison revealed that the Unified Protocol [$Q(1) = 3.92$, $p = .048$] and Spiritual-Based Interventions [$Q(1) = 5.93$, $p < .015$] also produced greater treatment effects on IU relative to Relaxation-Based Interventions. Finally, the Unified Protocol

	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Andersson et al. 2017	0.519	0.171	0.029	0.184	0.854	3.038	0.002
Avdagic et al. 2014	0.225	0.277	0.077	-0.317	0.767	0.814	0.416
Beheshti et al. 2018	1.053	0.422	0.178	0.225	1.881	2.492	0.013
Black & Grisham, 2014	-0.007	0.355	0.126	-0.703	0.690	-0.019	0.985
Boswell et al. 2013	0.648	0.360	0.130	-0.058	1.353	1.799	0.072
Chen et al. 2013	3.091	0.420	0.177	2.268	3.915	7.356	0.000
Dugas et al. 2003	0.629	0.280	0.079	0.080	1.179	2.245	0.025
Dugas et al. 2022	1.861	0.306	0.094	1.261	2.462	6.077	0.000
Fracalanza et al. 2014a	0.323	0.305	0.093	-0.274	0.921	1.060	0.289
Fracalanza et al. 2014b	-0.197	0.297	0.088	-0.779	0.385	-0.663	0.507
Goldman et al 2007	0.097	0.355	0.126	-0.600	0.794	0.272	0.785
Holmes et al. 2014	0.490	0.308	0.095	-0.113	1.094	1.593	0.111
Hui & Zhihui, 2017	0.982	0.264	0.070	0.465	1.499	3.721	0.000
Khakpoor et al. 2019	1.559	0.437	0.191	0.702	2.416	3.567	0.000
Koszycki et al. 2010	0.891	0.432	0.186	0.045	1.737	2.065	0.039
Koszycki et al. 2014	1.126	0.435	0.189	0.273	1.979	2.586	0.010
LeBouthillier & Asmundson, 2017a	-0.218	0.326	0.106	-0.857	0.420	-0.670	0.503
LeBouthillier & Asmundson, 2017b	1.187	0.371	0.138	0.460	1.914	3.199	0.001
Li et al. 2021	0.385	0.296	0.087	-0.195	0.964	1.301	0.193
Mathur et al. 2021	0.498	0.259	0.067	-0.009	1.006	1.925	0.054
Mousavi et al. 2020	0.519	0.362	0.131	-0.189	1.228	1.437	0.151
Nasiri et al. 2020a	3.511	0.576	0.332	2.382	4.639	6.096	0.000
Nasiri et al. 2020b	3.299	0.555	0.308	2.212	4.386	5.948	0.000
Ovanessian et al. 2019a	-0.148	0.253	0.064	-0.645	0.348	-0.586	0.558
Ovanessian et al. 2019b	0.039	0.251	0.063	-0.453	0.531	0.156	0.876
Perrin et al. 2019	1.680	0.362	0.131	0.970	2.390	4.636	0.000
Rosmarin et al. 2010a	1.369	0.178	0.032	1.020	1.719	7.688	0.000
Rosmarin et al. 2010b	0.779	0.158	0.025	0.470	1.088	4.944	0.000
Simpson et al. 2013a	0.928	0.283	0.080	0.372	1.483	3.274	0.001
Simpson et al. 2013b	0.743	0.229	0.052	0.294	1.192	3.243	0.001
Treanor et al. 2011	3.454	0.561	0.315	2.354	4.554	6.155	0.000
van der Heiden et al. 2012a	0.549	0.259	0.067	0.041	1.057	2.117	0.034
van der Heiden et al. 2012b	0.965	0.266	0.071	0.443	1.487	3.624	0.000
Wilson et al. 2020a	0.502	0.283	0.080	-0.052	1.056	1.775	0.076
Wilson et al. 2020b	0.790	0.291	0.085	0.220	1.360	2.716	0.007
Zemestani et al. 2021	1.061	0.381	0.145	0.315	1.807	2.787	0.005
Pooled	0.893	0.119	0.014	0.660	1.126	7.525	0.000
Prediction Interval	0.893			-0.409	2.195		

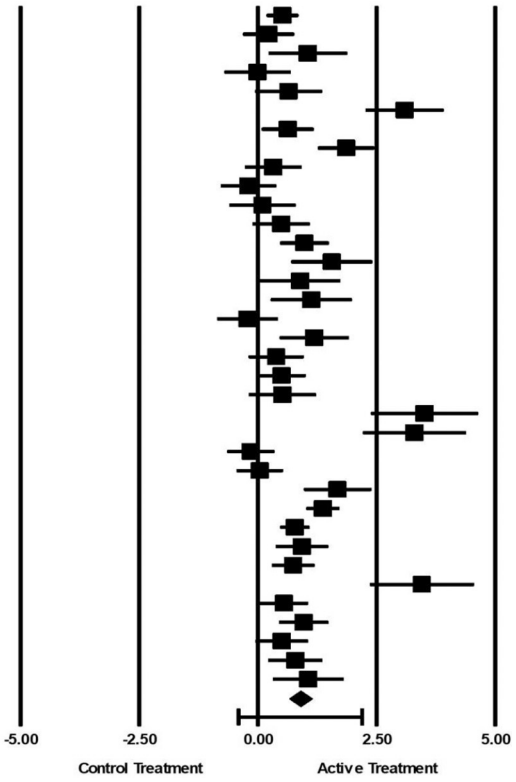

Fig. 2. Forest Plots for the random effects meta-analysis of interventions on Intolerance of Uncertainty (IU). Box size represents study weighting. Upper and Lower Limits in Forest plots represent 95% confidence intervals.

[$Q(1) = 7.20$, $p < .007$], Spiritual-Based Interventions [$Q(1) = 15.63$, $p < .001$], Cognitive-Based Interventions [$Q(1) = 7.34$, $p < .001$], and Relaxation-Based Interventions [$Q(1) = 4.02$, $p < .04$] all produced greater therapeutic effects than Cognitive Bias Modification Interventions.

Despite differences across intervention types, there was no significant difference between individual intervention delivery approaches ($n = 28$, $g = 0.92$, $t = 6.76$, $p < .001$) and group intervention delivery approaches ($n = 8$, $g = 0.82$, $t = 3.11$, $p < .002$).

3.5. Trial design characteristics as a moderator of treatment effects on IU

When examining intervention comparison groups, a clear pattern emerged. Descriptively, waitlist-controlled trials ($n = 21$, $g = 1.23$, $t = 7.39$, $p < .001$) exhibited larger therapeutic effects relative to trials that used active comparison conditions ($n = 6$, $g = 0.65$, $t = 4.69$, $p < .001$) and/or non-active comparison conditions ($n = 9$, $g = 0.27$, $t = 1.82$, $p = .07$). Follow-up pairwise comparisons revealed that waitlist-controlled trials exhibited larger treatment effects relative to both active comparison conditions [$Q(1) = 7.19$, $p < .007$] and non-active comparison conditions [$Q(1) = 18.93$, $p < .001$].

Furthermore, there were significant differences between IU outcome measures. Descriptively, trials that used the IUS-5 ($n = 1$, $g = 1.68$, $t = 4.64$, $p < .001$) had larger treatment effects relative to trials using the more commonly used IUS-27 ($n = 23$, $g = 0.99$, $t = 5.57$, $p < .001$) and the IUS-12 ($n = 8$, $g = 0.79$, $t = 4.24$, $p < .001$), with the intolerance of uncertainty subscale on the OBQ-44 detecting more modest effects ($n = 4$, $g = 0.59$, $t = 3.38$, $p < .001$). However, follow-up pairwise comparison only detected significant differences between the IUS-5 and both the IUS-12 [$Q(1) = 4.83$, $p < .03$] and subscale of the OBQ-44 [$Q(1) = 7.36$, $p < .007$].

Meanwhile, trial sample size, treatment attrition, and trial publication year were not found to have a significant relationship with treatment effects for IU (see Table 3). Additionally, there was no statistically significant difference between trials that had "some risk" of bias ($n = 9$, $g = 0.75$, $z = 2.49$, $p < .001$) and "low risk" of bias ($n = 27$, $g = 0.94$, $z = 7.37$, $p < .001$, see Table 3).

3.6. Comprehensive examination of all significant moderators of treatment effects on IU

When adding in all significant dimensional moderators into a single model, the model accounted for approximately 66 % of the variance in treatment effects (R^2 analogue). Treatment duration in weeks ($B = 0.08$, $SE = 0.02$, $z = 3.30$, $p < .001$) and the percent of depressive disorders in the sample ($B = 0.02$, $SE = 0.01$, $z = 4.26$, $p < .001$) remained significant predictors, but total treatment time in hours did not ($B = -0.02$, $SE = 0.01$, $z = -1.40$, $p = .16$). Given that one included RCT reported that all participants exhibited a comorbid depressive disorder (Nasiri et al., 2020), the model was re-examined with these comparisons removed as a precautionary step. When doing so, the model still accounted for 56 % of the variance, but only treatment duration in weeks was significant ($B = 0.09$, $SE = 0.02$, $z = 3.86$, $p < .001$) but not percent of depressive disorders in the sample ($B \leq 0.01$, $SE = 0.01$, $z = 0.28$, $p = .78$) or total treatment hours ($B = - < 0.01$, $SE = 0.01$, $z = -0.47$, $p = .64$).

3.7. Preliminary test whether treatment effects on IU predict reductions in symptom severity

Twenty-eight comparisons had clinical outcome data and were included in the following analyses (see Table 2). A random effects meta-analysis found a large therapeutic effect of identified interventions on symptom severity outcomes when compared to control conditions ($g = 1.89$; 95 % CI, 1.33 to 2.46; $z = 6.56$; $p < .001$, see Fig. 3). The prediction

	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Mousavi et al. 2020	3.068	0.532	0.283	2.025	4.111	5.766	0.000
Treanor et al. 2011	6.150	0.856	0.733	4.473	7.828	7.186	0.000
Simpson et al. 2013a	2.009	0.327	0.107	1.368	2.649	6.149	0.000
Simpson et al. 2013b	1.609	0.255	0.065	1.109	2.110	6.301	0.000
Avdagic et al. 2014	0.701	0.284	0.081	0.144	1.258	2.465	0.014
Zemestani et al. 2021	1.609	0.412	0.169	0.802	2.415	3.909	0.000
van der Heiden et al. 2012a	0.971	0.267	0.071	0.448	1.495	3.638	0.000
van der Heiden et al. 2012b	1.440	0.279	0.078	0.893	1.987	5.159	0.000
Fracalanza et al. 2014a	0.621	0.310	0.096	0.013	1.229	2.001	0.045
Fracalanza et al. 2014b	-0.220	0.297	0.088	-0.803	0.362	-0.741	0.459
Goldman et al 2007	-0.032	0.355	0.126	-0.729	0.664	-0.091	0.927
Holmes et al. 2014	0.738	0.314	0.098	0.123	1.353	2.353	0.019
Hui & Zhihui, 2017	2.159	0.315	0.099	1.542	2.775	6.863	0.000
Khakpoor et al. 2019	1.126	0.411	0.169	0.321	1.931	2.742	0.006
Koszycki et al. 2014	1.363	0.450	0.202	0.482	2.245	3.031	0.002
Koszycki et al. 2010	0.713	0.424	0.180	-0.118	1.544	1.681	0.093
Nasiri et al. 2020a	3.483	0.573	0.328	2.360	4.606	6.078	0.000
Nasiri et al. 2020b	2.482	0.478	0.229	1.545	3.420	5.188	0.000
Ovanessian et al. 2019a	0.085	0.253	0.064	-0.410	0.581	0.338	0.735
Ovanessian et al. 2019b	0.119	0.251	0.063	-0.373	0.611	0.474	0.636
Perrin et al. 2019	2.212	0.397	0.157	1.435	2.990	5.579	0.000
Mathur et al. 2021	3.001	0.374	0.140	2.268	3.734	8.021	0.000
Li et al. 2021	0.376	0.296	0.087	-0.204	0.955	1.270	0.204
Andersson et al. 2017	1.432	0.189	0.036	1.062	1.801	7.590	0.000
Chen et al. 2013	4.182	0.507	0.258	3.187	5.177	8.241	0.000
Rosmarin et al. 2010a	6.369	0.396	0.157	5.594	7.144	16.098	0.000
Rosmarin et al. 2010b	6.042	0.354	0.126	5.347	6.737	17.044	0.000
Black & Grisham, 2014	0.075	0.355	0.126	-0.622	0.771	0.210	0.834
Dugas et al. 2022	2.405	0.336	0.113	1.746	3.064	7.150	0.000
Pooled	1.890	0.288	0.083	1.325	2.455	6.558	0.000

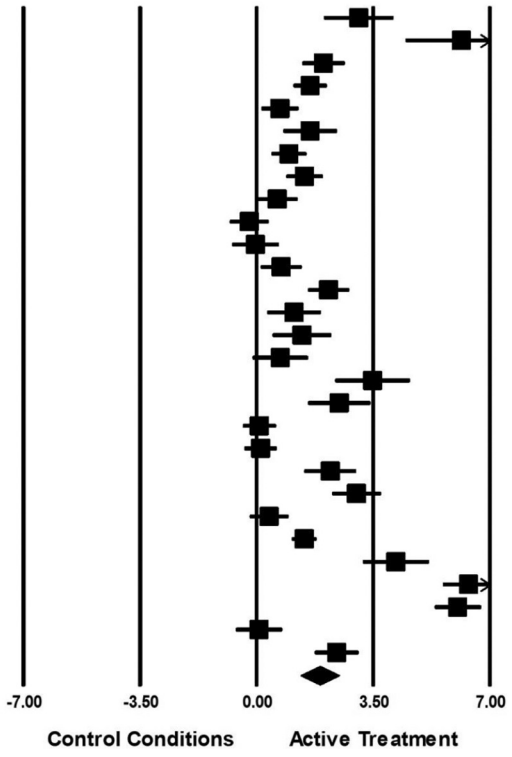

Fig. 3. Forest Plots for the random effects meta-analysis of interventions on Symptom Severity outcomes. Box size represents study weighting. Upper and Lower Limits in Forest plots represent 95% confidence intervals.

interval of treatment effects for this model ranged between −1.25 and 5.03, which suggests that the true ES in 95 % of all comparable populations falls in this interval.

Visual inspection of the forest plot, Q statistic, and I^2 statistic identified significant heterogeneity [$Q(19) = 605.79, p < .001, I^2 = 95.38\,\%$) and suggested the presence of treatment moderators. While visual inspection of the funnel plot did not suggest publication bias to be present, Egger test for bias was significant ($t = 2.71, p = .01$). Accordingly, Duval and Tweedie's trim-and-fill method was applied to account for potential publication bias. This method resulted in five additional studies to be "filled" to the right of the summary treatment effect, and produced a slightly larger estimated summary treatment effect of identified interventions ($g = 2.30$, 95 % CI, 1.68 to 2.93). This suggests that the interventions included in this meta-analysis had large therapeutic effects on symptom severity outcomes. Moderator analyses revealed that greater treatment effects on IU were associated with larger treatment effects for symptom severity, and accounted for 36 % of the variance in the model ($B = 1.07$, $SE = 0.23$, $z = 4.59$, $p < .001$).

4. Discussion

This study examined the therapeutic effects of interventions to improve IU in patients with anxiety-related disorders, explored potential moderators of treatment effects on IU, and investigated whether improvements in IU corresponded with improvements in symptom severity. Overall, a large therapeutic effect ($g = 0.89$) was observed for improvement in IU from identified interventions. This is consistent with the few initial RCTs that examined the benefit of CBT on IU (Boswell et al., 2013; Ladouceur et al., 2000), as well as with a recent meta-analysis that examined the impact of psychological treatments on IU for adults with GAD (Wilson et al., 2023). Notably, the treatment effects on IU corresponded with improvements in symptom severity and accounted for 36 % of variance. This supports initial findings linking greater improvements in IU with improved clinical outcomes across interventions (Boswell et al., 2013; Shapiro et al., 2020; Talkovsky and Norton, 2016). Taken together, these findings highlight the importance of IU as a therapeutic target in the treatment of anxiety-related disorders. However, several factors warrant consideration when considering approaches to optimize IU for future interventions.

First, it is important to consider the intervention characteristics that influenced therapeutic effect on IU. While most interventions produced moderate to very-large positive significant changes in IU (g = 0.54–2.20), the two interventions with the most robust effects included the Unified Protocol ($g = 2.20$) and Spiritual-Based Interventions (g = 1.34). Thus, while patients with high IU may show improvement from many interventions, the Unified Protocol and/or Spiritual-Based Interventions may be ideal interventions to try first. While the Unified Protocol is a standardized manualized treatment (Barlow, 2010), there can be greater variability regarding the content and implementation of Spiritual-Based Interventions. Thus, the Unified Protocol may be the optimal treatment to begin with for patients presenting with high IU. Relatedly, it is important to consider that a longer treatment duration was associated with greater therapeutic improvement in IU. This suggests that that changes in IU may not be immediately apparent and/or observed, as patients may require longer time to practice learned skills to experience benefit. For instance, Avdagic et al. (2014) found continued improvement in IU between post-assessment and a follow-up assessment for individuals who received CBT (Avdagic et al., 2014). Thus, improvements in IU may take time, and clinicians should hold steadfast in delivering evidence-based treatments even when improvement in IU are not immediately observed in treatment. While no differences were found between the delivery-format of interventions (i.e., individual versus group), it is important to consider that some prior meta-analytic reports have found reduced therapeutic effects of group versus individual CBT for the treatment of anxiety-related disorders (Bandelow and Michaelis, 2015). Indeed, when only focused on

psychological interventions that primarily consistent of CBT, Wilson et al. (2023) found individual therapy to be more efficacious for improvement IU relative to group therapy (Wilson et al., 2023). However, when meta-analytic reports have been more inclusive (i.e., including psychotherapies beyond CBT), there were not differences in the effects of group versus individual therapeutic approaches for anxiety-related disorders (Barkowski et al., 2020; Burlingame et al., 2016). Thus, further research is needed to better understand the factors that influences differences in IU and clinical outcomes in individual and group therapy approaches.

Second, it is important to consider the influence of trial-level characteristics on the therapeutic effects of IU. While trial sample size, attrition, publication year, and risk of bias did not influence treatment effects, the outcome measure used to characterize IU did. Specifically, pairwise comparisons found that the IUS-5 ($g = 1.68$) was associated with detecting larger treatment effects compared to the IUS-12 ($g = 0.79$,) and/or the OBQ-44 IU subscale ($g = 0.59$). As only one trial used the IUS-5, these findings should be interpreted with caution. Notably, the mostly commonly used measure to characterize IU was the IUS-27, which detected overall large treatment effects from interventions ($g = 0.99$). However, psychometric evaluations have shown that the IUS-12 is more trans-diagnostically robust as a function of items specific to worry (Carleton, 2012; Gentes and Ruscio, 2011; Hong and Lee, 2015; Khawaja and Yu, 2010). Indeed, the IUS-12 self-report scale is relatively brief (~5 min to complete) and could be easily integrated into regular clinical practice (i.e., administration and completion before therapy appointments). Aside from the specific IU outcome measures, waitlist-controlled trials were found to exhibit larger treatment effects compared to trials with an active comparison condition. This is consistent with existing literature on waitlist-control trials (Patterson et al., 2016), and highlights the importance of using active comparison conditions in future clinical research on IU.

Third, it is important to consider patient-level characteristics that influence the effect of interventions on IU. Most demographic and clinical characteristics did not influence treatment effects on IU (e.g., age, biological sex, psychiatric diagnostic characteristics, comorbid OCD diagnosis, concurrent SRI). This suggests that most patients would exhibit therapeutic benefit from these interventions if IU is the intended treatment target. Interestingly, comorbid depressive disorders emerged as the only patient-level characteristic associated with treatment effects on IU, with a greater co-occurrence of depressive disorders corresponding with greater improvement in IU. This finding is somewhat counter-intuitive as in many instances co-occurring depressive disorders can impede treatment effects (e.g., depressive symptoms lead to avoidance behaviors and/or reduced utilization of therapeutic strategies). However, depressive disorders are also characterized by cognitive symptoms (e.g., rumination) that share similar features to IU (Huang et al., 2019). Indeed, prior meta-analytic work has found a positive relationship between IU and depressive disorders (Boswell et al., 2013; Carleton et al., 2012; Gentes and Ruscio, 2011) and/or difficulties with emotion regulation (Sahib et al., 2023; Shu et al., 2022). Thus, the patients who present with an anxiety-related disorder and comorbid depressive disorders may have greater room for improvement in IU and/or may be more likely to exhibit therapeutic benefit in IU. This does not suggest that co-occurring depressive disorders will not continue to interfere with therapeutic skill implementation during interventions. Rather, patients with anxiety-related disorders and co-occurring depressive disorders are more likely to display therapeutic improvement in IU that may confer to improvement in symptom severity reductions over time. However, future research is needed on this topic to better understand and interpret these findings.

Despite several strengths, this meta-analysis is not without limitations. First, there was inconsistent reporting of variables across RCTs. Although study investigators were contacted to obtain information, data were unobtainable for some trials that resulted in a different number of studies available for each moderator analysis. Second and similarly, when interpreting treatment moderator analyses, it is important to consider that there were some instances in which disparate distributions were present for sub-group comparisons. As these disparate subgroup distributions may influence power to detect statistical significance, treatment moderators that did not reach statistical significance in this examination should not be interpreted as a conclusive lack of association. Third, this meta-analysis focused only on acute treatment outcomes and did not include long-term follow-up assessments. Although many studies included follow-up assessments, the timing of these follow-up visits varied widely from one week to two years. Moreover, information about interventions and/or other treatments received during follow-up intervals was largely unavailable. Thus, future research should aim to examine both acute and longer-term treatment outcomes on IU in a controlled manner. Fourth, there were limited characteristics available for extraction across RCTs. Thus, there may be unexamined factors that could also influence treatment effects on IU (e.g., therapeutic content of each intervention session, amount of time skills practiced between intervention sessions, the presence of other comorbid psychiatric conditions). Finally, the available data regarding age and biological sex suggested that the majority of RCTs primarily consisted of adult women. Future studies should seek to improve the diversity of participant samples—including age, biological sex, as well as racial background, ethnicity, and socioeconomic status. Indeed, very limited information is available on IU in diverse samples and/or children and adolescents (Osmanağaoğlu et al., 2018).

In summary, this meta-analysis found that therapeutic interventions were efficacious for improving IU and that improvements in IU corresponded with improved symptom severity for individuals with anxiety-related disorders. These findings highlight the importance of IU as a treatment target for individuals with anxiety-related disorders, and also identify that considerably more research is needed to optimize treatment outcomes for both IU and symptom severity. For instance, impairments in extinction learning are implicated in the etiology, development, and maintenance of anxiety-related disorders (Adolph et al., 2022; McGuire et al., 2016; Steuber and McGuire, 2022). While initial research has found a connection between IU and extinction learning (Morriss et al., 2021), further work is needed to replicate and build upon these promising findings. As extinction learning is a key therapeutic target in evidence-based treatment for anxiety-related disorders, a better understanding of the precise impairments in these underlying mechanisms can inform the development and optimization of future treatments (Adolph et al., 2023; McGuire and Storch, 2019). Beyond this, IU has been implicated in related conditions such as Anorexia Nervosa (Brown et al., 2017) for which many treatments have shown limited benefit on clinical outcomes (Murray et al., 2019). These findings highlight the potential benefit of interventions for patient populations in which IU may also be elevated and implicated as key treatment target. Although future research is clearly needed, these findings highlight the promise and potential of targeting IU in patient populations that might have once been considered treatment-refractory.

CRediT authorship contribution statement

Conception and design of study: MLM, JFM
Acquisition of data: MLM, JFM
Analysis and/or interpretation of data: MLM, JFM
Drafting the manuscript: MLM, JFM
Revising the manuscript critically for important intellectual content: MLM, JFM Approval of the version of the manuscript to be published: MLM, JFM

Declaration of competing interest

Authors declare no competing interests, financial or non-financial. Authors are not aware of their academic institutions or employment having any financial interest in or financial conflict with the subject

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