MEDIATORS OF YOUTH ANXIETY OUTCOMES 3 TO 12 YEARS AFTER TREATMENT

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ABSTRACT

Objective: Test changes in (a) perceived coping efficacy, (b) negative self-statements, and (c) interpretive biases to threat as potential mediators of the relationship between treatment condition and long-term follow-up (average of 6.5 years after intervention). Test moderating effect of age at time of randomization on mediational effect for the 3 putative mediators. **Method**: Participants included 301 youth who had participated in the Child/Adolescent Multimodal Study (CAMS) and agreed to participate in a naturalistic follow-up study beginning an average of 6.5 years after the end of the acute treatment phase. In the intervention phase, participants (ages 7 to 17) were randomized to cognitive behavioral therapy (CBT), pharmacotherapy (sertraline), combined CBT and sertraline, or pill placebo. Putative mediators were measured at 4 time-points over the course of the intervention phase. The follow-up study consisted of five annual assessment visits that included ratings of current anxiety based on an interview by an independent evaluator who was blind to the randomization of participants. **Results**: Reductions on a measure of interpretive biases to threat over the course of the combined intervention condition mediated anxiety outcomes at the first follow-up visit. No other significant mediated effects were found for any of the putative mediators. Age did not significantly moderate any mediated effects. **Conclusions**: The findings suggest that interpretive biases to threat, an often elevated characteristic of anxious youth, may be important to address as part of the treatment of anxiety in order to maintain reductions in anxiety in the years following treatment. The specificity of this finding to the combined CBT and sertraline condition offers support for the synergistic effect of CBT and sertraline when implemented in tandem to reduce anxiety-related cognitive factors with long-term implications.

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CHAPTER 1

MANUSCRIPT IN JOURNAL ARTICLE FORM

Mediators of Youth Anxiety Outcomes 3 to 12 Years After Treatment

Epidemiological estimates report that the prevalence of impairing anxiety is greater than 10% (Pine, Cohen, Gurley, Brook, & Ma, 1998). Anxiety disorders are linked to detrimental functional outcomes over time for youth with anxiety (Swan & Kendall, 2016), and thus there is a great need for interventions that improve the long-term trajectories for youth with these disorders. Cognitive behavioral therapy (CBT) and pharmacotherapy using selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective interventions for anxious youth (e.g., Birmaher et al., 2003; Kendall, Hudson, Gosch, Flannery-Schroeder, & Suveg, 2008), and the combination of CBT and the SSRI sertraline has been found to be even more effective for youth than these interventions individually (Walkup et al., 2008). However, we do not yet fully understand how these treatments impact long-term anxiety outcomes. Given the long-term stability of many disorders that emerge in childhood (Merikangas et al., 2010), it is particularly important to understand the treatment factors that optimize the maintenance of positive gains following treatment (Fossum, Handegård, Adolfsen, Vis, & Wynn, 2015). Research on how effective treatments impact symptoms can help inform providers of the most essential features of treatment, optimize outcomes, and remove unnecessary treatment components to lower costs and risks (Kraemer, Wilson, Fairburn, & Agras, 2002). The current study addresses the question of how treatments for youth anxiety relate to long-term outcomes by examining the impact of treatment components on anxiety symptoms

over the course of a naturalistic 5-year follow-up period spanning the 3 to 12 years (*M* = 6.5 years) after treatment.

Treatments for anxious youth aim not only to alleviate immediate symptoms but also to reduce the impact of anxiety on healthy development into adulthood (Nevo & Manassis, 2009). Research has only begun to examine how individuals fare over the years following treatment. In the adult anxiety literature, there is some evidence that symptoms continue to improve over the follow-up period after treatment, such that symptoms continue to significantly decrease in the 2 years following treatment (e.g., Dugas et al., 2003). Recent studies of youth anxiety treatment have also found some evidence for continued symptom improvement after treatment, such as on child-reported symptoms between posttreatment and 3-month follow-up (Hudson et al., 2009), clinician-rated anxiety severity between posttreatment and 6-month follow-up (Hudson et al., 2014), and on parent, child, and clinician-reported anxiety between posttreatment and 12-month follow-up (Spence et al., 2011). This pattern in youth may be due to the rapid cognitive development in childhood and adolescence that results in incremental increases in understanding of therapy-based skills and how to apply them to progressively more challenging situations after treatment has ended. Given that findings from longer follow-up studies of CBT for youth anxiety sometimes differ from results of shorter follow-ups (e.g., Benjamin, Harrison, Settipani, Brodman, & Kendall, 2013), it is important to study contributors to long-term gains as well as immediate treatment gains (Nevo & Manassis, 2009). Although not yet explored in the youth anxiety treatment literature, mediation studies may elucidate what aspects of treatment impact these symptom trajectories over follow-up.

Mediation analyses are one approach that can be used to study how treatment impacts long-term outcomes. In the treatment literature, mediation refers to the process by which the intervention is able to influence the target symptoms and in turn lead to successful outcomes after the intervention. However, more rigorous tests are needed to establish the temporal relationship between change in mediators and outcomes, and then establish a causal relationship between the two (Kraemer et al., 2002). In the youth treatment literature, few studies have considered mediators of long-term treatment outcomes, and none have examined mediators of outcomes more than two years post-intervention. Even among mediational studies of acute treatment response, few have included the methodological features necessary to establish the directionality of the proposed mediational relationship (Kazdin, 2007; Maric, Heyne, MacKinnon, van Widenfelt, & Westenberg, 2013).

The findings from studies of a variety of treatments for diverse psychopathologies of youth provide preliminary evidence for putative mediators of CBT (Maric, Prins, & Ollendick, 2015). With specific reference to positive outcomes of treatment for youth anxiety, two of the commonly identified direct targets of CBT and proposed mediators are (a) coping, and (b) anxious self-talk (also referred to as self-statements; Herres, Cummings, Swan, Makover, & Kendall, 2015). As such, these putative mediators are hypothesized to be related to long-term outcomes of treatment as well.

The development of coping skills can be broadly understood as the transition from inactive, passive behaviors (e.g., avoidance) to the active use of strategies (e.g., problem-solving) to endure stressful situations (Chu & Harrison, 2007). Coping skills are

theorized to impact anxiety symptoms through incorporating physiological, cognitive, and behavioral strategies that help youth successfully manage their emotions and environments in response to anxiety-provoking situations (Compas, Connor-Smith, Saltzman, Thomsen, & Wadsworth, 2001). Such coping skills are taught and practiced in CBT, including through exposure tasks (Kendall et al., 2005). Exposure tasks consist of individualized activities designed to provoke anxiety so that youth can practice employing strategies to endure the feared situations (Peterman, Read, Wei, & Kendall, 2015). Previous mediation studies of CBT for child anxiety suggest that increases in perceived use of coping strategies may mediate the reduction in anxiety symptoms at 3-month follow-up (Hogendoorn et al., 2014; Kendall et al, 2016). To date, there is no literature on how changes in perceived coping during intervention may differentially impact treatment gains over a longer follow-up period. After treatment ends, families may increasingly incorporate informal exposures into their children's lives to supplant previously therapist-led in-session exposures. Additionally, youth likely experience increasingly stressful situations that challenge and strengthen their coping skills over time as they move through developmental stages. There is some evidence to suggest that developmental age plays a role in the relationship between perceived coping and anxiety symptoms: low perceived coping has been shown to be a particularly salient trait of older anxious children (ages 10-12), whereas younger children with anxiety (ages 7-9) are less likely to show differences in perceived coping relative to their nonanxious counterparts (Creswell, Murray & Cooper, 2014). Therefore, age merits consideration as a potential moderator of the mediated effects of perceived coping.

Self-statements, another proposed mediator, refer to cognitive appraisals of situations and are considered a component of distressing anxiety (Cannon & Weems, 2010). Anxious children report more anxious and negative self-statements than nonanxious youth (Sood & Kendall, 2007). One goal of CBT is to help youth identify anxious or negative thoughts and to either accept or challenge their accuracy (Kendall & Hedtke, 2006). This aspect of treatment teaches youth to recognize and restructure cognitive distortions (i.e., catastrophizing thoughts) as well as to coach themselves through uncomfortable or negative situations when they do occur. Past studies have found associations between reductions in anxiety symptoms in CBT for child anxiety and decreases in anxious cognitions (Kendall & Treadwell, 2007; Lau, Chan, Li, & Au, 2010; Muris, Mayer, den Adel, Roos, & van Wamelen, 2009; Treadwell & Kendall, 1996). Relatedly, increases in positive cognitive appraisals during the course of CBT for youth anxiety were found to mediate the decrease in anxiety symptoms at 3-month follow-up (Hogendoorn et al., 2014).

In the largest mediation study of CBT for youth anxiety to date, changes in both coping and anxious self-statements were tested as mediators of acute treatment, though only change in perceived coping was found to significantly mediate treatment outcomes for the three active conditions: CBT, combined CBT and sertraline medication (COMB), and sertraline alone (SRT; Kendall et al., 2016). The lack of support for anxious self-statements as a mediator was unexpected in the context of previous findings (Kendall & Treadwell, 2007; Lau et al., 2010; Muris et al., 2009; Treadwell & Kendall, 1996). Although this study benefited from a large sample size, inclusion of active and placebo comparison conditions, and a prospective design, temporal precedence of changes in

mediators relative to changes in anxiety outcomes was not fully established (Gaynor, 2017; Kendall, Olino, Carper, & Makover, 2017). The unexpected findings regarding anxious self-statements suggest a need to examine other potential cognition-focused mediators of CBT to understand the function of cognitive components of treatment.

One cognitive variable not yet examined as a mediator of youth anxiety interventions is interpretive biases to threat. The literature to date on the association between interpretive biases to threat and youth anxiety supports this line of inquiry in mediation studies of youth CBT (Barry, Vervliet, & Hermans, 2015; Ehrenreich & Gross, 2002). Youth with anxiety diagnoses are significantly more likely to demonstrate negative cognitive schemas and interpretive and judgment bias than youth not meeting diagnostic criteria on parent-reported measures of symptoms (Cannon & Weems, 2010). This may be the case because anxiety impairs social information processing at the level of encoding information, interpreting information, and selecting a response (Daleiden & Vasey, 1997). Changes in this factor have been shown to be associated with the efficacy of CBT for adult anxiety (Smits, Julian, Rosenfield, & Powers, 2012), though the temporal relationship between change in biases to threat and anxiety outcomes has not been established. For youth, changes in this cognitive feature during CBT may also influence longer-term anxiety outcomes following treatment, as development progresses. As youth improve their social knowledge, such as the ability to accurately interpret others' behaviors and intent (Crick & Dodge, 1994; Muris, Mayer, Vermeulen, & Hiemstra, 2007), they likely also become more adept at applying cognitive skills learned in CBT to their social experiences. Therefore, cognitive skills related to interpretation of threatening situations may mediate long-term outcomes in particular.

The current longitudinal study prospectively examined the potential mediating roles of changes in (a) self-perceived and parent-perceived coping, (b) anxious self-statements, and (c) interpretive biases to threat on the relationship between treatment condition (CBT, SRT, or COMB) and anxiety outcomes over a naturalistic 5-year follow-up period beginning an average of 6.5 years after treatment. Putative mediators were measured four times over the course of the Child/Adolescent Multimodal Study (CAMS) interventions (at baseline, week 4, week 8, and week 12 [posttreatment]), and anxiety outcomes were assessed an average of 3.38 times during the naturalistic 5-year follow-up beginning an average of 6.5 years after treatment. We hypothesized that (a) increases in perceived coping, (b) reductions in anxious self-statements, and (c) reductions in biases to threat would mediate the relationship between the CBT-based treatment conditions (CBT and COMB) and lower anxiety during the 5-year follow-up period. We hypothesized that age at the time of treatment would moderate the mediation models, such that the relationship between mediators and anxiety outcomes for those in the CBT treatment conditions would be stronger for older youth.

Method

Participants

The current study included 319 families who participated in the Child/Adolescent Anxiety Multimodal Extended Long-term Study (CAMELS; Ginsburg et al., 2014), the naturalistic follow-up to CAMS. All former CAMS participants who had agreed to be re-contacted (465 of 488 participants) were eligible to participate in CAMELS. Participants were originally included in the CAMS trial if they were between 7 and 17 years of age, met diagnostic criteria for a primary diagnosis of Separation Anxiety Disorder (Sep),

Generalized Anxiety Disorder (GAD), or Social Anxiety Disorder (SAD; DSM-IV criteria; American Psychiatric Association, 2000), experienced substantial impairment associated with their anxiety disorder, and had an IQ $\geq$ 80. CAMS participants, recruited between 2002 and 2007, were randomly assigned to either the CBT, SRT, COMB, or pill placebo (PBO) conditions. The methodology (Compton et al., 2010), participant features (Kendall et al., 2010) and primary outcomes (Walkup et al., 2008) for CAMS have been reported.

Of the 319 CAMELS participants, 176 were female (55.2%), and the mean age at time of first assessment was 16.42 years and ranged from 10.22 to 24.48 years. The racial and ethnic makeup of this sample was 81.5% white, 8.8% African American, 2.8% Asian, 1.6% Native American, and 5.3% other. The sample included 8.2% who identified as Hispanic or Latino.

Procedure

CAMS consisted of a 12-week active intervention phase and a 6-month treatment maintenance period, in which responder participants could receive monthly booster visits with their providers and non-responders were referred to community providers. Participants were assessed at multiple points throughout the active phase of treatment. The CAMS variables included in the current study were assessed at baseline, week 4 of treatment, week 8 of treatment, and at posttreatment, which occurred 12 weeks following baseline.

The CAMELS study consisted of follow-up assessments conducted over the course of several years, beginning an average 6.5 years after the completion of the CAMS follow-up period, depending on the participants' timing of their decision to begin

participation in CAMELS. Participants were contacted to complete one long assessment visit and one short assessment visit per year during the CAMELS follow-up period, with 128 (40.12%) completing 5 long visits, 217 (68%) participants completing at least 4, 265 (83.07%) participants completing at least 3, and 316 (99%) participants completing at least 2 assessment visits. During long assessment visits, independent evaluators (IEs) who were blind to the participants' original CAMS treatment assignments administered the diagnostic interviews, completed IE-rated anxiety severity rating scales, and administered the parent and child-rated perceptions of coping. A Research Assistant and/or Study Coordinator met with the parent (or older adolescent) to complete demographic and contact data, and information on mental health and medical service use. Participants also completed self-report measures and parents completed parent-report measures.

CAMELS data collection occurred across the same six sites that conducted the CAMS trial. Participants were compensated for their time (reimbursed $130 for long assessments, and $50 for short assessments). In the final year of data collection, compensation for long visits was increased to $200. Transportation was reimbursed separately.

Intervention Conditions

The goal of CAMELS was to examine distal outcomes for participants in CAMS. CAMS randomized participants to either CBT, SRT, COMB, or PBO conditions. Participants in the PBO condition were provided with their choice of an active CAMS treatment after the acute phase.

Pharmacotherapy (SRT). For those randomized to the SRT condition, visits

with a psychiatrist consisted of reviewing of the participant's symptomatology, overall functioning, response to treatment, and presence of adverse events, all in a context of supportive clinical care. The first medication visit lasted 60 minutes, with all subsequent visits lasting 30 minutes, and took place every week through week 4, and then at weeks 6, 8, 10, and 12. Efforts were made to use the most effective and tolerated dose of sertraline. In general, participant medication dose was adjusted upward in 50 mg/day increments if the clinician-rated anxiety severity was rated as mild or greater. The dose was held or adjusted downward if participants were experiencing few anxiety symptoms or there were significant side effects. After week 12, treatment responders completed monthly maintenance visits during the 6-month follow-up period and continued to receive medication at their Week 12 dose.

Cognitive behavioral therapy (CBT). CAMS adapted the evidence-based CBT protocol *Coping Cat* as the approach used in the CBT condition (Kendall & Hedke, 2006). Guidelines assisted the therapist in adapting the manual flexibly and in a standardized manner for a client's age and developmental level. *The C.A.T. Project* (Kendall, Choudhury, Hudson, & Webb, 2002), a version of the *Coping Cat* modified for adolescents, allowed therapists to provide developmentally appropriate CBT across the full age range of the study. Across both child and adolescent CBT protocols, the number of sessions was reduced from the original 16 hour-long treatment sessions to 14. Twelve of these sessions were individual child/adolescent sessions and 2 were parent sessions, with the parent sessions scheduled immediately following the individual sessions at weeks 3 and 5.

The first six CBT sessions taught new skills to the participant (e.g., relaxation

exercises, cognitive restructuring, problem-solving) and the second six sessions provide opportunities to practice newly learned skills (exposure tasks) within and outside of the sessions. CBT responders received monthly 50-minute CBT maintenance sessions during the 6- month follow-up period after the intervention. During the maintenance sessions no new material was introduced.

Combination treatment (COMB). Participants in the combination treatment condition received all the components from the pharmacotherapy and CBT-only treatment conditions, with the exception that the participant, parents, and therapist were aware that the child was receiving active SRT and active CBT. Clinicians were encouraged to discuss the clinical status of each COMB patient to allow for treatment integration. For example, the pharmacotherapist could increase the dose of SRT or not, depending on the progress of the participant in CBT. With the exception of one site, COMB treatment visits were held at the same location. After the intervention period, treatment responders completed monthly maintenance visits during the 6-month follow-up period, during which participants continued to receive medication at their week 12 dose.

Measures

Assessments included semi-structured diagnostic interviews and other measures administered by an IE, youth self-report and parent-report measures.

Demographics. Information on participant gender and age at time of treatment were collected as part of the initial demographic data in CAMS.

Coping Questionnaire, Parent and Child/Youth Versions (CQ-C/P; Kendall, 1994). The CQ-C/P was administered at baseline, week 4 of treatment, week 8 of

treatment, and posttreatment (week 12) during CAMS. The CQ-C measures the youth's perceptions of their abilities to cope with anxiety-provoking situations (coping efficacy). The CQ-P measures the parents' perceptions of their child's ability to cope with these same situations. The CQ-C/P documents changes over time in youth's perceived coping efficacy. Before completing the CQ, the examiner explains the questionnaire and offers a sample item. The examiner, based on information collected during a diagnostic interview, enters the 3 situations that the youth or the youth's parents reported to be most anxiety provoking. For each situation, the child and parent raters assess their perception of ability to cope in such situations. In the CQ-C, youth are asked to rate their ability to cope (i.e., *Are you able to help yourself feel less upset?*) with the three anxiety-provoking situations that were identified during the diagnostic interview on a scale of 1 (*not at all able to help myself*) to 7 (*completely able to help myself*). On the CQ-P, parents are asked to rate their child's ability to cope with the same three situations, also on a scale of 1 (*not at all able to help himself/ herself*) to 7 (*completely able to help himself/herself feel comfortable*). The CQ-C/P has evidenced sensitivity to treatment effects (Kendall, 1994) and retest reliability and internal consistency (Lau et al., 2010). In the current study, parent and youth reports on the CQ correlated significantly with bivariate correlation coefficients of mean scores ranging from .73 to .98 at different time points.

Negative Affectivity Self-Statement Questionnaire (NASSQ; Ronan, Kendall, & Rowe, 1994). The full NASSQ consists of 70 anxious and depressive self-statements. Youth rate the frequency of the thought within the past week on a scale ranging from 1 (*not at all*) to 5 (*all the time*). Items on the NASSQ are empirically derived (Lerner et al., 1999; Ronan et al., 1994). Sood and Kendall (2007) identified an anxiety subscale, which

was found to be valid across different age groups. The anxiety subscale (Sood & Kendall, 2007), completed at baseline, week 4 of treatment, week 8 of treatment, and posttreatment (week 12), was assessed in the current study. Cronbach's α ranged from .92 to .96 across treatment time-points in the current study.

Ambiguous Situations Questionnaire (ASQ: Barrett, Rapee, Dadds, & Ryan, 1996; Langley, Bergman, Barrett, & Piacentini, 2007). The ASQ, administered at baseline, week 4 of treatment, week 8 of treatment, and posttreatment (week 12), is a six-item scale that provides a measure of threat bias in youth. The ASQ is independently completed by youth and their parents and was derived by Langley and colleagues (2007) from an observational paradigm developed by Barrett and colleagues (1996). For each ASQ item, participants are presented with an ambiguous situation and are asked to select one of four provided responses that they feel most accurately explains the situation. The four responses include nonthreatening interpretations as well as threatening interpretations at varying degrees of threat severity. The measure, when examined in the current sample, showed an internal consistency of .64. Detailed psychometric properties of this measure with the current sample are reported elsewhere (Gonzalez et al., 2016).

Pediatric Anxiety Rating Scale (PARS; The Research Units on Pediatric Psychopharmacology Anxiety Study Group [RUPP], 2002). The PARS was administered in both the CAMS and CAMELS phases of the current study. The PARS is a clinician-rated measure of anxiety in youth consisting of a checklist of 50 anxiety symptoms relating to diagnoses of Sep, SAD, and GAD. It includes seven global items that are administered to the youth and parent together. Severity ratings are made on a 6-point scale ranging from 0 (*none*) to 5 (*extreme*) based on the number and frequency of

symptoms, and the extent of distress, interference with functioning, avoidance, and accompanying physical symptoms. Six of the items were summed to produce a total score with a possible range of 0 to 30. Reliability and validity of the PARS has been reported (RUPP, 2002). In the CAMS, baseline scores on the PARS ranged from 7 to 29 and inter-rater reliability among the IEs was > .97. The current study uses PARS data from the across all assessment points over the CAMELS follow-up period.

Mental Health Service Utilization. In CAMELS, mental health service utilization was measured using the ADIS Supplemental Services Form (Silverman & Albano, 1996) which assesses medication use and psychotherapy or counseling for mental health. Participants were divided into four groups at each assessment time-point: no medication or psychological therapy since their last CAMELs assessment, medication only, therapy only, medication and therapy. Service utilization was dummy-coded with the medication and therapy category as the reference group and was controlled for in all analyses.

Analytic Approach

Latent growth curve (LGC) modeling using Mplus 7 software (Muthén & Muthén, 2007) was used to test mediational and moderated mediational hypotheses. LGC models have been used in a mediation framework in past studies by modeling change in mediator and outcome variables and by using an independent variable that represents the intervention condition (MacKinnon, 2008). For each mediation model, we computed an unconditional growth model for the mediator, which included parameters for the intercept (estimated score at CAMS intervention baseline assessment) and slope (rate of change over four time points during intervention) to evaluate trajectories of change over time. A

growth model for the anxiety symptom outcome measure was also created, including parameters for the intercept (estimated score at CAMELS first assessment) and slope (rate of change over time) to evaluate change in anxiety symptoms over the follow-up period. We considered models of static, linear, and quadratic change. After construction of the growth models, the intercept and growth factors of the mediator were regressed on treatment condition, and the intercept and growth factor of the outcome variable were regressed on the mediating intercept, mediating growth factors, and treatment condition. Models included baseline and posttreatment (week 12) anxiety symptom scores as covariates to isolate the mediational effect on the outcome variable specifically over the follow-up period. In addition, mental health service utilization between the CAMS and CAMELS studies, dummy-coded with combined medication and therapy as the reference group, was controlled for as a time-invariant predictor. Years since CAMS participation was controlled for as well. For moderated mediation models, interaction terms were computed using mean age and age at one standard deviation below and above the mean and were entered as predictors. Bias-corrected bootstrapping was used to assess the statistical significance of the indirect effects and conditional indirect effects.

All models were examined for goodness of fit (Kline, 2011) using the model chi-square statistic. Approximate fit indices were used to test goodness of fit, including the Steiger-Lind root mean square error of approximation (RMSEA; Steiger, 1990), and the Comparative Fit Index (CFI; Bentler, 1990). Goodness of fit using RMSEA was evaluated according to the close-fit hypothesis (p value $\leq .05$ suggesting "good fit", as calculated within Mplus) and the poor-fit hypothesis (RMSEA $\geq .10$ suggesting "poor fit"). Threshold values of CFI used to indicate adequate fit are CFI values $\geq .95$.

Results

Table 1 presents descriptive statistics for mediators and the outcome variable. Full information maximum likelihood (FIML) was used to address missingness in the data. FIML is an iterative model-based process that uses all available information from the observed data, and has greater statistical efficiency for longitudinal data when computing standard errors compared to other methods for handling missingness (Wothke, 2000). In the CAMELS dataset, an average of 3.38 long visits were completed per participant out of 5 possible visits. Although FIML is robust at handling missing data of these amounts for participants' second, third and fourth visits, there is not good evidence to support a robust handling of the missingness for the fifth visit data, as 71% of participants did not complete this assessment. Therefore, the data from participants' fifth visits were not included. To assess whether missingness was systematic or random, a Poisson regression was run to examine the association between number of CAMELS visits completed and baseline demographic and clinical characteristics. Age at CAMS randomization, age at first CAMELS follow-up visit, SES, and baseline and post-treatment PARS scores were entered as continuous predictors, and gender, race, treatment condition, treatment site were entered as categorical predictors. Only two of these examined variables predicted number of CAMELS assessments completed: age at CAMS randomization and age at first CAMELS follow-up visit. Therefore, mediation analyses were conducted both with and without controlling for these variables. No significant differences in findings emerged when these variables were included.

Table 1

Means and standard deviations for mediators and outcome variables

Variable	COMB condition (*n* = 87) *M (SD)*	CBT condition (*n* = 83) *M (SD)*	SRT condition (n = 87) *M (SD)*	PBO condition (n = 44) *M (SD)*
CQ parent				
baseline	2.31 (.98)	2.46 (1.12)	2.65 (1.18)	2.64 (1.11)
week 4	3.91 (1.22)	3.34 (1.05)	3.71 (1.23)	3.37 (1.26)
week 8	5.07 (1.09)	4.11 (1.25)	4.52 (1.37)	4.07 (1.30)
posttreatment	5.63 (1.02)	4.93 (1.27)	4.99 (1.45)	4.17 (1.19)
CQ child				
baseline	2.82 (1.39)	3.22 (1.51)	3.23 (1.42)	3.09 (1.28)
week 4	4.23 (1.33)	4.06 (1.26)	4.27 (1.54)	3.91 (1.39)
week 8	5.11 (1.35)	4.63 (1.27)	4.84 (1.34)	4.51 (1.43)
posttreatment	5.72 (1.31)	5.30 (1.19)	5.28 (1.47)	4.78 (1.36)
ASQ				
baseline	1.94 (1.63)	1.91 (1.58)	1.99 (1.63)	2.18 (1.70)
week 4	1.22 (1.49)	1.14 (1.53)	1.38 (1.56)	1.49 (1.61)
week 8	0.78 (1.13)	0.90 (1.52)	1.03 (1.42)	1.33 (1.76)
posttreatment	0.48 (0.86)	0.70 (1.26)	0.72 (1.23)	1.25 (1.74)
NASSQ-A				
baseline	70.50 (25.77)	64.94 (21.08)	67.31 (23.21)	67.80 (23.67)
week 4	51.01 (16.29)	49.51 (12.88)	50.45 (18.81)	54.00 (26.77)
week 8	44.96 (11.67)	46.44 (11.10)	45.03 (13.06)	47.74 (17.88)
posttreatment	43.20 (11.44)	43.87 (11.39)	43.89 (13.87)	45.98 (16.71)
PARS				
FU visit 1	7.43 (5.84)	8.29 (6.21)	7.65 (6.12)	9.11 (6.33)
FU visit 2	7.38 (5.92)	6.63 (5.59)	6.28 (5.54)	8.53 (5.70)
FU visit 3	7.04 (6.12)	7.07 (6.17)	5.85 (5.79)	8.88 (6.04)
FU visit 4	7.57 (6.63)	5.20 (5.44)	6.29 (5.70)	8.86 (7.27)

Note. COMB = combined CBT and sertraline condition; CBT = CBT only condition; SRT = sertraline pharmacotherapy only condition; PBO = pill placebo condition; CQ parent = parent-reported coping questionnaire; CQ child = child-reported coping questionnaire; ASQ = Ambiguous Situations Questionnaire; NASSQ-A= Negative Affectivity Self-Statement Questionnaire-Anxiety Subscale; PARS = Pediatric Anxiety Rating Scale; baseline = pre-treatment; week 4 = week 4 of intervention; week 8 = week 8 of intervention, posttreatment = week 12 treatment end point; FU = Follow-up.

Skewness values for all study variables fell within an acceptable range (Kline, 2011). The baseline and posttreatment levels of PARS were controlled for in all models in order to examine changes in PARS over follow-up specifically. In addition, number of years between the completion of treatment and the first follow-up visit was controlled for due to the variation in time lag between participants. The mean scores of mediating variables showed a reduction from pre- to post-treatment that slowed over time, suggesting a quadratic change over time. Thus, linear and quadratic models were examined.

Figure 1 depicts the general mediation model used for all three putative mediators of PARS outcomes. Only the indirect effects of the slope factors of the putative mediator, and not the intercept, were interpreted because it is the change in the variable, represented by the slope, that is hypothesized to mediate outcomes. The intercept of the putative mediator only refers to the pre-treatment level of the variable, and due to the randomization design no differences between treatment conditions were expected at pre-treatment.

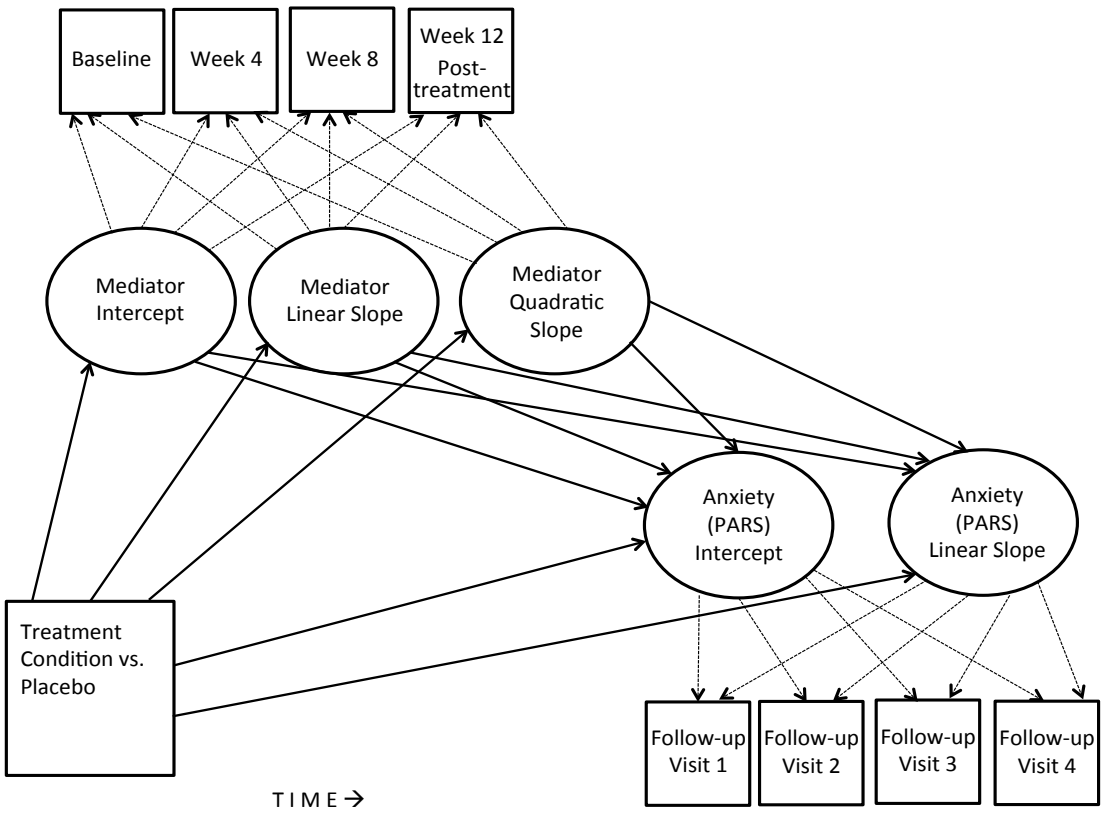

Figure 1. Mediation model with latent growth curve modeling of mediator and anxiety outcome variables. Separate models conducted for each mediator: Parent-reported perceived coping, child-reported perceived coping, anxious self-statements, and interpretive bias to threat.

Perceived Coping as Mediator

For the perceived coping mediator, separate variables for self-reported and parent-reported perceived coping were created using responses on the parent and child versions of the Coping Questionnaire. The first model tested whether parent-reported change in perceived coping mediated the effects of each treatment condition on change in anxiety outcomes at the first follow-up assessment and over the trajectory of the follow-up period. This model showed an acceptable fit (χ^2 = 143.74, p<.05, RMSEA = .05, CFI = .92). Significance was evaluated using the 95% confidence intervals from bias-corrected bootstrapping. There were significantly greater increases in parent-reported coping ability

over the course of treatment for youth in the COMB condition, relative to those in the PBO condition. However, there was no significant mediation effect for this model (Table 2).

Table 2

Modeling of changes in parent-reported perceived coping as mediator

Modeled effects for CQ-p slope	Estimate (*SE*)	95% CI
Treatment condition on mediator		
COMB condition on CQ-p slope	0.279 (0.092)**	[0.084, 0.447]
SRT condition on CQ-p slope	0.142 (0.088)	[-0.030, 0.323]
CBT condition on CQ-p slope	0.188 (0.083)	[-0.004, 0.350]
Mediator on outcome		
CQ-p slope on PARS intercept	0.179 (13.014)	[-27.267, 33.989]
CQ-p slope on PARS slope	-0.113 (5.803)	[-16.934, 9.287]
Indirect effect of treatment condition on outcome via mediator		
COMB condition on PARS intercept	0.050 (3.757)	[-7.302, 9.437]
COMB condition on PARS slope	-0.031 (1.610)	[-4.146, 2.757]
SRT condition on PARS intercept	0.025 (2.076)	[-3.593, 5.731]
SRT condition on PARS slope	-0.016 (0.912)	[-2.582, 1.572]
CBT condition on PARS intercept	0.034 (2.505)	[-4.369, 6.499]
CBT condition on PARS slope	-0.021 (1.060)	[-2.889, 1.961]

Note. COMB = combined CBT and sertraline condition; CBT = CBT only condition; SRT = sertraline pharmacotherapy only condition; PBO = pill placebo condition; CQ-p = parent-report on Coping Questionnaire.
* p<.05; ** p<.01; *** p<.001

The next model tested whether self-reported change in perceived coping mediated the effects of each treatment condition on change in anxiety outcomes at the first follow-up assessment and over the trajectory of the follow-up period. This model showed an acceptable fit (χ^2 = 121.03, p<.05, RMSEA = .04, CFI = .94). Significance was evaluated using the 95% confidence intervals from bias-corrected bootstrapping. However, there was no significant mediation effect for this model (Table 3).

Table 3

Modeled effects for CQ-c slope	Estimate (*SE*)	95% CI
Treatment condition on mediator		
COMB condition on CQ-c slope	0.131 (0.104)	[-0.072, 0.336]
SRT condition on CQ-c slope	0.006 (0.088)	[-0.187, 0.157]
CBT condition on CQ-c slope	0.047 (0.090)	[-0.130, 0.220]
Mediator on outcome		
CQ-c slope on PARS intercept	0.973 (4.420)	[-7.537, 11.019]
CQ-c slope on PARS slope	-2.602 (2.398)	[-7.268, 1.282]
Indirect effect of treatment condition on outcome via mediator		
COMB condition on PARS intercept	0.127 (0.739)	[-0.687, 2.400]
COMB condition on PARS slope	-0.210 (0.448)	[-1.807, 0.193]
SRT condition on PARS intercept	0.006 (0.370)	[-0.734, 0.853]
SRT condition on PARS slope	-0.010 (0.287)	[-0.481, 0.803]
CBT condition on PARS intercept	0.046 (0.400)	[-0.440, 1.330]
CBT condition on PARS slope	-0.075 (0.263)	[-1.079, 0.212]

Note. COMB = combined CBT and sertraline condition; CBT = CBT only condition; SRT = sertraline pharmacotherapy only condition; PBO = pill placebo condition; CQ-c = child-report on Coping Questionnaire.
* p<.05; ** p<.01; *** p<.001

Anxious Self-Statements as Mediator

For anxious self-statements, a latent variable was created using the sum of item responses on the NASSQ that form the Anxiety scale (Sood & Kendall, 2007). LGC modeling as previously described examined the mediating effects of change in anxious self-statements across the four time-points in CAMS on the relationship between treatment condition and anxiety symptom outcomes on the PARS at the first CAMELS time-point and across the four CAMELS time-points. The NASSQ variable showed good fit to the model when the latent growth factor was regressed onto treatment condition (χ^2 = 27.46, p<.05; RMSEA = .07, CFI = .96) and the latent growth factor for PARS

outcomes (χ^2 = 45.46, p<.05; RMSEA = .06; CFI = .96), but the data did not converge for the mediation model.[1]

Interpretive Biases to Threat as Mediator

Change in interpretive biases to threat, as measured by the ASQ, was examined as a mediator of the effects of each treatment condition on PARS at the first follow-up assessment and over the trajectory of the follow-up period. This model showed an acceptable fit (χ^2 = 136.52, p<.05, RMSEA = .05, CFI = .94). Significance was evaluated using the 95% confidence intervals from bias-corrected bootstrapping. The confidence intervals for the indirect effect of ASQ slope and COMB condition on the PARS intercept did not include zero, indicating a significant mediation effect (Table 4). The regression coefficients for the constituent direct effects indicated that relative to the PBO condition, the COMB condition is associated with greater reductions on the ASQ, which in turn are associated with lower PARS scores at the first long-term follow-up visit. There was no significant mediating effect found for ASQ slope on the PARS slope over the follow-up period in any condition.

[1] The mediation model resulted in an error message implying that the model was misspecified. The failure to converge seems to be due to an issue of negative residual variance for the NASSQ slope. Despite attempts to fit the model, such as setting the correlation between the linear and quadratic factors for the NASSQ at -.99 and setting the quadratic factor to 0, the mediation model did not converge.

Table 4

Modeling of changes in interpretive biases to threat as mediator

Modeled effects for ASQ as mediator	Estimate (*SE*)	95% CI
Treatment condition on mediator		
COMB condition on ASQ slope	-0.183 (0.083)*	[-0.347, -0.006]
SRT condition on ASQ slope	-0.145 (0.081)	[-0.291, 0.025]
CBT condition on ASQ slope	-0.092 (0.074)	[-0.231, 0.061]
Mediator on outcome		
ASQ slope on PARS intercept	6.797 (6.199)**	[0.987, 25.095]
ASQ slope on PARS slope	-1.135 (2.066)	[-7.113, 2.000]
Indirect effect of treatment condition on outcome via mediator		
COMB condition on PARS intercept	-1.243 (1.482)*	[-7.139, -0.023]
COMB condition on PARS slope	0.207 (0.409)	[-0.197, 1.752]
SRT condition on PARS intercept	-0.983 (1.225)	[-6.586, 0.039]
SRT condition on PARS slope	0.164 (0.334)	[-0.160, 1.511]
CBT condition on PARS intercept	-0.625 (1.008)	[-4.887, 0.282]
CBT condition on PARS slope	0.104 (0.264)	[-0.105, 1.047]

Note. COMB = combined CBT and sertraline condition; CBT = CBT only condition; SRT = sertraline pharmacotherapy only condition; PBO = pill placebo condition; ASQ = Ambiguous Situations Questionnaire.
* p<.05; ** p<.01; *** p<.001

Age as Moderator of Mediated Effects

Age (in years) at time of the acute intervention phase of the study (CAMS) was examined as a moderator of the mediational relationship between change in putative mediators and PARS outcomes for the three treatment conditions.

To test age as a moderator, we created centered age variables, which included average age of youth (*M*= 10.64), younger youth (one standard deviation below the mean; *M* – 1 *SD* = 7.85), and older youth (one standard deviation above the mean; *M* + 1 *SD* = 13.43). Interaction terms were then created between each dummy-coded treatment condition and the centered age variables. The indirect effects of the mediation occurring

through the intercept and slope for each treatment condition relative to the PBO condition was estimated for younger youth, average age youth, and older youth.

The moderated mediation model for the parent-reported CQ showed an acceptable fit (χ^2 = 143.74, p<.05, RMSEA = .05, CFI = .92), though there were no significant interaction effects. The moderated mediation model for the child-reported CQ showed an acceptable fit (χ^2 = 153.29, p<.05, RMSEA = .04, CFI = .94), though there were no significant interaction effects. The moderated mediation model for the ASQ also showed an acceptable fit (χ^2 = 169.65, p<.05, RMSEA = .04, CFI = .94), though there were no significant interaction effects. Given that the NASSQ mediation model did not converge with the data, moderated mediation analyses were not conducted.

Discussion

The current study examined the impact of putative mediators of youth anxiety outcomes measured 3 to 12 years after treatment. The results provide mixed support for the study hypotheses. Changes in interpretive biases to threat, as measured by the ASQ, significantly mediated the relationship between treatment condition and anxiety symptom outcomes, as measured by the PARS at follow-up visit 1. For youth randomized to the COMB condition, greater reductions on the ASQ from pre- to post-treatment were associated with lower PARS scores at follow-up visit 1, an average of 6.5 years after treatment. The significant mediational relationship was specific to follow-up visit 1 PARS ratings, in that no link was found between change on the ASQ and the trajectories of PARS scores over the subsequent three follow-up visits.

Unlike prior findings that changes in perceived coping mediated acute treatment outcomes (e.g., Hogendoorn et al., 2014; Kendall et al., 2016), youth and parent-reported

changes in perceived coping did not significantly mediate the relationship between treatment condition and PARS follow-up visit 1 or over time in the current study. Change in anxious self-statements, as measured by the NASSQ-A, could not be modeled as a mediator in the LGC framework due to convergence problems possibly caused by the negative residual variance of the slope factor. Finally, the hypothesized moderating effect of age during treatment on the tested mediational relationships was not supported for any of the putative mediators.

The mediational role of interpretive biases to threat on long-term outcomes of youth anxiety treatment is a novel finding in the literature. The relationship between biases to threat and youth anxiety is well-supported in the research (Barry et al., 2015; Ehrenreich & Gross, 2002), though there is some evidence to suggest that it is a transdiagnostic cognitive factor underlying internalizing and externalizing disorders in youth (Gonzalez et al., 2016). Although there are few studies of changes in threat biases over the course of CBT, one such study found that anxious youth show significant reductions on some measures of interpretive biases to threat from pre- to post-treatment (Waters, Wharton, Zimmer-Gembeck, & Craske, 2008). The current finding that reductions in threat-biased interpretations over the course of COMB treatment predicted lower anxiety at follow-up underscores the benefit of targeting this aspect of cognition in treatment to optimize the maintenance of treatment gains. CBT is theorized to impact threat biases through the implementation of exposure tasks, which are in turn believed to impact impairing anxiety by activating fear structures and then encouraging reappraisal of the perceived threat based on more objective information (Waters & Kershaw, 2015a). Exposing youth to ambiguous or mildly threatening circumstances opens up the

opportunity for the therapist to guide the individual towards broader and more flexible interpretations of the feared situation (Waters, Potter, Jamesion, Bradley, & Mogg, 2015b). The current findings add support to the possibility that change in interpretive bias to threat, through engagement in exposure tasks, is a mechanism of symptom change in CBT.

Interestingly, change in interpretive bias to threat was found to mediate outcomes only for the COMB condition relative to the PBO condition, and not for the CBT or SRT monotherapy conditions. As was found for reductions in anxiety symptoms over the intervention period (Walkup et al., 2008), the combination of CBT and SRT seemed to have a synergistic effect on interpretive biases to threat. The addition of sertraline to CBT-based exposure tasks may reduce anxious discomfort just enough for youth to face the perceived threat bravely and successfully. The process of activating fear structures in exposure tasks (Waters & Kershaw, 2015a) may also activate uncomfortable and interfering somatic symptoms of anxiety, which selective serotonin reuptake inhibitors (SSRIs) have been shown to reduce (Ginsburg, Riddle, & Davies, 2006; Hale et al., in press). It may be that both CBT and sertraline are necessary to control symptoms enough for youth to engage in the highest-level exposure activities and fully address their threat biases. Additional research is needed to clarify the relationships between components of treatment, such as SSRI utilization in relation to engagement in CBT-based exposure tasks.

Another novel finding of the current study was that change in interpretive biases to threat only mediated anxiety outcomes for those in the COMB condition for anxiety measured at the first follow-up visit, but did not mediate outcomes for anxiety symptom

trajectories over the follow-up period. One possibility for this is that anxiety levels are so highly stable over time for COMB participants that anxiety trajectories are unaffected by changes in specific cognitive factors. For those in the COMB condition, the mean PARS scores for the four follow-up time points were stable (Table 1), and the variation over time may be too small to detect differences related to mediators. Another possibility, though not directly tested in the present study, is that the trajectories of anxiety on the PARS over follow-up reflect state anxiety (not trait anxiety), which unlike trait anxiety has little association with interpretive biases to threat (Muris, Rapee, Meesters, Schouten, & Geers, 2003).

Although changes in perceived coping were found to mediate the short-term outcomes of anxiety (Kendall et al., 2016), the current findings did not support the hypothesis that these changes would also mediate anxiety outcomes an average of 6.5 years after the intervention and over a follow-up period. There are several possible methodological and theoretical explanations for this finding that warrant investigation. One possibility is that the measure used in the study assesses perceived coping only in specific situations that are relevant to the child's anxiety at the time. It may be that reductions on this measure signify increased coping in those specific situations but do not generalize to coping ability in new anxiety-provoking situations as they emerge. Another possible explanation for the lack of support for the hypothesis is that perceptions about coping efficacy are not reinforced over the course of development. It is possible that the validation provided by therapists and parents during acute treatment, while powerful at the time, did not persist after treatment and therefore was not enough to sustain beliefs about coping efficacy later in life. This possible explanation could be examined in future

studies by measuring perceived coping efficacy to newly emerging developmental challenges at the time of the follow-up anxiety assessments.

The findings did not support the hypothesized moderating effect of age on the mediation models. Despite research findings that anxiety differentially impacts cognitive processes (e.g., Waite, Codd, & Creswell, 2015), the literature on age as a moderator of CBT outcomes is mixed (Herres et al., 2015). In fact, recent reviews of the literature have found that most studies show no significant differences between adolescents and children on anxiety outcomes of CBT (Kendall & Peterman, 2015). One explanation is that findings from basic research on cognitive processes do not necessarily translate into outcomes of interventions that address cognitive processes as one component of treatment. Given that youth are considered collaborators in their own treatments and CBT is designed to flexibly adapt to developmental needs, it may be that clinicians are able to optimize treatments for a broad range of ages (Kendall & Peterman, 2015).

There are potential limitations of the current study. For one, the model including the measure of anxious self-statements, the NASSQ-A, did not converge, and therefore could not be tested as a mediator of outcomes. This could be because the measure includes statements that represent both anxious thoughts and symptoms in the anxiety subscale, which could artificially inflate correlations between symptom and cognitive measures (Hogendoorn et al., 2010). Although this measure was used as an assessment of pretreatment and posttreatment anxious self-statements in the mediation analyses of acute treatment outcomes (Kendall et al., 2016), the current study suggests that it might not be robust for modeling trajectories of change over multiple proximal time points.

Another limitation was the reliance on self- and parent-report measures of putative mediators. For example, there are behavioral measures of bias to threat in the literature (Ehrenreich & Gross, 2002) but these were not included. Although behavioral tasks are not appropriate for measuring all types of bias to threat, such measures would broaden our perspective on the construct and permit comparisons with self-reported bias to threat. Despite these limitations, the study benefited from having the anxiety outcomes assessed by IEs over the 5-year follow-up period who were blind to study condition randomization.

Additionally, there were structural differences between the administration of a combined treatment and the administration of two monotherapy conditions. As a function of implementing two different types of treatment to the COMB condition simultaneously, participants in this condition received twice as much clinician contact as participants in the other conditions. Although it is unlikely that this increase in clinician contact explains the reductions in biases to threat in the COMB condition relative to the PBO condition, it is possible that the increased contact inspired youth to be more involved and engaged in their treatment and acted as a reminder to incorporate therapy skills into their daily lives.

Finally, there is a chance that the mediator of change was not the reduction in interpretive bias to threat but rather that this variable changed as a result of another, unmeasured factor that actually acted as the mediator. It is also possible that pretreatment factors such as cognitive functioning may have influenced the relationship between interpretive threat bias and long-term anxiety symptom outcomes.

Clinical Implications

The current findings have implications for treatment design and future intervention research. The identification of a treatment mediator of long-term outcomes can be used to enhance clinical approaches to maintaining treatment gains. Booster sessions are often implemented to maintain gains after acute treatment, but the focus of these sessions is typically open ended. The use of booster sessions as a way to continue reducing interpretive bias to threat may be a particularly fruitful way to extend the maintenance of treatment gains. Further, youth with heightened threat appraisal, a predictor associated with poorer long-term prognosis of anxiety symptoms (e.g., Britton, Lissek, Grillon, Norcross, & Pine, 2011), might benefit from an early and more direct focus on interpretive bias to threat.

Increasing the quality of mediation studies can increase the identification of effective treatment components, and therefore improve the quality of treatments being implemented in practice (Maric, Wiers, & Prins, 2012). This study contributes to the literature in that it uses a longitudinal design, bias-corrected bootstrapping, and a temporal separation between measured mediators and outcomes. In addition to the outcome assessments on the PARS beginning an average of 6.5 years after the final assessment of the putative mediators, the current study established the temporal precedence of the change in mediator by controlling for pretreatment and posttreatment levels of anxiety on the PARS. Therefore, anxiety severity as modeled over the long-term follow-up can be considered change in anxiety specifically after the acute intervention phase of the study.

A next step to improving interventions using the results of mediation studies is to further assess the causal relationship between certain treatment components and outcomes. This can be studied by manipulating the intervention to either remove or enhance the suspected mechanism of change (MacKinnon, 2008). Several innovative interventions have been developed in recent years to specifically target biases to threat in youth and adults given the strong association between this factor and anxiety (Van Bockstaele et al., 2014). One study involving an intervention of only attention training towards positive stimuli for anxious youth found significant reductions in anxiety symptoms for youth randomized to the active treatment condition relative to waitlist (Waters et al., 2015c). Although this relatively small study offers only preliminary evidence for enhancing the treatment focus on biases to threat, it suggests one type of treatment enhancement that can be paired with CBT and sertraline to further investigate changes in biases to threat as a mechanism of treatment.

CHAPTER 2

LITERATURE REVIEW

Mediation helps us understand possible mechanisms through which changes in one variable bring about changes in an outcome (Little, 2013). Properly designed and implemented mediation studies have the potential to provide valuable information regarding how treatments work and to identify the mechanisms of change in a given treatment. However, findings from mediation studies are often obfuscated by inadequate designs and analytic approaches that degrade the potential contribution of these studies to the literature (Kline, 2015).

When discussing mediation, it is essential to clearly define terminology to ensure that the conceptualizations and statistical findings are interpreted accurately (Holmbeck, 1997). Mediation refers to the process by which an independent variable is able to influence a dependent variable (Baron & Kenny, 1986). In the treatment outcome literature, mediation typically refers to the process by which an intervention influences treatment outcomes. Mediating variables must be assessed after randomizing participants to treatment to demonstrate that treatment condition has an effect on the mediating variables (i.e., that changes in the mediating variable are specific to a given treatment). Mediating variables should also be assessed prior to the posttreatment assessment to demonstrate that changes in the mediator occurs prior to change in the outcome (termed "temporal precedence;" Gollob & Reichardt, 1991; Kazdin, 2007).

When discussing mediation in the context of treatment outcomes, it is important to distinguish between mediators of treatment outcome and true mechanisms of change, as not all mediators of treatment outcome are mechanisms of change. To declare a

mediational process a mechanism of change, a causal relationship between the mediating variable and treatment outcomes must be established which requires both study design and analytic considerations (Kraemer, Wilson, Fairburn, & Agras, 2002). For example, once a putative mediator has been identified, mechanisms of change can be examined by conducting a randomized controlled trial (RCT) in which a treatment that is enhanced with components associated with putative mediator variables is shown to be more efficacious than the original treatment protocol (Kraemer et al., 2002). An understanding of putative mediators that do not act as mechanisms of change is also important so that treatment providers can remove unnecessary components of intervention to lower cost and risks to patients (Kraemer et al., 2002).

Prevailing Analytic Approaches for Testing Mediation

The increasing emphasis on understanding mediators of interventions is apparent in the rapid improvement of analytic approaches to studying mediation over the last 3 decades. However, use of inappropriate analytical techniques continues to be a great obstacle in the design and analyses of studies, and investigators and practitioners should critically consider the analytic approaches used in a given study before relying on the study's findings.

The most widely used test of mediation is the causal steps approach, popularized by Baron and Kenny (1986). This approach is typically evaluated through a three-step process. First, the mediator (M) is regressed on the independent variable (path a) and the path coefficient must be statistically significant. Second, the dependent variable is regressed on the independent variable (path c) and the path coefficient must be statistically significant. Third, the dependent variable must be regressed on both the

independent variable (path c') and the mediating variable (path b). To say that a variable M mediates the relationship between X and Y, path b must be significant in the third regression equation and the parameter associated with path c' must reduce in magnitude from the parameter associated with path c. Sobel (1982) developed a statistical test (aptly termed the Sobel Test) to determine whether the indirect effect (i.e., the effect of X on Y through M) is statistically significant. This approach requires an estimate of the standard error of the product of path *a* and path *b,* and the ratio of the product to its standard error is the test statistic for testing the null hypothesis that the true indirect effect is zero, with a *p* value derived from a normal distribution.

Both the Baron and Kenny (1986) causal steps approach and the Sobel Test (Sobel, 1982) have been heavily criticized by statisticians over the years (Hayes, 2009). The causal steps approach has the lowest power in terms of actually detecting the effect of *X* on *Y* through *M* (Fritz & MacKinnon, 2007; MacKinnon et al., 2002) and depends on logical inferences from the outcome of a set of hypothesis tests rather than a direct quantification of the intervening effect. Further, it is possible for an indirect effect to be statistically different from zero even though one of its constituent paths is not (Hayes, 2009). The Sobel Test has primarily been criticized for the assumption that the sampling distribution of the indirect effect is normal when in actuality the product of coefficients tends to be asymmetric, with nonzero skewness and kurtosis (Bollen & Stine, 1990; Stone & Sobel, 1990; Hayes, 2009). Further, the Sobel Test is not ideal because a mediated effect may be present whether or not the treatment effect (path c') is non-significant after adjustment for the mediator.

Other strategies have been developed to test the significance of indirect effects that do not suffer from the same flaws as the Sobel test. For example, a more powerful test is bootstrapping, which tends to have higher power and the best Type I error control. Bootstrapping generates an empirical representation of the sampling distribution of the indirect effect by treating the obtained sample size as a population, and repeatedly resampling during analysis as a means of mimicking the original sampling process (Hayes, 2009). The variables are then estimated in the resampled data set and the product of the path coefficients is calculated a large number of times (typically 1000-5000 times; Hayes, 2009). The resulting distribution of estimates of the indirect effect is an empirical approximation of the sampling distribution of the indirect effect, and inference is made about the size of the indirect effect in the population (Hayes, 2009).

Structural equation modeling (SEM) is a multivariate technique that can provide a more appropriate inference framework for mediation analyses (Gunzler, Chen, Wu, & Zhang, 2013). SEM can be used in a variety of complex situations, including when the mediation model includes multiple independent variables, mediators, or outcomes. SEM also includes robust mechanisms for handling missing data while standard regression analyses use listwise deletion by default (Gunzler et al., 2013). SEM also allows for extension to longitudinal data within a single framework, and concurrently tests the mediating variable as both a cause for the outcome and an effect of the intervention (Gunzler et al., 2013).

For more complex mediation models in which researchers have several putative mediators in mind that account for a relationship, multiple mediation models can be conducted in an SEM framework (Preacher & Hayes, 2008). The advantages of using a

single multiple mediation model over separate mediation models for each putative mediator include the ability to determine overall mediating effects, the ability to determine the extent to which specific variables mediate the relationship, and a reduction in the likelihood of parameter bias due to omitted variables (Preacher & Hayes, 2008). Besides using the SEM framework, approaches to multiple mediation modeling include the product-of-coefficients approach and bootstrapping (Preacher & Hayes, 2008).

For mediation models that include longitudinal data, the SEM approach of latent growth curve models allow for the inclusion of all available measurement points in one model, and enhances reliability. This increases sensitivity for detecting behavioral change (Speer & Greenbaum, 1995) and avoids inflation of Type I errors (Hertzog & Rovine, 1985). Further, latent variable growth models allow intervention researchers to test initial status and growth in one outcome while simultaneously testing them as predictors of growth in another outcome, to create models to examine how intervention-produced changes in proximal mechanisms are potentially associated with more distal outcomes, to partial out time-specific measurement error, and to accommodate missing data (e.g., Degarmo, Patterson, & Forgatch, 2004). Other innovative analytic approaches such as cross-lagged panel analyses, have been developed to address complex questions of mediation in treatment studies and are just beginning to be used in studies of youth interventions (e.g., Chu et al., 2015).

Critiques of Extant Literature

Previous reviews of the mediation literature indicate that we have not yet sufficiently examined fundamental questions regarding how youth psychological treatments work (Kendall et al., 2009; Prins & Ollendick, 2003; Weersing & Weisz,

2002). This is particularly true for the youth treatment literature, which has examined mediation models less frequently than the adult treatment literature (Hinshaw, 2002; Kraemer et al., 2002). Weersing and Weisz (2002) reviewed 67 studies of youth interventions and found that although over half of the studies reviewed measured potential mediators, only six studies included a formal mediation test. The authors note that mediational findings in these six studies were diminished because in all studies reviewed, the mediating variable was assessed at posttreatment (i.e., concurrent with outcome), which does not allow for examination of the temporal relationship between mediator and outcome. Overall, recent reviews conclude that of the few studies that have conducted mediation analyses, few have actually fulfilled best practice requirements for mediation studies (Maric, Wiers, & Prins, 2012).

These literature reviews highlight some of the conceptual and methodological issues limiting the utility of most of the mediational studies conducted to date. However, these flaws do not arise in all mediation studies, and some studies convey more meaningful information about mechanisms of change than others (Schmidt & Schimmelmann, 2015). A close review of the literature helps disentangle what we have learned about mediation in youth treatment and what we still wish to know.

Shortcomings Specific to Child Treatment Literature

In addition to the design and analytic shortcomings that plague both the adult and child mediation literatures, there are considerations specific to youth treatments that have not been addressed. For example, it is a concern that none of the mediation studies of youth treatments focused on developmental factors as potential moderators of mediational relationships, despite some studies having sufficient age ranges.

Kingery and colleagues (2006) noted that developmental considerations are needed in the implementation of CBT for children and for adolescents. They point out that, for example, exposure tasks constitute a critical feature of CBT-based interventions (e.g., Peris et al., 2015), but will not be effective if not designed to be developmentally appropriate for the youth. It is crucial that children understand the rationale for exposure tasks to fully engage in them, but the explanations provided must be presented in a manner that the child understands (Kendall et al., 2005). Some suggest that given the incremental changes that occur in cognitive development, a child's developmental stage should be considered on an individual basis when determining the appropriateness of treatment (O'Connor & Creswell, 2008). Kingery and colleagues (2006) suggest that future research systematically evaluate developmentally sensitive variables as mediators of treatment outcome in order to provide empirically-based information as to how manual-based treatments can best be adapted to suit a particular child's developmental needs.

Best Practices in Mediation Studies

A close review of the mediation literature reveals that most studies to date have not followed what we now know to be best practices (Kendall, Olino, Carper, & Makover, in press). A look at the recommendations in several publications reveals the repeated call for more rigorous and accurate testing of mediators and the provision of detailed guidelines for best practices. Kraemer, Wilson, Fairburn, and Agras (2002), for example, defined distinguished the proper analytic approach from moderation. Kazdin (2009) emphasized the multiple study designs possible for testing mediators and

recommendations for how best to conceptualize and design studies to meet these requirements.

Unfortunately, our review of the literature to date reveals that few mediation studies in the youth intervention literature have adhered to these guidelines since their publication. Given the lack of adequate mediation studies and the continued need for this knowledge, Maric, Wiers, and Prins (2012) published guidelines for improving mediation analyses and a justification for why these conceptual and methodological issues impact the applicability of identified mediators.

Maric, Wiers, and Prins (2012) guidelines. Maric and colleagues proposed 10 steps for improving mediation studies in the youth treatment outcome literature. Their framework allows for integration of their own recommendations with the recommendations of other experts in the field, such as Kazdin (2007, 2009) and Kraemer and colleagues (2002).

First, theory provides the basis for the selection of mediators to be investigated. It is crucial to consider the theoretical underpinning of the intervention to identify what mechanisms are expected to bring about change, in order to test whether treatment is impacting the processes believed to cause or maintain the disorder they were designed to impact. Kazdin (2009) specifies that it is crucial not only to identify a conceptually relevant construct but also to understand how it operates as a means of producing symptom change. Additionally, multiple types of studies of mediating processes should be considered to make fully informed hypotheses about putative mediators of therapeutic change (Kazdin, 2009). For example, nonhuman animal laboratory research and naturalistic studies can shed light on how the proposed mediator varies naturally and how certain behavior changes my relate to neurological or endocrine changes in other species.

Second, mediation analyses may be improved by investigating the effects of potential non-mediators. A non-mediating variable can be one that is expected not to be affected by the treatment being tested, or a variable that is expected to be changed by another treatment. Importantly, Kraemer and colleagues (2002) point out the importance of being careful when selecting a part of the definition of one of the treatments being investigated as the putative mediator. For example, if a therapeutic process only occurs in one of two interventions being compared, the mediator may be collinear with the treatment and would not show a mediating role when compared to the other treatment.

Third, it is essential to use adequate measures of mediators when examining statistical mediation. Structural equation modeling (SEM) is one way to compensate for unreliable measures, though it requires larger sample sizes that are often hard to obtain in youth clinical trials (Hoyle & Kenny, 1999). To enhance the validity of the mediation study, multiple informants and methods of assessment should be used when possible.

Fourth, studies should include at least three assessment time points in order to establish temporal precedence of change in the mediator. Measures of both mediators and treatment outcomes should be taken at all assessment points to test for the reciprocity of mediating effects by comparing the timing of the changes in variables. Besides pretreatment and posttreatment assessments, timing of assessments should reflect theory regarding when changes in the mediator are expected to occur so that measurements are taken at times when the greatest change in the mediator is expected to occur and prior to these changes having an effect on the outcome. Measurements taken too early prevent researchers from showing that treatment has an effect on the mediating variable whereas

measurements taken too late prevent researchers from showing temporal precedence of the mediator (i.e., that changes in the mediator occur prior to changes in the outcome).

Fifth, mediation studies should always include at least two treatment conditions. A control group or an alternative active treatment can be used to compare changes in mediating variables, though use of another active treatment condition allows for ruling out nonspecific therapeutic factors that may mediate outcome. In order to assess the influence of individual treatment components that are typically nested within a treatment program, studies using a dismantling design can assess the influence of specific treatment components by separating them out into different treatment conditions.

Sixth, after a study meets the requirement of temporal precedence, it is possible to establish the causal relationship between the mediator and the outcome variables. This can be tested using an experimental manipulation of the mediating variable. MacKinnon (2008) outlines the blockage and enhancement designs as two approaches to this type of manipulation, whereby the mediating process is either removed from one treatment condition or enhanced in one treatment condition. By comparing two treatment conditions where the only difference is a manipulation in the mediating process and participants are randomized into conditions, it is possible to draw more definite causal conclusions. Kazdin (2009) notes that ideally a study testing a proposed mediator will include groups assigned to low, high, and medium levels of a proposed mediator to examine how outcome varies directly as a function of levels of the manipulated dose.

Seventh, in future studies, researchers should make efforts to include both moderators and mediators of treatments in the same model, in order to detect moderation of a mediated effect, or mediation of a moderated effect. Inherent in this point is the idea

that moderators and mediators must be clearly differentiated and defined. Kraemer and colleagues (2002) promote the theory that one variable cannot be both a moderator and a mediator of treatment. They define a moderator as a process that occurs prior to treatment, and a mediator as a process that occurs during treatment; this delineation allows for a clearer understanding of the roles of these different constructs and consequences they have on outcomes.

Eighth, to address the possibility of different orders of causal relations among the mediator and dependent variables, researchers should closely examine the temporal relationship between mediator and outcome. For instance, relying only on statistical significance of mediation models could lead researchers to incorrectly conclude that a particular variable mediates treatment outcomes when change in the outcome variable precedes change in the mediating variable. Straightforward mediation models also do not capture sequential mediation patterns, whereby two or more mediators intervene in a series between an independent and a dependent variable.

Ninth, single-case experimental designs are recommended for initial testing of mediators. This is a statistical approach in which mediators of newly developed treatments are investigated on a small scale, and allow for the capturing of multiple mechanisms that may relate to a youths' functioning (MacKinnon, 2008). This approach increases the ease of frequent assessment time points and results can be generalized through replication of the study with multiple participants. This point warrants further consideration and will be discussed explicitly in the next section.

Finally, statistical challenges pose a major obstacle to the study of mediation in youth treatment outcome research (Kraemer et al., 2002; Kraemer, Shrout, & Rubio-

Stipec, 2007; Weersing, & Weisz, 2002) and can be corrected for by using recently developed advanced approaches.

Kazdin (2009) identifies issues inherent in all nomothetic studies of processes of therapeutic change, which limits the overall utility of these studies even if conducted following best practices. He points out that even if all patients change on the basis of an identical mechanism of treatment, the timing and patterns of change may vary, as has been shown across past studies.

Mediation Studies of Youth Interventions

The following section briefly reviews the literature on mediators of youth-focused interventions through the lens of these methodological and analytic critiques and recommendations. The literature review is organized by target problem because most interventions are designed to treat specific disorders and use symptoms as the primary outcome, and there is evidence to suggest that mediating factors impact disorders differentially (Chu & Harrison, 2007).

Interventions for Defiant and Conduct Problems

Most interventions for youth defiance and conduct problems target parenting-related issues. On the whole, the mediation literature in this area suggests that targeting parenting practices can be an effective way of addressing youth disruptive and conduct problem behaviors. This was found to be the case for decreases in negative parenting and increases in positive parenting (Beauchaine, Webster-Stratton, & Reid, 2005; Bjørknes, Kjøbli, Manger, & Jakobsen, 2012; Gardner, Burton, & Klimes, 2006; Gardner, Hutchings, Bywater, & Whitaker, 2010; Hanisch, Hautmann, Plück, Eichelberger, & Döpfner, 2014; Somech & Elizur, 2012). From a research perspective, however, a

concerning limitation is that most studies did not establish temporal precedence of changes in parenting behaviors prior to changes in disruptive behavior outcomes. The findings suggest that these putative mediators are potential mechanisms of change in the interventions.

Less clear is the mediating role of parent perceptions of family functioning. One study found that changes in parents' perception of family cohesion did not relate to treatment outcomes (Hagen, Ogden, & Bjørnebekk, 2011), whereas another found that increases in parents' perceptions of their own competence in running the family over the course of treatment led to more positive outcomes for youth (Deković, Asscher , Manders, Prins, & van der Laan, 2012). It may be that age plays a role: Hagen and colleagues' (2011) study looked at parenting as a putative mediator with participants under age 12 (Hagen et al., 2011), whereas the study supporting perceptions of family functioning included youth over 12 (Deković et al., 2012).

Interventions with a primary focus on youth factors, such as social-emotional development and family cohesion, to bring about changes in conduct and disruptive behaviors have also been found to be effective in reducing negative behaviors (Dadds, Cauchi, Wimalaweera, Hawes, & Brennan, 2012; Henry, 2012; Stoltz, Deković, van Londen, de Castro, & Prinzie, 2013). Some of these interventions include family members as well as youth in the intervention, and changes in parenting practices were ultimately the significant mediators of outcomes even though the interventions included direct work with youth (Eddy & Chamberlain, 2000; Henggeler et al., 2009; Henry, 2012; Stoltz et al., 2013). These findings suggest that for conduct problems there is merit in addressing the relationship between youth and parent, whether or not parents are directly

included in the intervention. However, these studies do not establish the directionality of the relationship between change in mediators and change in disruptive behaviors, and some lack an adequate number of assessment time points (Henggeler et al., 2009; Fossum, Mørch, Handegård, Drugli, & Larsson, 2009; Henry et al., 2012; Stolz et al., 2013) or analytic approaches (Eddy & Chamberlain, 2000) to detect the directionality of the mediation relationship.

Interventions for Anxiety Disorders

The mediation literature on youth anxiety treatments has analyzed cognitive and coping factors as mediators of cognitive behavioral therapy (CBT), the empirically supported intervention most widely studied and used for youth anxiety (Hollon & Beck, 2013). Changing the anxious self-talk of youth is a core component of CBT and a proposed mediator of CBT outcomes because cognitive theories of anxiety suggest that it is associated with chronic overactivity of schemas organized around danger, harm to self, and personal vulnerability (Beck & Emery, 1985; Kendall, 1985). Coping has also been studied as a putative mediator because problem-focused coping has been shown to be associated with better adjustment and increased coping efficacy (Compas, Connor-Smith, Saltzman, Thomsen, & Wadsworth, 2001).

Although cognitive and behavioral factors such as self-talk, thinking styles, coping, and self-efficacy have been evaluated as potential mediators of CBT outcome studies, few of these studies to date meet the necessary standards for establishing mediators as mechanisms of change (Normann, Lønfeldt, Reinholdt-Dunne, & Esbjørn, 2015). Mediation studies are rarely designed to assess the temporal precedence of change in mediator prior to change in anxiety outcomes (Maric, Heyne, MacKinnon, van

Widenfelt, & Westenberg, 2013; Hogendoorn et al., 2014). As a result, it remains unclear whether the changes seen in putative mediator variables lead to the changes in anxiety, or whether the cognitive and behavioral changes are the result of reduced anxiety. In the only mediation study of social skills, results suggested that improving social competence may be another route by which to reduce anxiety for youth (Alfano et al., 2009), though this study also failed to establish temporal precedence and lacked a comparison condition.

Interventions for PTSD

Findings from the mediation literature for PTSD-specific interventions suggest that reducing negative cognitive appraisals effectively reduces PTSD symptoms. Interestingly, the results suggest that mediating effect of change in cognitive appraisals may not be specific to one type of intervention, in that prolonged exposure, psychosocial intervention, and trauma-focused CBT all seemed to significantly reduce these cognitions and predict reductions in PTSD symptoms (Smith et al., 2007; Tol et al., 2010; McLean, Yeh, Rosenfield, & Foa, 2015). Although two of the three studies in this area with youth did not include more than 2 time points, McLean and colleagues (2015) did establish that the reduction in negative cognitions during treatment preceded the reduction in PTSD symptom outcomes.

Interventions for Obsessive-Compulsive Spectrum Disorders

Only one OCD-focused intervention study to date has examined mediators of youth intervention outcomes. Chu and colleagues (2015) used data from a RCT of exposure and response prevention (ERP) to measure session-by-session levels of mediating and outcome variables through observational coding of therapy sessions.

Results indicated that youth coping and therapist interventions mediated anxiety change across exposures. Reductions in youth interfering behaviors, such as avoidance or safety behaviors, and increases in youth coping, such as use of cognitive and behavioral strategies, were related to symptom reduction over time. In contrast, change in coping followed symptom change but did not precede it, and this unexpected directionality suggests the need for further investigations. Although this study did not include a comparison condition to assess the specificity of these findings to ERP, it benefited from using advanced statistics and session-by-session measurements to look at specificity and temporal sequence of mediators in a multilevel structure.

Interventions for Mood Disorders

Few studies have assessed mediators of interventions for youth mood disorders such as major depressive disorder and pediatric bipolar disorder, and those that do primarily examine mediators of CBT interventions. While other interventions such as interpersonal psychotherapy (IPT) has been found to be effective for treating adolescent depression, no formal mediation analyses have been conducted to date (Weersing, Schwartz, & Bolano, 2015). The relatively narrow focus of this literature provides some insight into the consistency of putative mediators across studies with different populations.

The most commonly tested mediating factors in the depression and bipolar disorder treatment literature are coping, cognitions, family functioning, and parenting. The mediation literature has found some support for these factors changing during treatment, although there is currently only one study that establishes temporal precedence (Stice, Rohde, Seeley, & Gau, 2010). Results supported reductions in negative cognitions

as a significant mediator of symptom reduction, and increases in pleasant events as partially mediating symptom reduction. However, only a small percentage of participants actually experienced change in the mediating variable prior to changes in the outcome variable, suggesting a need for studies of additional potential mediators (Kolko et al., 2000; Pineda & Dadds, 2013; Jacobs et al., 2014). In a recent mediation study of family-focused CBT for youth with pediatric bipolar disorder (MacPherson, Weinstein, Henry, & West, 2016), parenting skills, coping, family flexibility, and positive reframing mediated mood symptom outcomes and global functioning for youth 6 months after treatment. However, analyses demonstrated concurrent change in mediators and outcome variables, suggesting a transactional relationship rather than a causal one.

Interventions for Attention Deficit/Hyperactivity Disorder (ADHD)

The literature on mediation studies of interventions for ADHD is surprisingly sparse. While several studies have explored changes in putative mediators such as parenting practices, few studies have conducted formal mediation analyses (Chronis-Toscano et al., 2011; Pfiffner, Villodas, Kaiser, Rooney, & McBurnett, 2013; Haack, Villodas, McBurnett, Hinshaw, & Pfiffner, 2016). Findings from two of the three studies reviewed are limited by methodological concerns about these mediation studies, such as the absence of a control condition, use of analyses with a high likelihood of Type I errors, and the use of data from only two time points (Chronis-Toscano et al., 2011; Pfiffner et al., 2013). These studies preliminarily suggest that changes in negative parenting (Chronis-Toscano et al., 2011) and improvements in organization (Pfiffner et al., 2013) have a mediational relationship with ADHD symptom outcomes for youth. The initial support for both changes in negative parenting and improved organizational skills

suggests that these intervention approaches may be most useful and effective when implemented in tandem. In line with these findings, there is recent evidence to suggest that a multicomponent psychosocial intervention was most effective at improving child functioning across domains. Whereas parent-focused treatment improved negative parenting and home functioning, multicomponent treatment also improved positive parenting and academic functioning. However, the temporal relationship between mediators and outcome variables was not established statistically, limiting our understanding of the mechanism of change at work.

Interventions for Substance Use

The literature on youth-targeted interventions for substance use understandably focuses on prevention programs to delay or prevent the onset of drug and alcohol use among teenagers. Studies of interventions generally identify parenting factors as the mediators of outcomes. While parent involvement in interventions are most often seen in programs designed for young children, the substance use literature suggests that targeting both adolescents and their parents simultaneously may be the most effective preventive intervention to influence adolescent outcomes as well (Smit, Verdurmen, Monshouwer, & Smit, 2008; Wu et al., 2003). Specifically, parental monitoring and rule-setting have been identified as mediators of the emergence of substance use disorders for adolescents (Henderson et al., 2009; Koning et al., 2011; Koning et al., 2015). In addition, increases in sense of self-control also seem to mediate positive outcomes (Koning et al., 2015). By including multiple assessment time points and using rigorous analytic approaches, researchers were able to establish the directionality of the mediational relationships (Henderson, Rowe, Dakof, Hawes, & Liddle, 2009; Koning,

van den Eijnden, Engels, Verdurmen, & Vollebergh, 2011; Koning, Maric, MacKinnon, & Vollebergh, 2015). However, the specificity of mediators to particular treatment protocols is unknown due to the absence of active control groups (Koning et al., 2011; Koning et al., 2015) and inactive control groups (Henderson et al., 2009).

Interventions for Chronic Pain

CBT has been found to have positive outcomes for youth with chronic pain (e.g., Palermo, Eccleston, Lewandowski, Williams, & Morley, 2010), but the processes of change are sometimes different than those for CBT targeting other mental health disorders. Within the umbrella of chronic pain there are subtypes that cannot be assumed to all respond to CBT in the same way. Therefore, mediators of intervention outcomes have been considered for several types of chronic pain.

Amongst youth with abdominal pain, findings of mediational analyses of a CBT intervention suggest that changes in parental perceptions may be the mechanism of change in treatment (Levy et al., 2014). In a CBT study targeting juvenile fibromyalgia, outcomes were not mediated by the significant changes in coping strategies, catastrophizing, or coping efficacy (Kashikar-Zuck et al., 2013). This study utilized a rigorous approach to mediational analyses (Kraemer et al., 2002) and established temporal precedence by assessing changes in mediating variables from baseline to post-treatment and outcomes at 6-month follow-up. The role of parents warrants further consideration in future studies of interventions for junior fibromyalgia, as should other youth-focused mediators.

Interventions for Eating Disorders

The literature on mediators of eating disorders focuses on preventive interventions and family-based treatment for anorexia. Changes in both cognitive and behavioral factors were expected to influence outcomes of both types of programs.

The results of prevention studies (Stice, Presnell, Gau, & Shaw, 2007; Stice, Marti, Rohde, & Shaw, 2011) suggest that individuals at risk for eating disorders may benefit from preventive interventions by addressing cognitions about body ideals. A test of the mediators indicated good specificity of some mediators, such that the healthy weight intervention did not produce significant reductions in thin-ideal internalization, and the cognitive dissonance intervention did not produce significant increases in physical activity, consistent with hypotheses. These findings are limited by the reliance on self-report data, which might have biased the magnitude of the relationship, and the absence of testing for possible bidirectional effects between change in mediators and outcomes. In fact, the reduction in outcome variables preceded the reductions in the mediator for about a quarter of participants (Stice et al., 2007), and although statistically under-powered, the follow-up study also indicated support for this reverse mediation model (Stice et al., 2011). In a study of family-based intervention for anorexia, analyses of similar cognitive factors did not suggest a mediational relationship with symptom outcomes (Le Grange et al., 2012).

Future Directions for Examining Mediation of Youth Treatment Outcomes

Future mediation studies need to address the methodological issues plaguing the literature. That said, there are additional factors to consider in the study of mediators of youth treatment to advance our understanding of how treatments work. In particular, mediation studies of youth interventions would be wise to consider how mediators of

treatment outcomes might differ based on participants' developmental level. Second, mediators of treatment *maintenance* should be considered in order to understand which treatment factors affect youth outcome years after completing treatment.

Developmental Considerations

It is notable, and a concern, that none of the mediation studies of youth treatments focused on developmental factors as potential moderators of mediational relationships, despite some studies having age ranges that span developmental levels. Kingery and colleagues (2006) noted that developmental considerations are needed in the implementation of CBT for children and for adolescents. They point out that, for example, exposures constitute a critical feature of CBT-based interventions, but will not be effective if not designed to be developmentally appropriate for the client. It is crucial that children understand the rationale for exposure tasks in order to fully engage in them, but the explanations provided must be presented in a manner that the child understands (Kendall et al., 2005). They suggest that future research systematically evaluate developmentally sensitive variables as mediators of treatment outcome in order to provide empirically based information as to how manualized treatments can best be adapted to suit a particular child's developmental needs.

In addition to lack of consideration of developmental influence on mediators, measurements used to define treatment success often fail to account for specific developmental age features that might impact symptom presentations (Albieri & Visani, 2014). For example, some symptoms considered pathological for people at certain ages might be common and developmentally appropriate for youth during transitional periods. Further, the clinical presentations of affective disorders evolve with children's physical,

emotional, cognitive, and social developmental stages, and thus might fall into different diagnostic categories depending on the point in development at which it is measured. As such, changes in psychopathology over time should not be assessed only within the specific diagnostic category that the symptoms were originally conceptualized in. Given these age differences in symptom presentation, a longitudinal consideration of the development of disorders may be more appropriate when making clinical decisions and planning treatment than using only a cross-sectional approach based on diagnostic criteria only (Fava & Kellner, 1993).

Mediation studies should be conducted in youth samples, even if mechanisms of change for a given treatment approach have been established in the adult literature. For example, McLean and colleagues (2015) explored mediators of a treatment for PTSD among adolescents, despite having some evidence of mediators in the adult literature, because of the unique rapidity of development and integration of cognitive and emotional regulation that occurs during adolescence (Steinberg, 2005) which might result in a different role of cognitive factors in treatment.

The need for developmental considerations is particularly salient in the application of CBT principles to youth interventions, and concerns about developmental appropriateness have caused hesitation in the use of CBT with younger clients (Sudhir, 2015). Past developmental research has suggested that CBT in young children has limited applicability because of the pace of cognitive development and the cognitive resources needed for CBT (e.g., Vygotsky, 1988). Some suggest that given the incremental changes that occur in cognition development over many years, a child's developmental stage should be considered on an individual basis when determining the appropriateness of

treatment (O'Connor & Creswell, 2008). More research is needed to understand whether children are able to benefit from the intended mechanisms of change in cognitive-based approaches.

Mediators of Follow-up Outcomes

Studies looking at effects of treatment mechanisms on symptom change after treatment tend to focus on immediate outcomes, measured immediately post-treatment. However, one major barrier to the applicability of the mediation literature is the limited data on longer-term outcomes, particularly 2 or more years after the end of treatment. Identified mediators of interventions may be part of a more complex mediated pathway that improves functioning over a longer term, and long-term follow-up data should be included in mediation study outcomes in the future (Henry, 2012). Knowledge of how treatments impact symptoms over longer periods of time following the end of treatment is particularly valuable for youth interventions, as previously noted. For instance, it is possible that as children develop cognitively and emotionally, the therapeutic skills they gained as children might not be sophisticated enough to help them cope with more complex or severe symptoms. On the other hand, it is possible that symptom remission after treatment at any age serves a protective factor against later symptomatology, despite the youth-focused mechanisms of change employed.

In an evaluation of the current state of the CBT literature, Arch and Craske (2009) identified gaps in the literature and conflicting findings that complicate our understanding of how CBT works. Two major areas that they identified as being in critical need of further research were long-term outcomes and mediators of CBT. There is a particular dearth of information about outcomes more than two years post-treatment and

about mediators of these outcomes. Along with measurement of long-term outcomes comes the question of whether different treatment mechanisms differentially predict long-term outcomes, and whether those mechanisms are the same or different from those predicting short-term outcomes. It is possible that components of treatment that do not impact immediate outcomes may contribute to the maintenance of treatment gains over time, particularly for children and adolescents who are constantly developing and learning. Youth might be more competent at implementing a skill they learned in treatment only after they have had time to learn more, adapt, or digest the new skills.

There are few follow-up studies published in the literature, relative to the number of pre-post evaluations of treatments. The dearth of studies may be attributable to the difficulty and cost of following participants over the period of time after services have been rendered, or as Hagen and colleagues suggest (2011), might be due to the higher frequency of non-significant effects at follow-up, which are less often published.

Conclusions

The mediation literature for youth interventions is in its infancy, and the findings to date do not yet definitively support any specific mechanisms of change that explain why some interventions are efficacious. However, the findings do point to particular processes in treatment that may explain treatment outcomes. For one, the literature suggests that changes in parent-related factors over the course of treatment may be crucial in bringing about meaningful change. Interventions for conduct disorders and ADHD seem to impact outcomes by teaching parents active skills for addressing problematic or dysregulated behaviors. In addition, studies of treatments for chronic pain suggest that parent perception of pain also impacts treatment outcomes.

Some findings suggest that changes in both parent- and youth-related factors are necessary for desired symptom reductions. When treating conduct or disruptive behavior disorders by working with youth, changes in self-perception and social groups are crucial for youth to be successful in treatment, and parents must simultaneously learn in treatment to shift their behavioral approaches with their children.

Putative mediators for anxiety and depression interventions center on negative self-statements, social skills, coping, and perceived control. However, studies have not found consistent mediators across CBT-based studies, and therefore more research is needed to hone in on which features of the intervention are most important for the participant to master in order to benefit from treatment.

There are very few mediation studies in the youth literature that meet current standards for assessing mediation. Before findings from past mediation studies are over-interpreted, it is crucial that mediation studies are replicated with updated methodology, following the guidelines laid out by Maric and colleagues (2012). The studies conducted to date should be used to inform the future studies of mechanisms of treatment, and there must be acknowledgement among the youth treatment research community regarding the limitations of existing studies. In addition to replicating tests of putative mediators using more rigorous methodological and statistical approaches, there is a need to further our understanding by testing the same mediators across intervention protocols and also across outcome measures. To determine which interventions are worth investing in for implementation and dissemination, it is imperative that we first understand how the interventions work, identify redundancies between treatment approaches, and remove aspects of the interventions that do not seem to induce meaningful changes. It is also

important to consider what mediates the long-term success of interventions to maximize the impact of treatment on an individual's life and to determine how youth at different developmental stages might react differently to treatment mechanisms.

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