DEPRESSIVE AND EXTERNALIZING COMORBIDITY AND THE RELATIONS TO CHILD ANXIETY TREATMENT RESPONSE TIME-COURSE

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ABSTRACT

Objective: The present study examined the potential roles of externalizing and depressive co-occurring psychopathology on the *time-course* to anxiety treatment response among youth receiving different treatment conditions. ***Method:*** Participants were 488 youth (aged 7-17 years) who received either Cognitive-Behavioral Therapy (CBT) ($N = 139$), sertraline (SRT) ($N = 133$), CBT+sertraline (COMB; $N = 140$), or pill placebo (PLB; $N = 76$) in the Child/Adolescent Anxiety Multimodal Study (CAMS; Walkup et al., 2008). ***Results:*** Findings did not demonstrate a significant relation of comorbid psychopathology with treatment response time-course. Participants in CBT and SRT had significantly different overall treatment response trajectories, though comorbid psychopathology did not significantly relate to the observed treatment response trajectories. Exploratory analyses revealed that parental treatment assignment reaction to CBT was positively associated with more favorable treatment response time course, whereas parental treatment assignment reaction to SRT did not significantly relate to treatment response time course. ***Conclusions:*** Our results are consistent with the notion that current interventions (CBT, SRT) produce improvements that generalize across co-occurring depressive and externalizing psychopathology. Clinical implications for the treatment of anxious youth with regard to comorbidity and contextual factors are discussed and suggestions for future research are offered.

Keywords: anxiety, comorbidity, treatment response, survival analysis

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CHAPTER 1

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Depressive and Externalizing Comorbidity and the Relations to Child Anxiety Treatment Response Time-Course

Anxiety disorders, specifically Generalized Anxiety Disorder (GAD), Social Phobia (SoP), and Separation Anxiety Disorder (SAD), are among the most common mental health problems in children and adolescents (Kessler et al., 2005) and high rates of comorbidity have been well documented in youth (Kendall et al., 2010; Masi, Mucci, Favilla, Romano, & Poli, 1999) suffering from anxiety disorders. Co-occurring psychopathology is especially problematic with anxiety, as anxiety is commonly comorbid with other nonanxiety disorders (Last, Hersen, Kazdin, & Orvaschel, 1991).

The issue of comorbidity complicates research and treatment of childhood anxiety disorders, as the comorbidity of mental health disorders in youth with anxiety disorders is the rule rather than the exception. Individuals with more than one diagnosis have been shown to have associated difficulties that include greater life dissatisfaction, less social stability, greater use of mental health services, and more suicide attempts (Newman, Moffit, Caspi, & Silva, 1998). Comorbidity has been described as chiefly, the product of a nosological system that classifies mental disorders categorically, presupposing discrete diagnostic entities or disease states (Belzer & Schneier, 2004; Clarkin & Kendall, 1992; Kendall & Clarkin, 1992). Regardless of the current categorical methods used to account for co-occurring symptoms, researchers and practitioners continue to struggle with the

challenges involved in addressing patients with complex symptom presentations (Belzer & Schneier, 2004). The term comorbidity can be used in a therapeutic sense to describe how a disorder can impact the treatment efficacy of a co-occurring disorder (Lilienfield, Waldman, & Israel, 1994). For present purposes, "comorbid anxiety" (or comorbid depression, comorbid externalizing, etc.) is a diagnosed anxiety disorder that co-occurs but is secondary to a principal (i.e., more impairing) anxiety disorder. As we refer to general terms such as depression, anxiety disorders, and externalizing disorders, unless it is otherwise specified, they indicate the presence of disorder whether that disorder is comorbid or principal.

Overlap of mood symptoms and anxiety disorders in youth are distressing, impairing, and prevalent (e.g., Costello et al., 2003), interfere with interpersonal relationships and academic achievement, and increase the risk of suicide and other psychopathology (e.g., Gould et al., 1998; O'Neil et al., 2012; Rodriguez & Kendall, 2014; Wolk, Kendall, & Beidas, 2015). Existing research on comorbid anxiety and depressive disorders shows that great variability exists for estimates of comorbidity (Axelson & Birmaher, 2001). Among youths with depressive disorders, anxiety disorders are the most common comorbid mental health disorders, with comorbidity estimates ranging from 15% to 75% (Angold, Costello, & Erkanli, 1999). In youths with anxiety disorders, rates of comorbid depressive disorders are generally lower, ranging from 10% to 15% (Angold et al., 1999; Axelson & Birmaher, 2001; Costello et al., 2003). Substantial comorbidity between these difficulties, as evidenced by both high correlations between dimensional measures of anxious and depressive symptoms (Stark & Laurent,

2001), as well as high symptom overlap (Drabick & Kendall, 2010) help to explain these rates of disorder co-occurence (Cummings, Caporino, & Kendall, 2014).

There are also sizeable comorbid rates of ADHD with anxiety (~25% in epidemiology, Angold, Costello, & Erkanli, 1999; ~15% in diagnosed cases, Verduin & Kendall, 2003). ADHD is a pervasive and persistent mental health disorder defined by the features of inattention, impulsivity, and hyperactivity (American Psychiatric Association [APA], 2000). As a neurodevelopmental disorder that is mostly diagnosed in childhood, ADHD tends to continue into adolescence in 50% to 70% of individuals (Barkley, Murphy, & Fischer, 2010; Foaraone, Biederman, & Mick, 2006). Although comorbid with a range of other difficulties (Brown, 2000), ADHD has a very high co-occurrence with anxiety in referred and community samples (Hammerness et al., 2010; Sorenson, Plessen, Nicholas, & Lundervold, 2011). In contrast to the strong relationship between anxiety disorders and ADHD, studies that have evaluated the impact of disruptive disorders (specifically, ODD and conduct disorder) on anxiety disorders have found inconsistent results; some report that anxiety disorders are related to less impairing conduct problems, while others report a positive relationship between anxiety disorders and disruptive disorders (Bilgic et al., 2013; Kazdin & Whitley, 2006; Marmorstein, 2007).

Research examining comorbid rates among anxiety disorders show that GAD, SoP, and SAD are highly comorbid with one another (Kendall et al., 2010) and, consistent with research findings, can be treated with an intervention that flexibly targets features that are similar across anxiety disorders. Cognitive-Behavioral therapy (CBT)

for anxious youth (e.g. *Coping Cat*; Kendall & Hedtke, 2006a; 2006b) is an individual therapy for child anxiety that has been adapted for groups (Flannery-Schroeder & Kendall, 2000), school-based settings (Masia-Warner, Nangle, Hansen, & David, 2006), and adolescents (e.g., the *C.A.T. Project*; Kendall, Choudhury, Hudson, & Webb, 2002). Although the findings from studies indicate that the treatment is efficacious (Hollon & Beck, 2014), studies that have examined principal anxiety diagnosis and baseline anxiety severity as a predictor or moderator of treatment outcome have generally yielded non-significant results (Barrett et al., 1996; Cobham et al., 1998; Hedtke et al., 2009; Kendall et al., 1997; Legerstee et al., 2010; Ollendick et al., 2009; Panichelli-Mindel et al., 2005; Puleo & Kendall, 2011; Shortt et al., 2001). Of importance, a recent examination of treatment response found that high baseline severity predicted poorer symptom change (Liber et al., 2010; also see Southam-Gerow et al., 2001). In this study, Liber and colleagues (2010) examined symptom reduction using the Reliable Change index in parent-reported internalizing and externalizing symptoms, and also found that non-anxiety comorbidity explained more variance in treatment response above and beyond principal severity alone. Such studies meet a growing need to probe the relation of comorbidity to treatment response in more nuanced ways, though the use of separate (externalizing/depressive) treatment response variables may problematically define response too narrowly. There remains a need to examine treatment response and the potentially nuanced impact of comorbidity using *global* response variables. Overall, a number of studies that have examined treatment outcome have not found significant differential effects based on the assigned principal anxiety disorder, though pretreatment

anxiety disorder severity has been shown to be associated with greater treatment *response.*

There is a common assumption that the existence of comorbid disorders complicates treatment and decreases treatment efficacy (Rapee, 2013). However, several studies have examined general comorbidity as a predictor of treatment response, and the majority have found equal treatment gains for anxiety disordered youths with or without additional comorbid diagnoses (Beidel, Turner, & Morris, 2000; Berman, Weems, Silverman, & Kurtines, 2000; Hedtke et al., 2009; Cooper, Gallop, Willetts, & Creswell, 2008; Panichelli-Mindel et al., 2005; Rapee, 2003; Rapee, 2013). In a review of the literature, Ollendick and colleagues (2008) concluded that the existence of comorbid diagnoses does not appear to influence the response to treatment for children with primary anxiety disorders.

Less is known about how comorbid nonanxiety disorders, also called heterotypic comorbidity, impact the response to youth anxiety treatment. Brodman and Kendall (in preparation) examined different operationalizations of comorbidity in a sample of anxious youth receiving CBT. Variables that combine symptom severity ratings for comorbid disorders were calculated from diagnostician and participant ratings gathered during the Anxiety Disorders Interview Schedule child and parent (ADIS-C/P) interview. Recursive partitioning analyses and subsequent regression analyses revealed two variables that predicted a less favorable treatment response: presence of a comorbid nonanxiety disorder (a measure of heterotypic comorbidity) and greater pretreatment impairment.

Studies examining depressive comorbidity generally report non-significant relations with treatment outcome (Kendall et al., 1997; Kendall et al., 2001; Legerstee et al., 2010; Ollendick, Ost, Reuterskiold, & Costa, 2010; Rapee, 2003; Shortt, Barrett, Fox, 2001; Ost, Svensson, Hellstrom, & Lindwall, 2001). For example, a CBT trial of 91 youth (aged 8-16 years) that examined subclinical symptoms of depression at baseline (Legerstee et al., 2010) did not find that it predicted a differential treatment response and the analysis by Shortt and colleagues (2001) found that presence of comorbid major depressive disorder did not significantly predict differential treatment outcomes for anxiety-disordered youth. Though the majority of studies found no link between comorbid depression and outcome, there are a couple notable exceptions. Southam-Gerow and colleagues (2001) found depressive and withdrawal symptoms reported by mothers and teachers to be predictive of poor anxiety treatment response. In addition, Berman and colleagues (2000) in a CBT trial examining 106 youth (aged 6-17) found significant associations with comorbid depressive *diagnoses* to be a predictor of poorer treatment outcome. Note however, that only 7 of the 106 youth in the sample presented with a diagnosis of depression. There are multiple possible explanations for these mixed findings; (a) studies may be underpowered to examine the comorbidity or moderation with treatment, (b) studies examine endpoint determinants rather than trajectory or long-term follow-up, and (c) studies have an inconsistent operationalization of comorbidity or examine treatment response using anxiety-specific rather than global measures of improvement.

It has been suggested that among the comorbid disorders in anxiety-disordered youth, comorbid mood disorders have been associated with the worst overall presenting psychopathology and subsequent response to treatment (Rapee, 2013). Despite this sentiment, there appear to be few previous studies that have found support. Although children with mood disorders are likely to be characterized by additional difficulties (e.g., negative thinking), only the endpoint of treatment has been found to be associated with comorbid mood disorders (in only several studies), and depressive symptomatology has yet to be shown in relation to the rate of change over time (Rapee et al., 2013). One limitation in an examination of aggregate RCT data by Rapee et al. (2013) is that the youth with comorbid depressive disorders did not achieve their endpoint of treatment response until the follow-up phase of the study, and change over time was measured using three time points (i.e., pre- and post-treatment, and follow-up assessment that occurred between 3 to 12 months after treatment). Although three time points is reasonable to examine "change over time," more frequent assessments (e.g., weekly or biweekly) and subsequent analysis would allow for increased temporal resolution of the treatment response time course. More research is needed in this area, using multiple time-points, large sample sizes, combined categorical-dimensional operationalizations of comorbidity, inclusive definitions of treatment response, and more nuanced examination of the impact of comorbidity.

Studies that have examined psychosocial treatments for youth with principal anxiety and externalizing comorbidity (Kendall et al., 1997; Kendall et al., 2001; Manassis et al., 2002; Rapee, 2000; Southam-Gerow et al., 2001) have generally reported

non-significant results when examining differential treatment response of youth with or without comorbid externalizing symptoms and/or disorders. Yet other studies have shown that, specifically, symptoms of comorbid ADHD as determined by questionnaires, may evidence posttreatment response following treatment for principal child anxiety (Kendall, Brady, & Verduin, 2001; Levy, Hunt, & Heriot, 2007). Regardless, anxiety symptoms appear more beneficially impacted by CBT than do ADHD symptoms (e.g., see Jarrett & Ollendick, 2012). The relation of family functioning and parental accommodation has been shown to be an important factor in the maintenance of anxiety and externalizing disorders (Kepley & Ostrander, 2007). Given the potential generalizability of anxiety-targeted CBT to other domains, further inquiry is needed into other contextual variables (e.g., family functioning, caregiver burden) that may co-vary with successful treatment response or may be an important predictor of treatment response above and beyond comorbidity. Given the scarcity of literature, future studies are needed to better understand the treatment of co-occurring anxiety and externalizing disorders, and the associated processes of contextual variables (Jarrett, 2013), with treatment response time-course.

Medications have also been researched as a treatment for child anxiety, though researchers' understanding of Selective-Serotonin Reuptake Inhibitors (SSRIs) and their impact on treatment response in youth with comorbid mood, anxiety, and externalizing disorders is limited in a number of ways. SSRIs are frequently prescribed for principal anxiety disorders (Baldwin et al., 2005) and depression in youth (Birmaher & Brent, 2002), and are considered promising for addressing both sets of symptoms (Hughes et al.,

2007). Of interest, comorbid disorders were not associated with fluoxetine outcomes among youth in three large trials (Cheung et al., 2010; Tao et al., 2009). One study found that depressive symptoms predicted poorer response to fluvoxamine among anxious youth, but none of the youth in this study met criteria for MDD (Walkup et al., 2003). In an analysis of the CAMS data, no significant relation of comorbid externalizing diagnosis with sertraline treatment outcomes was detected (Compton et al., 2014). In sum, SSRIs may be effective in reducing comorbid anxiety and mood symptoms but the current state of the research is too limited for a strong conclusion. At this juncture, if medication is pursued as a treatment option for anxious and depressed youth, combined treatment (CBT + SSRI) appears to be the best option (Walkup et al., 2008; TADS Team, 2004).

The role of comorbidity on treatment is either poorly understood or non-existent. It is possible the studies that found a relationship between comorbidity and treatment outcome may have been idiosyncratic, due to a small sample of youth with heterotypic comorbidity (as in Berman et al., 2000). In cases where heterotypic comorbidity was found to be associated with treatment outcome (e.g., Liber et al., 2010; Rapee, 2013), the authors indicated that comorbidity only related to differential outcome when assessed at endpoint determinants (i.e., diagnosis-free rates), or response was defined using narrow metrics of domain-specific improvement. It remains possible or likely that truly heterotypic comorbidity is associated with worse overall pretreatment severity, though it is unclear if comorbidity is associated with *slower* improvement. With regard to SSRI treatment, research has indicated treatment efficacy for depressive disorders and for anxiety disorders, but no research to date has indicated specific comorbidities that are

negatively associated with treatment outcome. Although it is useful to know what to expect when starting treatment, prognostic factors (i.e., predictors) are of little use in deciding what treatment to select (Driessen & Hollon, 2010). On the other hand, prescriptive information (i.e., *moderators*) can detect different patterns of outcomes between different treatments for different types of patients and provide a basis for choosing the best treatment for a given patient (Kraemer et al., 2002). Identification of comorbid subgroups that demonstrate a differential response to available treatments is important in guiding clinical and cost-effective decision-making. In order to identify such subgroups, a clear understanding of potential treatment moderators is required (Driessen & Hollon, 2010). To illustrate, it may be possible that families with worse pretreatment family burden garner greater benefit from CBT compared to SSRI, especially as behavioral treatment generalizes to other areas of contextual dysfunction during the second half of treatment. In sum, the literature has shown the vast number of studies to examine comorbid predictors of outcome for child anxiety (e.g., Hedtke et al., 2009), though few have tested treatment moderators; those comorbid factors measured prior to treatment indicating who is likely to gain greater benefit from a particular treatment. Few have also examined comorbidity and treatment response with respect to both rate of change and treatment endpoint (Rapee et al., 2013). Sample sizes in many of the reviewed studies were underpowered to effectively examine comorbidity as a moderator of outcomes. Without a properly powered sample of anxiety-disordered youth with comorbid psychopathology, a more detailed analysis of heterotypic comorbidity and the influence of clinical-level depressive/externalizing disorder severity has not been

possible. Finally, a number of studies were further restricted by age, and did not include older adolescents which limits the number of youth with possible comorbidities. The present study addressed these gaps by having an adequately powered sample to examine comorbidity, to examine treatment trajectories using weekly improvement ratings of global functioning, and to examine the role of comorbidity in treatment response time course between both CBT and SSRI treatment (i.e., moderation). The present study also examined the impact of contextual variables (e.g., family functioning, caregiver burden) in treatment response time course between both CBT and SSRI treatment. Examination of interactions between CBT and SSRI allows for nuanced inquiry into the effect of comorbidity and how comormid psychopathology may differentially impact the response of participants between treatments.

The present study focused on depressive and externalizing comorbidity by addressing the following questions: (1) Does the presence of externalizing or depressive comorbidity predict differential time-course when comparing CBT to SRT? More specifically, for youth in CBT we hypothesized that the presence of a comorbid externalizing disorder would be associated with more rapid time-course to successful treatment response compared to youth in the SRT condition. We also hypothesized that for youth in the SRT treatment condition, higher severity of co-occurring depressive symptoms would be associated with more rapid time-course to successful treatment response compared to youth in the CBT condition. (2) Do dimensional measures of baseline comorbid externalizing severity predict less rapid treatment response time course above and beyond categorical measures of externalizing comorbidity? (3) Do factors such

as caregiver burden or other baseline contextual factors relate to differential treatment response time-course when comparing CBT to SRT? Specifically, we hypothesized that for youth in the CBT treatment condition, higher severity of caregiver burden would be associated with more rapid time-course to successful treatment response compared to youth in the SRT condition. Exploratory analyses probed for differential role of comorbidity factors in predicting treatment response time-course between participants of combined treatment (CBT + SSRI) and monotherapy conditions (CBT or SSRI).

Method

Participants

Participants included 488 (246 male and 242 female) youth that were examined in the CAMS study (Walkup et al., 2008). The racial and ethnic makeup of this sample reflected the population of anxious youth that were a part of treatment-seeking families (79% were White, 9% Black, 2.5% Asian, 0.4% Pacific Islander, 1.2% American Indian, 12% Hispanic, and 7% were other ethnicity in this sample).

Participants were included in the CAMS trial if they (a) were between 7 and 17 years of age; (b) met diagnostic criteria for a primary diagnosis of SAD, GAD, or social phobia (DSM criteria); (c) experienced substantial impairment associated with their anxiety disorder; and (d) had an IQ $\geq$ 80. Participants were randomly assigned to their treatment condition. Youth were excluded from CAMS if they had an unstable medical condition or exhibited school refusal. Youth who had not responded to two adequate trials of SSRIs or one adequate trial of CBT were also excluded. Finally, youth who were taking psychiatric medications other than stable doses of stimulants, youth who had diagnoses of comorbid conditions that made study participation clinically inappropriate, or youth who presented a significant risk to themselves or to others were excluded from the CAMS trial.

Both parent and child had the entire experimental procedure explained, including the interviews, physical examination and treatment procedures. The parent and child were explained that acceptance or refusal would not influence their ability to receive care and that they were free to withdraw at any time. Entry into the study was predicated on

obtaining written informed consent from parents or legal guardian of the child, and assent from the child. The participants were informed that the study was designed to examine the impact of cognitive-behavioral and/or SSRI treatment for youth with anxiety disorders. Participants were informed that they would complete a diagnostic interview for anxiety disorders and that they may be invited to participate in the study but that participation in the study was not guaranteed. Following the diagnostic interview, youth and their parents were informed that they would be asked to complete several self-report questionnaires assessing their current levels of anxiety, depression, and parenting style. They were also told that they would be randomized to one of four treatments (CBT, SRT, COMB, placebo pill) and that they would not know whether or not they received sertraline or placebo.

Procedure

Participants were enrolled in the CAMS study after partaking in a phone screen and a subsequent diagnostic interview. Data were collected at pre and post treatment from self-report questionnaires and information gained from a semi-structured diagnostic interview by an independent evaluator. All interviews were video recorded to review for reliability purposes. Participants were informed of this recording and may have chosen to opt out of this procedure. In our experience conducting diagnostic assessments for studies in anxiety disorder samples, few people opt out of the recording option, as was the case for CAMS. Data from all sources were assigned to a numeric, de-identified code and kept in an encrypted electronic spreadsheet on a secure, HIPAA-compliant network that were available to all principle investigators.

CBT. The referral procedures, intake procedures, treatment method, and treatment materials for the existing sample have been described (Compton et al., 2010; Walkup et al., 2008). Briefly, diagnosed cases received 14 sessions of CBT, lasting 60 minutes once a week. The CAMS CBT was *The Coping Cat* (Kendall & Hedtke, 2006a; b) for children and *The C.A.T. Project* (Kendall, Choudhury, Hudson, & Webb, 2002a; b) for adolescents. During the first half, youth learned skills to cope with anxiety (i.e. the FEAR plan). The second half consisted of exposure tasks to have the youth face, rather than avoid, anxiety-provoking situations. CBT responders received monthly CBT maintenance sessions. All sessions were video-recorded.

Pharmacotherapy. All medication was administered twice daily, in the morning and evening, in a "fixed-flexible" fashion. The dose was increased as scheduled in the event the participant remained symptomatic with minimal side effects. Specifically, to best reconcile dose-response and time-action effects, CAMS used a fixed-flexible dosing schedule that is dependent on pharmacotherapist-assigned CGI-S score and the ascertainment of clinically significant side effects (see Walkup et al., 2008). Scored 25mg and 50mg SRT tablets were purchased from Solvay Pharmaceuticals. Identical capsules of SRT and PLB were prepared and readied for distribution by the Investigational Pharmacy at Johns Hopkins Hospital. All participants and their parents were given explicit verbal and written (medication diary) instructions on when and how to take their medication.

At the conclusion of the initial efficacy trial (12-weeks), participants who failed to respond to their study assigned treatment program would have generally required further

treatment. All end-of-treatment recommendations were coded for data entry. Families were given a list of possible providers for the recommended treatment and were told that a clinical report could be sent with the parents' authorization to any new treatment provider(s) (see Compton et al., 2010 for description of referral procedures).

Measures

Assessment instruments included a semi-structured diagnostic interview, clinician-administered measures, as well as self- and parent-report. Youth were assessed for the presence of anxiety disorders as well as comorbid conditions at pretreatment, and the treatment provider (i.e., pharmacotherapist, therapist, or both) assessed for symptom severity at each visit. All participants (regardless of treatment status) underwent a comprehensive baseline assessment to ascertain study eligibility. Primary outcome measures were administered by Independent Evaluators (IE) at baseline and weeks 4, 8 and 12 or early termination during the acute efficacy trial. A comprehensive self-report and interview-based assessment designed to provide more specific symptom information and track supposed mediators and moderators of outcome was administered according to the same schedule as the IE assessments. Unlike past CAMS reports, the present study used treatment *provider* Clinical Global Impression- Improvement Scales (CGI-I; (Guy, 1976) ratings made at each treatment visit (rather than IE ratings for pre- mid- and post-treatment). In the COMB condition, both a pharmacotherapist and psychotherapist completed these ratings at each time-point. When scores differed at a time point, we used the more conservative (less improved) value of the two CGI-I scores.

Anxiety Disorders Interview Schedule for Children (ADIS-IV-C/P; Silverman & Albano, 1996). The AIDS-IV-C/P are semi-structured diagnostic interviews to assess anxiety, mood disorders, and other psychopathology in accordance with the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*, American Psychiatric Association, 1994), as reported by children aged 7-17 years, and their parents. The ADIS-IV-C/P demonstrates excellent interrater and retest reliability for diagnostic ratings and clinician severity ratings (CSRs), based on both child and parent interviews (Silverman, Saavedra, & Pina, 2001), as well as good to excellent inter-rater reliability (Lyneham, Abbott, & Rapee, 2007). Concurrent validity of ADIS-IV-C/P ratings has been demonstrated with parent-rated scores from the Multidimensional Anxiety Scale for Children (MASC; Villabo, Gere, Torgersen, March, & Kendall, 2012; Wood, Piacentini, Bergman, McCracken, & Barrios, 2002). Parent and child interviews were conducted separately by two reliable diagnosticians. ADIS-IV-C/P training required the attainment and maintenance of interrater reliability levels of .85 and above (Cohen's K). During the interviews, youth and their parents provided Global Interference Ratings (GIR) and diagnosticians provided Clinical Severity Ratings (CSR) for each diagnosis on a 9-point scale (0-8). A minimum CSR of 4 is required for a diagnosis; ratings below 4 denote subclinical difficulties. The parent-child composite diagnosis will be generated based on CSRs of the symptoms endorsed during each interview according to the "or" rule (a diagnosis is given if the child *or* the parent interview endorses criteria sufficient to warrant a clinical diagnosis; Silverman & Albano, 1996).

Clinical Global Impression-Severity and Improvement Scales (CGI-S and I;

(Guy, 1976). The CGI-S score provides a global rating of baseline severity ranging from 1 (not at all ill) to 7 (extremely ill) while the CGI-I provides a global rating of clinical improvement ranging from 1 (Very Much Improved) to 7 (Very Much Worse) and serves as the study primary categorical outcome measure. CGIs are commonly used in clinical trials. The CGI-I is related to self-report and clinician-administered measures of improved symptomatology and improved functional impairment (Zaider, Heimberg, Fresco, Schneier, & Liebowitz, 2003).

Mood and Feelings Questionnaire (MFQ; (Costello et al., 1991). This measure is a 32-item measure designed to detect DSM-defined depression in children and adolescents. Two versions, a child self report version and a parent reported version on the child, were used in this study. The psychometric properties of the MFQ have been formally and comprehensively tested and suggest that the MFQ is a valid instrument for detecting depression in clinical samples (Wood et al., 1995). The MFQ was administered at monthly intervals throughout Phase I and every three months during Phase II. The MFQ total score has shown internal consistency of .75 to .78, alphas (Costello, Benjamin, Angold, & Silver, 1991; Wood, Kroll, Moore, & Harrington, 1995).

Achenbach Child Behavior Checklist (CBCL; Achenbach, 1991). This measure is a 118-item self-report scale assessing behavioral problems and social and academic competence. The CBCL is one of the most extensively tested rating scales available and possesses excellent psychometrics. It was completed at baseline, the end of the acute trial, and at each major maintenance phase evaluation visit. The CBCL-

externalizing score will provide a continuous measure of baseline externalizing symptoms for our analyses.

Service Provider CGI's. In addition to the IE, the present study used ratings by pharmacotherapists and psychotherapists who independently completed CGI Improvement and Severity ratings at each visit. Although these ratings were not completed blind to treatment status (except for PLB vs. SRT) they will be of heuristic value in tracking the time course of therapist perceptions of symptom change.

Burden Assessment Scale (BAS; Reinhard et al., 1994). The BAS is a 21-item scale that measures objective and subjective caregiver burden associated with having a child with a mental health disorder. Parents indicated the degree to which the child's anxiety disrupts family life and routines on a scale ranging from 1 (not at all) to 5 (very much). A higher score signifies greater burden. Consistent with high internal consistency in initial studies, Cronbach's alpha for the current sample was .91 at pretreatment and .93 at posttreatment.

Brief Family Assessment Measure-III (BFAM-III; Skinner Steinhauer, & Santa-Barbara, 1995). The BFAM-III is a 14-item questionnaire answered by parents and children that assesses perceptions of family functioning during the last 2 weeks. Items such as "We take the time to listen to each other" and "When things aren't going well it takes too long to work them out" are scored on a 5-point scale. Items are summed to create a total score that is converted into a T score. Higher scores reflect greater levels of perceived family dysfunction. Cronbach's alpha ranged between .76 and .87 for children and parents across pre- and posttreatment assessments.

Treatment Assignment Reaction (TAR). The TAR was completed at baseline by the diagnostician who informed the subject and the parent of their randomization status. The TAR reflects on the diagnostician's observation of the parent's reaction to the news of their assignment status. Scores are rated as Extremely Disappointed = 1, Disappointed = 2, Neutral = 3, Pleased = 4, Extremely Pleased = 5. The measure was developed for use in CAMS. Diagnostician rating of the *parent* reaction was used in the present study.

Data Analysis

Dependent Variable. Survival analysis is a collection of statistical procedures for data analysis for which the outcome variable of interest is time until an event occurs (Kleinbaum & Klein, 1996). One binary measure of global response (CGI-I) was used longitudinally to examine the cumulative rate of participants who achieve treatment response over the course of treatment. As such, the time-point (week of treatment) in which service providers *first assign* a CGI-I of 2 or better (i.e., rated as "very much" or "much improved"), was utilized as the binary primary measure for signifying the "event" of treatment response. CGI-I ratings were completed by therapists in the CBT condition or pharmacotherapists in the SRT condition.

Missing Data. Cases were excluded listwise due to missing data. That is, in cases where a participant was missing items of a measure, they were excluded from analyses involving that measure. Missingness was examined for all variables in the model, though of note, missingness was quite low and never exceeded 1%.

Preliminary Analyses. Logistic and linear regressions examined the relationships between the demographic factors of age and gender and rates of comorbidity in our sample (i.e., separate regressions examined presence of externalizing disorder, depressive symptoms, and externalizing symptoms as dependent variables). Demographic variables (e.g., age, gender, race, socio economic status), that were found to be significantly associated with other comorbidity or dependent variables were included as covariates and entered in all analyses (e.g., entered in Step 1 of hierarchical Cox regressions). Age and gender were entered into step 1 of all subsequent analyses (see results for details).

Primary Analyses. Data were assessed at weekly time points (e.g., CGI-I ratings). We used Cox regression and survival analysis (Maki, 2006) and examined the role of factors that relate to change over time until the "event" of treatment response (see below). Stepwise Cox regressions in SPSS Statistics Version 22.0 statistical package tested the interaction of pretreatment externalizing or depressive comorbidity and treatment condition in its relation to the time-course of treatment response. We used interactions to test the role of comorbidity between the CBT and SSRI conditions.

We hypothesized that for youth in the CBT treatment condition, the presence of a comorbid externalizing disorder would be associated with more rapid time-course to successful treatment response than for youth in the SRT condition. Presence of a pretreatment comorbid externalizing diagnosis was dummy coded, and treatment condition (dummy coded as CBT versus SRT) were entered in step 2 of a Cox regression. The interaction of externalizing comorbidity and treatment condition was entered into Step 3 of the model to assess the differential effect of externalizing diagnosis in

predicting treatment response time course among youth who received CBT compared to youth who received SRT.

We hypothesized that for youth in the SRT treatment condition, higher severity of co-occurring depressive symptoms will be associated with more rapid time-course to successful treatment response than for youth in the CBT condition. We ran two separate analyses utilizing depressive symptoms from child self-report and from parent report of child. Severity of pretreatment co-occurring depressive symptoms (MFQ Total score at baseline) were mean centered, and treatment condition (dummy coded as SRT versus CBT) were entered in step 2 of a Cox regression. The interaction of co-occurring depressive symptoms and treatment condition was entered into Step 3 of the model to assess the differential effect of depressive symptoms in predicting treatment response time course among youth who received SRT compared to youth who received CBT.

We hypothesized that higher severity of co-occurring externalizing symptoms would be significantly associated with less rapid time-course to successful treatment response above and beyond the association of externalizing diagnostic status (a categorical measure). Presence of a pretreatment comorbid externalizing diagnosis was dummy coded and entered in step 2, while co-occurring externalizing symptoms was mean-centered and entered into step 3 of a Cox regression model. Dimensional co-occurring externalizing symptoms were assessed for its association to the time-course of treatment response, above and beyond the role of categorical externalizing comorbidity, through examination of change statistics between Step 2 and Step 3 of this analysis.

We hypothesized that for youth in the CBT treatment condition, higher severity of caregiver burden would be associated with more rapid time-course to successful treatment response than for youth in the SRT condition. We ran two separate analyses utilizing the BAS total score (a metric of family burden) and the BFAMG total score (a metric of family dysfunction). Severity of caregiver burden (BAS or BFAMG, mean centered), and treatment condition (dummy coded as CBT versus SRT) were entered into step 2 of a Cox regression. The interaction of caregiver burden and treatment condition was entered into Step 3 of the model to assess the differential effect of caregiver burden in predicting treatment response time course for youth who received CBT compared to youth who received SRT. Post-hoc analyses were run examining the differential impact of parent treatment assignment reaction on treatment response time course between participants in CBT and SRT conditions. Parental treatment assignment reaction, and treatment condition (dummy coded as CBT versus SRT) were entered in step 2 of a Cox regression. The interaction of treatment assignment reaction and treatment condition was entered into Step 3 of the model.

The present study used exploratory analyses, involving separate Cox regressions probing for differential impact of pretreatment factors (externalizing diagnostic status, co-occurring depressive symptoms, caregiver strain) in predicting treatment response time-course between participants of combined treatment (CBT + SSRI) and monotherapy conditions (CBT or SSRI). Main effects probing the association of all pretreatment factors on treatment response time-course was also examined for CBT and SRT participants in the present study.

Results

Preliminary Analyses

Examination of demographic factors and youth characteristics indicated that female participants were associated with faster treatment response time-course than males (B = -.244, SE = .113, Wald χ^2 = 4.66, p = .031, Exp(B) = .78, N = 488; Table 1). Age was significantly associated with baseline youth depressive symptom severity reported by youth (β = .17 p < .001, n = 486) and reported by parents (β = .17, p < .001, N = 488); age was also associated with baseline externalizing symptom severity reported by parents (β = -.14, p = .003, N = 488). Given the relation of age with baseline symptom severity and gender with treatment response time-course, "Age" and "Gender" were included as covariates in the following analyses. No other demographic factors or youth characteristics examined were included as covariates given that no other factors were associated with dependent or independent variables.

As expected, treatment condition was associated with differential treatment response trajectories over time (Breslow χ^2 = 37.09, p < .001, N = 488). Analyses of contrasts indicated that participants in the CBT condition were associated with significantly different treatment response time-course compared to participants in the SRT condition (B = -.385, SE = .151, Wald χ^2 = 6.49, p = .011, Exp(B) = .68, N = 272). Subsequent contrasts indicated significant differences when comparing the CBT condition to the COMB condition in treatment response time-course (B = -.499, SE = .141, Wald χ^2 = 12.49, p < .001, Exp(B) = .607, N = 279). Of note, when comparing the

SRT condition to COMB condition there is no significant difference in treatment response time-course (*B* = -.071, *SE* = .145, Wald χ^2 = .237, *p* = .626, Exp(*B*) = .932, N = 272).

Comorbid Psychopathology in Relation to Treatment Response Time-Course

None of the apriori hypotheses tested with regard to comorbidity yielded a significant interaction or main effects with treatment response time course. In comparison of CBT to SRT, baseline externalizing disorder comorbidity was not significantly associated with differential treatment response time-course (Wald χ^2 = .56, *p* = .45, N = 272), such that presence of a comorbid externalizing disorder was not significantly associated with more rapid treatment response time course for youth in the CBT condition compared to the SRT condition. Among youth in monotherapy conditions (i.e., CBT and SRT), presence of a baseline comorbid externalizing disorder did not predict a significant difference in treatment response time course (Breslow χ^2 = .001, *p* = .973, N = 272).

In comparison of SRT to CBT, severity of child-reported baseline depressive symptoms was not significantly associated with differential treatment response time-course (*B* = -.013, *SE* = .014, Wald χ^2 = .859, *p* = .354, N = 272). Similarly, when comparing SRT to CBT, severity of parent-reported depressive symptoms was also not significantly associated with differential treatment response time-course (*B* = .001, *SE* = .015, Wald χ^2 = .001, *p* = .996, Exp(*B*) = 1.00, N = 272). There was also no significant main effect for child- or parent-reported depressive symptoms in relation to treatment response time-course among youth receiving CBT and SRT (*B* = -.003, *SE* = .007, Wald

χ^2 = .14, *p* = .70, Exp(*B*) = .99; *B* = -.004, *SE* = .008, Wald χ^2 = .001, *p* = .996, Exp(*B*) = 1.00, N = 272, respectively).

Severity of co-occurring parent-reported externalizing symptoms was not significantly associated, above and beyond the association of externalizing comorbid diagnosis, with treatment response time-course (Chi Square χ^2 = .056, *df* = 1, *p* = .813). As such, neither dimensional nor categorical measures of externalizing severity significantly predicted the rate of treatment response.

Of note, separate exploratory Cox regressions were analyzed comparing COMB to Monotherapy (CBT/SRT), with independent comorbidity variables (e.g., baseline externalizing disorder, parent-reported externalizing severity, parent-reported depressive severity, child-reported depressive severity), and none of the models demonstrated a significant differential treatment response time course.

Contextual Factors in Relation to Treatment Response Time-Course

In comparison of CBT to SRT, severity of parent-reported baseline caregiver burden was not significantly associated with differential treatment response time-course (*B* = -.003, *SE* = .012, Wald χ^2 = .062, *p* = .804, Exp(*B*) = .997, N = 272). Moreover, among youth in monotherapy conditions (i.e., CBT and SRT), severity of caregiver burden associated with having a child with a mental health disorder did not predict a significant difference in treatment response time course (*B* = -.002, *SE* = .006, Wald χ^2 = .176, *p* = .675, Exp(*B*) = .99, N = 272). Moreover, exploratory analyses comparing COMB to Monotherapy, did not show severity of parent-reported caregiver burden to be

significantly associated with differential treatment response time-course (Wald χ^2 = .012, p = .91, Exp(B) = .99, N = 412).

The findings did identify one baseline factor to be related to differential treatment response time course. “Parental treatment assignment reaction” was significantly related to treatment response time-course. Analyses comparing CBT to SRT indicated that baseline parental treatment assignment reactions is significantly associated with differential treatment response time-course (Wald χ^2 = 7.97, p = .005, N = 272). This interaction was significant, such that parents with more enthusiastic treatment assignment reaction to CBT were associated with more favorable treatment response time-course, whereas more enthusiastic treatment assignment reaction to SRT was somewhat negatively related to treatment response time-course (Table 2; Figure 1). Among youth in monotherapy conditions (i.e., CBT and SRT), the main effect of parental treatment assignment reaction did not predict a significant difference in the time-course of treatment response (B = -.065, SE = .077, Wald χ^2 = .71, p = .40, Exp(B) = .94, N = 272). There is a significant simple main effect for CBT but not a significant simple effect for SRT, such that for CBT more enthusiastic parental treatment assignment reaction predicted more favorable treatment response time course (B = .31, SE = .13, Wald χ^2 = 6.00, p = .014, Exp(B) = 1.37, N = 139), whereas for SRT no significant association was found for parental treatment assignment reaction with treatment response time-course (B = -.16, SE = .12, Wald χ^2 = 1.67, p = .20, Exp(B) = .86, N = 133).

Discussion

By investigating trajectories of treatment response over 12 weeks of intervention, the present study examined the relation of comorbid factors and treatment condition with provider-rated treatment response. Findings did not demonstrate a significant relation of comorbid psychopathology and condition with treatment response time-course. Comorbidity was operationalized with externalizing comorbid diagnostic status as rated by independent evaluators, and with child- and parent reported depressive symptom severity at baseline, yet neither of these comorbidity metrics predicted differential treatment response trajectories between CBT and SRT over 12 weeks of intervention. The absence of significant findings in this regard are analogous to a number of studies that did not find comorbid psychopathology to be a significant factor in relation to treatment response (e.g., Hedtke, Kendall, & Tiwari, 2009; Cooper, Gallop, Willetts, & Creswell, 2008; Panichelli-Mindel, Flannery-Schroeder, Kendall, & Angelosante, 2005). Moreover, the importance of heterotypic (i.e., externalizing or depressive) co-occurring psychopathology, in a sample of anxiety-disordered youth receiving treatment was not supported. Given that most studies used *endpoint determinants* of treatment response (e.g., Liber et al., 2010; Rapee, 2013) and that only the occasional study has found heterotypic comorbidity to be associated with treatment outcome, perhaps the absence of significant comorbidity findings in the present study when examining *trajectories* of treatment response should not be unexpected. After all, the variability of treatment response trajectories for CBT and SRT are somewhat limited by their similar endpoints. Although participants in CBT and SRT had significantly different overall treatment response trajectories, comorbid psychopathology did not significantly impact the

observed treatment response trajectories. Lack of significant results are consistent with the notion that current interventions (CBT, SRT) produce improvements that generalize well across depressive and externalizing psychopathology.

Regarding the notion that a *dimensional* measure of externalizing psychopathology may provide an added effect above and beyond a categorical measure, results indicate that regardless of categorical or dimensional operationalization, externalizing psychopathology was not significantly related to treatment response time-course for CBT and SRT. Given that there were no significant findings for the a priori comorbid psychopathology hypotheses tested in this study, it is difficult to discern the added benefit of utilizing a combined categorical-dimensional approach for operationalizing comorbidity. Although others have highlighted the importance of utilizing both categorical and dimensional operationalizations of comorbidity in treatment studies (Brodman & Kendall, in preparation; Bubier & Drabick, 2009; Drabick & Kendall, 2010), it is perhaps not surprising that the current study has similarly failed to report categorical and dimensional measures of comorbidity that relate to treatment outcome.

Given that some symptomatology cuts across anxiety, depressive, and externalizing domains and can be impacted by a shared influence (e.g., caregiver burden), it stands to reason that differences in that influencing factor may result in concurrent or differential symptom change (Jarrett & Ollendick, 2013). It was our intention to further examine the impact of more global measures of family burden outside of standard symptom/comorbidity. Nonetheless, the impact of baseline caregiver burden was also not

found to be significantly associated with treatment response time-course. Although the present study employed a large sample size, multiple treatments, and weekly treatment response trajectories with its (arguably) added benefit of "temporal resolution", the present study did not find support for anxious youth with heterotypic comorbidity or dysfunctional family environments that benefited more or less readily with one treatment versus the other. As such, the uncertainty of how comorbid psychopathology may inform "for whom" (after Kiesler, 1966) treatments work best (Kendall & Comer, 2011), may remain a particularly complicated and elusive question to answer. This study did not detect differential treatment response time-courses for youth with particular co-occurring conditions, which is in line with a number of other studies that failed to do so (Ollendick et al., 2008). Nonetheless, future investigations may hopefully elucidate important factors and eventually replicate findings related to improving the cost-effectiveness and specificity of CBT/SRT treatment.

To our knowledge, this is one of the first studies to examine treatment response time-course as predicted by treatment intervention and comorbid psychopathology. The present study used survival analysis with the outcome event corresponding to overall *anxiety* improvement (e.g., CGI-I rated weekly/bi-weekly by provider, at the treatment visit the provider first awarded a CGI-I of "2" or better). We used this primary outcome for examining treatment response time-course, and it is our view that future research should continue to use global measures of functional impairment outcomes, or family dysfunction outcomes in order to broaden the search for how heterotypic comorbidity or co-occurring baseline factors may impact treatment outcomes.

The present study explored potential differences in treatment response trajectories between treatment conditions, and factors that may predict if youth will more readily benefit from COMB relative to the monotherapy (CBT/SRT) conditions. Similarly to the many of our reported non-significant findings comparing between CBT and SRT - exploratory analyses also failed to identify significant factors (e.g., baseline comorbid psychopathology and/or baseline family functioning) that related to differential treatment response time-course between COMB and Monotherapy.

Findings that were not necessarily the focus of this study, though nonetheless important, are overall main effects of treatment condition and the appraisal of the different treatment response time-courses by condition. Unsurprisingly, the impact of treatment condition is apparent in the observed dissimilarity of survival analysis curves. Contrasts revealed that CBT time-course is different from SRT and COMB, though SRT time-course is not significantly dissimilar from COMB. Out of these four conditions, CBT, appears to 'stand alone' with the most unique treatment response trajectory. This uniqueness may be partly due to study design, as CBT was the only condition that did not involve taking a pill (i.e.., placebo or sertraline). The survival curves highlight the slow start that youth receiving CBT exhibit in the first half of treatment (e.g., during psychoeducation), such that youth in the CBT condition appear to initially benefit even less than the placebo condition! The week-to-week benefit of CBT begins to substantially widen by week 6 to 8, which is analogous with a number of other CBT authorities that have stressed the importance of exposure as an active ingredient of treatment response (Peris et al., 2015; Peterman et al., 2014), and is further indication of the impact of

exposures in the second half of treatment (e.g., weeks 8-12) (Kendall et al, 2008). Conversely, youth in the SRT condition appear to most readily benefit during the first 4 to 6 weeks - superficially even more so than the COMB condition. That improved early likelihood is short-lived, as COMB treatment "catches" SRT in response rate by week 6, and the time-course of SRT treatment response slows during the second half of treatment. Although speculative, we suggest that the "slow start" of youth in CBT may not be a 'waiting period' for the exposure tasks to begin in the second half of treatment, but may perhaps be related to an skill building and incubation period in which delayed expectations for change (by provider, parent, and child) have been established.

The present study explored the impact of therapist-rated parental treatment assignment reaction by condition, and found that there is a significant differential impact (CBT vs. SRT) on treatment response time-course. Inclusion of "treatment assignment reaction" as a measure was not a part of our a priori hypotheses. Interestingly, the therapist-rated parental reaction to being assigned to CBT was related to the treatment response trajectory of CBT. Although the implications of "treatment assignment reaction" on treatment are potentially fascinating, we must acknowledge limitations. The study included only one placebo condition, therefore when families first learned they were assigned to SRT they had to contemplate the possibility they may have been assigned to the PLB condition. Conversely, families assigned to CBT knew that they were going to receive an evidence-based treatment. As such, the distribution of treatment assignment reactions is not equivalent between CBT and SRT. Therefore generalizing these findings to a real-world treatment facility is limited. Moreover, the ratings of

parental reactions to treatment assignment do not have available psychometric data. With these caveats in mind, our finding highlights how co-occurring contextual factors may impact treatment above and beyond comorbidity or symptom severity.

The use of a 12-week time period, although sufficient time for a typical RCT that examines endpoint determinants, may not be as ideal as a longitudinal study over a much longer time-frame- allowing for more nuanced treatment response trajectories to develop. Future investigation can take advantage of time-course analysis by utilizing data points captured more often than weekly or bi-weekly (e.g., use of personal devices, automated informatics) to measure meaningful real-world outcomes and to provide substantially more temporal resolution to analyses. Although the use of global improvement as a primary outcome measure in an RCT can be questioned by some (e.g., De Los Reyes, Alfano, & Beidel, 2011), the use of a global dependent variable that cuts across domains (e.g., CGAS) may be well suited for capturing the impact of baseline comorbid psychopathology on treatment outcome (Brodman and Kendall, in preparation). This study design used weekly assessments of *treatment providers*, rather than independent evaluators. Although not ideal, it does offer one advantage of being a "real-world" assessment of treatment response, given that treatment-as-usual rarely if ever utilizes independent evaluators. Nonetheless, future investigations that can utilize blinded and frequent (e.g., weekly) assessment would be beneficial. Demographically, the majority of participants was Caucasian and reported mid- to high- SES; further research among parents and youth of ethnic minority backgrounds and lower income households is needed to determine generalizability of results to other populations.

There are several clinical implications of the present findings. The current results are consistent with the notion that current treatments (CBT, SRT, COMB) produce results that generalize well across comorbid psychopathology. Our findings are also consistent with the premise that typical depressive or externalizing co-ocurring psychopathology for treatment-seeking anxious youth may not be exceptionally heterotypic (Lillienfield, 1994), and are rather part of a larger anxiety disordered group where these difficulties appear to "co-vary" rather than truly co-occur. Comorbidity has been dubbed the rule, rather than the exception, which emphasizes the need to determine *actual comorbid exceptions*. It may be that a more limited, but meaningful, subset of complex-comorbid youth is better suited for a particular treatment. Lastly, utilization of treatment response time-course is a feasible approach and examination of rates of change has the potential to help investigators assess more appropriate and cost-effective treatments targeted to youth.

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Table 1

Descriptive Information for Study Participants in Relation to Tx Response Time-Course

Variable	*n*	(%)	Significance Test for Relationship with Tx Response Time-Course
Child age in years	*M* = 11.17	*SD* = 2.81	χ = .22, *p* > .05
Gender			
Females	242	50	χ = 4.6, *p* = .031
Race			
Caucasian	385	78.9	
Black	44	9.0	
Asian	12	2.5	χ = 4.77, *df* = 5, *p* > .05
Pacific Islander	2	.4	
American Indian	6	1.2	
Other	39	8.0	
Principal Anxiety Diagnosis			
GAD[a]	236	48.4	χ = 3.5, *p* > .05
Social Phobia[a]	247	50.6	χ = 1.3, *p* > .05
SAD[a]	144	29.5	χ = .62, *p* > .05
Comorbid Externalizing Dx			
ADHD	49	10.0	
ODD	46	9.4	
Total SES Score[b]			
08 to 19	8	1.6	
20 to 29	33	6.8	
30 to 39	62	12.7	χ = .57, *df* = 4, *p* > .05
40 to 54	218	44.7	
55 to 66	167	34.2	

Note. GAD = Generalized Anxiety Disorder, SAD = Separation Anxiety Disorder, OCD = Obsessive Compulsive Disorder, AD-NOS = Anxiety Disorder, Not Otherwise Specified
[a]Significance test for severity of disorder based on Clinician Severity Rating (CSR) in relation to treatment response time-course. [b]Socioeconomic status based on the Hollingshead's (1975) Four-Factor Index of Social Status.

Table 2

Cox Regression for Parental Treatment Assignment Reaction predicting Treatment Response Time Course, for youth in CBT compared to SRT condition

	B	**SE B**	**Wald χ**
Step 1			
Male	-.20	.15	1.77
Age	-.003	.002	1.25
Step 2			
Male	-.26	.15	2.81
Age	-.003	.002	1.54
CBT Tx Condition	-.43	.17	6.79**
Parent TAR	.018	.083	.045
Step 3			
Male	-.28	.15	3.39
Age	-.002	.002	1.12
CBT Tx Condition	-2.1	.62	11.45**
Parent TAR	-.22	.12	3.34
CBT Tx * Parent TAR	.49	.17	7.97**

Note. n = 272. CBT Tx Condition is dummy coded '1' for CBT and '0' for SRT. Parent TAR = Parental Treatment Assignment Reaction. χ^2 = 3.04 for Step 1 (p = .22); $\Delta\chi^2$ = 7.42, for Step 2 (p = .024); $\Delta\chi^2$ = 8.20 for Step 3 (p = .004). *p < .05, **p < .01.

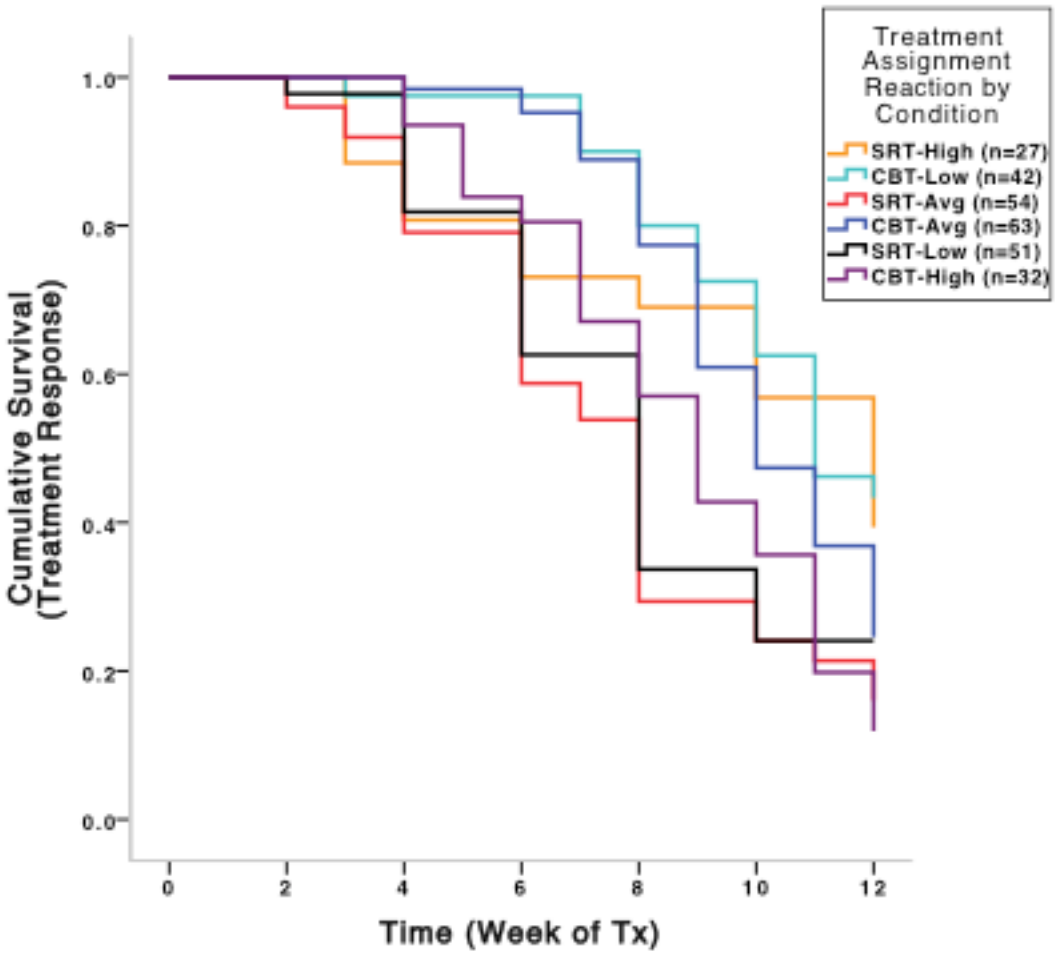

Figure 1. Interaction of Clinician-Rated Parental Treatment Assignment Reaction predicting Treatment Response Time Course, for youth in CBT and SRT condition. Y-axis described as proportion of participants ongoing in study before achieving treatment response. Treatment Assignment Reaction categories include Extremely Disappointed = 1, Disappointed = 2, Neutral = 3, Pleased = 4, Extremely Pleased = 5; Categories were combined for parsimony and visual simplicity as follows, SRT-High=4,5; SRT-Avg=3; SRT-Low=1,2; CBT-High=5; CBT-Avg=4; CBT-Low=1,2,3.

CHAPTER 2

LITERATURE REVIEW

Anxiety disorders, specifically Generalized Anxiety Disorder (GAD), Social Phobia (SoP), and Separation Anxiety Disorder (SAD), are among the most common mental health problems in children and adolescents (Kessler et al., 2005) and high rates of comorbidity have been well documented in children (Kendall et al., 2010; Masi, Mucci, Favilla, Romano, & Poli, 1999; Newman et al., 1996) suffering from anxiety disorders. Co-occurring psychopathology is especially problematic with anxiety, as anxiety is commonly comorbid with other nonanxiety disorders (Last, Hersen, Kazdin, & Orvaschel, 1991). The issue of comorbidity complicates research and treatment of childhood anxiety disorders, as the comorbidity of mental health disorders in youth with anxiety disorders is the rule rather than the exception.

As Klein and Riso (1993) explain, comorbidity refers to the presence of two or more distinct, co-occurring disorders in one patient. First introduced into the medical literature by Feinstein (1970), individuals with more than one diagnosis have been shown to have associated difficulties that include greater life dissatisfaction, less social stability, greater use of mental health services, and more suicide attempts (Newman, Moffit, Caspi, & Silva, 1998). Comorbidity has been described as chiefly, the product of a nosological system that classifies mental disorders categorically, presupposing discrete diagnostic entities or disease states (Belzer & Schneier, 2004; Clarkin & Kendall, 1992; Kendall & Clarkin, 1992). Regardless of the current categorical methods used to account for co-

occurring symptoms, researchers and practitioners continue to struggle with the challenges involved in addressing patients with complex symptom presentations (Belzer & Schneier, 2004). The term comorbidity can be used in a therapeutic sense to describe how a disorder can impact the diagnosis of treatment efficacy of a co-occurring disorder (Lilienfield, Waldman, & Israel, 1994). For the purposes of this review, we define "comorbid anxiety" (or comorbid depression, comorbid externalizing, etc.) as a diagnosed anxiety disorder that co-occurs but is secondary to a principal (i.e., more impairing) anxiety disorder. When we use general terms such as depression, anxiety disorders, and externalizing disorders, unless it is otherwise specified, they indicate the presence of disorder whether that disorder is comorbid or principal.

Research in children and adolescent mental health issues has shown dramatic increases in comorbidity (Angold Costello, & Erkanli, 1999) with anxiety. In this review we use the term "anxiety disorder" to refer to a child with a principal diagnosis of one of the "big 3" child anxiety disorders (i.e., GAD, SoP, and SAD). Disorders that are most frequently comorbid in youth with one of these three principal anxiety disorders is the focus of this review. Common comorbid disorders can be classified, broadly, into comorbid affective disorders (i.e., depression), and comorbid externalizing disorders (such as ADHD, oppositional defiant disorder, and conduct disorder). This review will first discuss how affective and externalizing disorders are comorbid with principal anxiety, examining issues such as prevalence, age of onset, comorbid subtypes, and symptom overlap. Next, we will review treatment outcome studies for principal anxiety in youth that have examined the relation of comorbidity with outcome. Lastly, the review

will integrate the research findings, discuss issues related to comorbidity, and identify salient questions that have yet to be answered.

Anxiety with Comorbid Depression

One issue linked to the co-occurrence of anxiety and depression is related, simply and directly, to their definition. Both constructs have affective, cognitive, behavioral, and physiological components that are similar. Although anxiety and depression are believed to share similar emotional features of negative affect, a key component of anxiety is perceived threat (physiological hyperarousal), and a key in depression is distress or anguish (Blumberg & Izard, 1986). Nevertheless, as Clark and Watson (1991) propose in their tripartite model, both depressed and anxious individuals exhibit a broad range of self-reported negative emotional features. According to Watson and colleagues (1988), differentiation between anxiety and depression can be achieved when accounting for a lack of positive affectivity. Positive affectivity is a broad construct that reflects positive emotional states such as joy, enthusiasm, and energy. This combination of high negative affectivity and low positive affectivity was thought to help in distinguishing depression from anxiety (Watson, Clark, & Carey, 1988).

Watson (2005) later noted limitations of the tripartite model. one main concern is that anxiety disorders are diverse and the tripartite model may not apply to all anxiety disorders (Anderson & Hope, 2008). For example, the physiological arousal component of the model was not shown to be characteristic of all anxiety disorders but was linked specifically to panic disorder (Brown et al., 1998; Chorpita, 2002) and to post-traumatic stress disorder (PTSD) (see Brown et al., 2001). Moreover, factors initially related

uniquely to depression have also been associated with certain anxiety disorders. For instance, lack of positive affect has been shown to have a consistent negative relation with social phobia in addition to depression (Watson, Gamez, & Simms, 2005). Recent factor analyses confirmed that while co-occurrence of anxiety and depression in youth is in part due to the "higher-order factor" of negative affectivity, negative affectivity was found to substantially account for GAD's high co-occurrence with depression, more so than with other anxiety disorders (Trosper, Whitton, Brown, & Pincus, 2012). Such results are helpful in addressing the question of how anxiety disorders and depression are related to each other, though it appears that these disorders are related in complex and sometimes inconsistent patterns, and no one factor can explain co-occurrence or discriminate between such disorders.

With regard to co-occurrence of anxiety disorders and depression, a related perspective involves the finding that anxiety and depression both respond to selective-serotonin reuptake inhibitors (SSRIs; i.e., Walkup et al., 2008). Treatment response to SSRIs is also consistent with imaging studies that have indentified overlapping functional and structural brain neuropathology (see review by Cameron, Abelson, & Young, 2004). Although such research is outside the scope of this paper a wealth of research on this topic exists (see, Beesdo et al., 2009; Hettema, 2008; Lau et al., 2009; Morilak & Frazer, 2004; Thibodeau, Jorgensen, & Kim, 2006).

Prevalence

Anxiety and mood symptoms and disorders in youth are distressing, impairing, and prevalent (e.g., Costello, Mustillo, Erkanli, Keeler, & Angold, 2003), interfere with

interpersonal relationships and academic achievement, and increase the risk of suicide and other psychopathology (e.g., Gould et al., 1998; Rohde, Lewinsohn, & Seeley, 1994). Existing research on comorbid anxiety and depressive disorders shows great variability that exists in estimates of comorbidity (Axelson & Birmaher, 2001). In children with anxiety, rates of co-occurring depression range anywhere from 5% to 55% (Avenevoli et al., 2001). There is substantial comorbidity between these difficulties, as evidence by both high correlations between dimensional measures of anxious and depressive symptoms (Stark & Laurent, 2001) and diagnostic comorbidity rates as high as 75% in some samples (Weersing, Gonzalez, Campo, & Lucas, 2008). Lewinsohn and colleagues (1997) found major depression to be significantly associated with many anxiety disorders (e.g., GAD, SAD, SoP), but did not find a relationship between depression and obsessive-compulsive disorder (OCD). Masi and colleagues (2000) examined the effect of depressive comorbidity and GAD in children. In a sample of 108 children with GAD, 55 (51%) had comorbid depression. Although the groups did not differ significantly by age, gender, and socioeconomic status, the patients with comorbid depression had significantly more anxiety symptoms than those without. As other authors have found, the link between anxiety and comorbid depression seems to be associated with more impairing overall severity, poor prognosis, and suicidality (Foley et al., 2006; Masi et al., 1999). Moreover, comorbidity rates do not appear to be interchangeable between principal diagnoses, as youth with principal depression are more likely to have comorbid anxiety (25% to 50%), compared to youth with principal anxiety disorder with a concurrent depressive disorder (~15%) (Brady & Kendall, 1992; Axelson & Birmaher,

2001; Costello et al., 2003). Such difference in the comorbidity rates may suggest that the nature or etiology of depression is more impairing when it is primary or principal to anxiety disorders. Research involving longitudinal analysis has indicated that depression secondary to an anxiety disorder may be associated with a less severe form of depression (Olino, Klein, Lewinsohn, Rohde, & Seeley, 2010).

Age of Onset

When conceptualizing the development of comorbid conditions we must consider "equifinality" and "multifinality." Equifinality relates to the idea that unique developmental pathways may lead to the same outcome, while multifinality refers to one pathway that may result in multiple outcomes depending on related contextual factors (e.g., Cicchetti & Rogosch, 1996). Findings from longitudinal studies suggest onset of anxiety often occurs before onset of depression. For instance, in a longitudinal follow-up study, two-thirds of children with co-occurring anxiety disorders and depression experienced onset of their anxiety disorder before onset of depression (Kovacs, Gatsonis, Paulauskas, & Richards, 1989). Although there is some evidence that earlier depression predicts later anxiety disorders among youth and vice versa (Costello et al., 2003), the bulk of the data indicate that the onset of anxiety most often occurs before the onset of depression (e.g., Avenevoli et al., 2001; Fichter, Quadflieg, Fischer, & Kohlboeck, 2010;). Other studies have found that common childhood anxiety diagnoses (i.e., GAD, SAD, SoP) more often precede diagnoses of MDD, but that OCD and panic disorder are more likely to occur after the onset of depression (Lewinsohn et al.,1997). As we see,

GAD, SAD, and SoP are generally more prevalent during childhood, and depression tends to increase in prevalence during adolescence. Youth with comorbid anxiety and depression tend to be older than those with either disorder alone (Brady & Kendall, 1992). This may be partly due to differences in the differentiation of mood over the course of development. In young children, anxiety and depression form a more closely unified construct of negative affectivity, whereas in older children, multipart models appear to be more appropriate (Cole, Truglio, & Peeke, 1997). As such, higher rates of comorbid anxiety and depressive disorders tend to be found in adolescents than in younger children (Ollendick, Shortt, & Sander, 2005).The tripartite model best fits data related to high school-age adolescents (especially girls), as supported in a study that sampled elementary and high school boys and girls, (Jacques & Mash, 2004). Ollendick and colleagues (2003) found that the two-factor model fit data relating to younger children (particularly boys). As such, it may be easier to differentiate between anxiety and depression as youth become older. Yet contradicting support for the application of the tripartite model also exists, as Turner and Barrett (2003) found that a tripartite model provided an appropriate fit to data from across third, sixth, and ninth grade age groups.

It is possible that anxiety disorders put individuals at risk for depression, likely due to a result of interpersonal, biological, and contextual processes (Cummings, Caporino, & Kendall, 2014); this suggests the potential role of developmental multifinality, as it remains unclear whether anxiety in some cases "causes" onset of depression or if correlates or associated sequelae of anxiety disorders confer risk for the development of later depression. As discussed, lack of positive affect was one such

associated factor common to both SoP and depression (Watson, Gamez, Simms, 2005), so how might this factor impact developmental equifinality/multifinality in SoP? Perhaps youth with SoP are more likely to develop depression, as a result of social isolation and potential peer victimization. However, as suggested by Epkins and Heckler (2011), the developmental pathway to depression from SoP is complex, and research does not always indicate a direct causal path from early anxiety to later depression (Rice, van den Bree, & Thapar, 2004).

A combination of factors that are related to anxiety are likely to lead to later depression, though how can we account for these factors? Consideration given to specific anxiety disorders (as mentioned previously with SoP) may help to explain the link between anxiety onset and later depression. A longitudinal study of girls by Keenan and colleagues (2009) indicated that *symptoms* of SoP, SAD, and depression were relatively stable and did not predict increases in each other across time. However, increases in SoP symptoms in childhood did predict depressive *disorders* in early adolescence, though depressive symptoms were the strongest predictors of later depression. This pattern suggests that anxiety and depression are related yet still separate (Keenan, Feng, Hipwell, & Klostermann, 2009). Work by Hammen and colleagues (2008) suggests that an earlier onset of depression has been found to be associated with worse anxiety comorbidity and presenting impairment. For example, in youth that experience an earlier onset of depression before the age of 15, co-occurring anxiety (in particular, GAD and SoP) appears to be more prevalent (Hammen, Brennan, Keenan-Miller, & Herr, 2008). In a longitudinal study of 816 youth, the combination of a primary anxiety disorder and early

stressors predicted increased depressive symptoms in response to low levels of current stress (Espejo, Hammen, Connolly, Brennan, Najman, & Bor, 2007). The authors proposed that an anxiety disorder and early stress create a sensitivity to stress, and a subsequent vulnerability to depression (Espejo et al., 2007).

A further complicating matter is that less is known about subsyndromal levels of symptoms in relation to the study of comorbidity. Said another way, children diagnosed with anxiety disorders may have concurrent depressive symptoms even they do not meet full criteria for a depressive diagnosis. These co-occurring subclinical symptoms may account for the apparent link between anxiety and subsequent depressive disorder onset (Garber & Weersing., 2010). Moreover, sub-diagnostic depressive symptoms have been found to be a more consistent predictor of subsequent depressive disorders than symptoms of either SAD or SoP (Keenan et al., 2009).

All told, early onset of GAD, SAD, and SoP put individuals at risk for subsequent depression in a number of instances, due to biological and contextual factors. Though given that not *all* anxious youth develop later depression, and given the large number of associated factors, it is difficult to conclude whether certain anxiety disorders lead to unique developmental pathways (equifinality). Further longitudinal studies beginning in early childhood that examine specific anxiety disorders, will be helpful in clarifying these relationships.

Symptom Overlap

One artificial explanation for comorbidity involves symptom overlap across diagnostic categories (e.g., “difficulty concentrating,” “easily fatigued,” and “difficulty

sleeping"). The rates of comorbidity between anxiety and depression may be due to overlap of these "similar comorbid symptoms" (SCSs) or more general overlapping core difficulties that define these disorders. For example, less participation in social activities can characterize both depression and SoP, although the underlying reason for and function of the avoidance may differ. One of the most pronounced examples of symptom overlap is between GAD and MDD. In children, such symptoms include fatigue, sleep disturbance, concentration difficulties, and irritability. As we see, one significant problem in the study of comorbidity is that a number of symptom criteria between disorders are similar or even identical. Investigations that have excluded all overlapping items on self-report measures of anxiety and depression, however, have found that the correlations of the abbreviated measures were still significant ($r = .34$) (Stark & Laurent, 2001). Longitudinal data suggest that GAD and MDD are associated with each other more strongly than each disorder even predicts itself over time (Copeland, Shanahan, Costello, & Angold, 2009; Moffitt et al., 2007; Pine, Cohen, Gurley, Brook, & Ma, 1998). In Copeland et al. (2009), only childhood depression predicted young adult GAD and only adolescent GAD predicted later depression. Further, childhood and adolescent GAD and MDD predicted different adult disorders, and young adult GAD and MDD were predicted by different childhood and adolescent disorders. The National Comorbidity Survey that examined participants between the ages of 15-54 years found that nearly one-third of all non-chance co-occurrences of a major depressive episode and GAD onset occurred in the same year (Kessler et al., 2008).

Anxiety disorders (especially GAD) and depression can be difficult to discriminate in community samples, but are easier to differentiate at more severe clinical levels (Gurley, Cohen, Pine, & Brook, 1996). Overall, findings support MDD as separate but more closely related to GAD than other anxiety disorders. The overlap of co-occurring GAD, SAD, or SoP and depression are likely to vary by developmental stages, which supports the notion of these disorders as distinct in youth (Kessler et al., 2005; Cummings et al., 2014). Despite this, future studies need to attend to the overlap of GAD and Depression in the diagnostic criteria, and symptom criteria may account for the underlying cause of such similar comorbid symptoms (SCSs).

Anxiety with Comorbid Externalizing Disorders

Comorbid externalizing disorders (e.g., ADHD, oppositional defiant disorder; conduct disorder) require consideration in the assessment and treatment of anxiety. In this section we review comorbid ADHD and disruptive behavior disorders, including data related to their prevalence, and a brief discussion of symptom overlap and why such difficulties may co-occur.

Anxiety with Comorbid ADHD

The associations between anxiety and externalizing disorders such as ADHD may be due to several phenomena. It has been stated that certain risk factors for anxiety and externalizing disorders could be similar (Marmorstein, 2007) or alternatively, children with externalizing disorders may generate anxiety-provoking situations around themselves leading to consecutive comorbidity (Frick, Lilienfeld, Ellis, Loney, &

Silverthorn, 1999). Though, methodological confounders may also be responsible, the co-occurring conditions of ADHD and anxiety disorders also share some overlapping diagnostic criteria (Marmorstein, 2007), such as difficulties concentrating. A common influence may be in the area of neurocognitive functioning. Numerous studies have provided support for ADHD involving diminished functioning in areas such as working memory (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005) and executive control (Barkley, 1997). In addition, there is evidence that youth with ADHD and anxiety may have even greater difficulties with certain types of working memory (Jarrett, Wolff, Davis, Cowart, & Ollendick, 2012; Tannock, 2009). Eysenck and colleagues (2007) noted that an adverse effect of high anxiety in normal populations is difficulty with executive functions such as working memory, shifting, and inhibitory control. In addition, anxious participants completing cognitive tasks often show greater brain activation relative to nonanxious participants in brain areas related to cognitive control such as the prefrontal cortex (Eysenck, Derakshan, Santos, & Calvo, 2007). Such research suggests that participants with high levels of anxiety often have to recruit greater cognitive resources during demanding tasks, given that areas such as the prefrontal cortex serve both cognitive and emotional control functions (Barkley, 2003). As such, symptoms of ADHD and anxiety may be influenced by common process of neurocognitive functioning. Beyond potential cognitive or emotional control deficits, theoretical explanations for comorbidity of anxiety and ADHD can be difficult to pinpoint.

Prevalence of Anxiety with comorbid ADHD

There are sizeable comorbid rates of ADHD with principal anxiety diagnoses (~25% in epidemiology, Angold, Costello, & Erkanli, 1999; ~15% in diagnosed cases, Verduin & Kendall, 2003). ADHD is a pervasive and persistent mental health disorder defined by the features of inattention, impulsivity, and hyperactivity (American Psychiatric Association [APA], 2000). Mostly diagnosed in childhood, ADHD tends to continue into adolescence in 50% to 70% of individuals (Barkley, Murphy, & Fischer, 2010; Foaraone, Biederman, & Mick, 2006). Although comorbid with a range of other difficulties (Brown, 2000), one of the most consistent findings in ADHD research over the past 25 years has been its very high co-occurrence with anxiety in referred and community samples (Hammerness et al., 2010; Sorenson, Plessen, Nicholas, & Lundervold, 2011). Specifically, 25% to 50% of individuals with principal ADHD also exhibit a comorbid anxiety disorder (Mancini, Van Ameringen, Oakman, & Figueiredo, 1999; Tsang et al., 2015; Vloet, Konrad, Herpertz-Dahlmann, Polier, & Günther, 2010).

Considerations of ADHD Subtypes

ADHD is characterized as having two symptom domains – inattention-disorganization and hyperactivity. This yields three clinical subtypes: primarily inattentive, primarily hyperactive, and the combined type. These subtypes of ADHD carry their own individual difficulties and may relate to differential temperamental styles (Nigg et al., 2004). Inattention-disorganization (e.g., losing of important materials, difficulty sustaining attention) is often associated with regulatory constructs such as effortful control. Hyperactivity is related to the classic temperament domain of activity level (Escalona, 1968). Impulsivity can be characterized by negative and/or positive

approach (Nigg et al., 2004), and includes features such as interrupting others and/or initiating new and novel activities. Comorbid depression and anxiety disorders appear to be most notable in ADHD-inattentive type and also occur in approximately 25% of cases with ADHD-Combined type (Tannock, 2000). In one study, Newcorn and colleagues (2001) found that children with co-occurring ADHD and anxiety diagnoses were relatively more inattentive than impulsive, while children with ADHD and co-occurring ODD/conduct disorder were rated as more impulsive than inattentive. Gender and its association with comorbidity has also been observed. Girls were less impaired than boys on most ratings, particularly impulsivity, and girls with ADHD and anxiety disorders made fewer impulsivity errors on a computerized test of attention than girls with only ADHD (Newcorn et al., 2001). As we see, diagnosed anxiety disorders appear to be consistently associated with inattentiveness, and may relate to less impulsivity overall.

Anxiety with Comorbid Disruptive Behavior Disorders

In contrast to the strong relationship between anxiety disorders and ADHD, studies that have evaluated the impact of disruptive disorders (more specifically, ODD and conduct disorder) on anxiety disorders have found inconsistent results; some report that anxiety disorders are related to less impairing conduct problems, while others report a positive relationship between anxiety disorders and disruptive disorders (Kerr et al., 1997; Marmorstein, 2007; Pliszka, 1989). It has been suggested that this inconsistency may be due to the frequent overlap of two related but distinct aspects of anxiety/avoidance; ‘‘behavioral inhibition’’ and ‘‘social withdrawal’’ (Maughan & Rutter, 2004). Behavioral inhibition is defined as a tendency to exhibit fearfulness,

restraint and withdrawal in the presence of novel stimuli and may represent an underlying vulnerability for anxiety disorders (Morris & March, 2004). One previous study stated that behavioral inhibition may act as a protective factor, as aggressive but behaviorally inhibited boys were less likely to be delinquents. Yet, socially withdrawn but disruptive boys were at risk for social problems and mood difficulties (Kerr et al., 1997). A recent study by Bilgic and colleagues (2013) found that children exhibiting fear of anxiety symptoms related to social situations were less likely to have severe disruptive behavior symptoms, though conversely, the same study found that conduct symptoms predicted greater severity of anxiety symptoms. Of note, no relationship was detected between anxiety disorders and oppositional behavior (Bilgic et al., 2013).

Treatment Outcome

GAD, SoP, and SAD are highly comorbid with one another (Kendall et al., 2010), and can be treated with one intervention that targets similar features across anxiety disorders. Cognitive-Behavioral therapy (CBT) for anxious youth (for e.g. see *Coping Cat*; Kendall & Hedtke, 2006a; 2006b) is an extensively researched psychosocial intervention for child anxiety, and has been adapted for groups (Flannery-Schroeder & Kendall, 2000), school-based settings (Masia-Warner, Nangle, & Hansen, 2006), and adolescents (e.g., the *C.A.T. Project*; Kendall, Choudhury, Hudson, & Webb, 2002). CBT has been designated as "efficacious" (Hollon & Beck, 2013) for treating GAD, SoP, and SAD in youth according to the criteria set by the Division of Clinical Psychology of the APA (Chambless & Hollon, 1998). A number of RCTs have evidenced moderate to large

effect sizes when comparing CBT to wait-lists, placebos, or alternative treatments (Silverman, Pina, Viswesvaran, 2008).

In the largest RCT targeting anxiety disorders to date, 488 youths (ages 7-17) were randomized to receive 12 weeks of CBT, sertraline (SRT), combined sertraline and CBT (COMB), or pill placebo (Child-Adolescent Anxiety Multimodal Study (CAMS); Walkup et al., 2008). The COMB treatment condition resulted in the greatest percent of youth that were rated as "very much" or "much" improved on a global measure of impairment by independent evaluators (IE) after 12 weeks of treatment; COMB had the highest response rate (81% responders), compared to CBT alone (60% responders) and sertraline alone (55%). The response rates for the monotherapies did not significantly differ from each other, but were both superior to the placebo condition (24% responders). Rates of remission at 1 year were also greatest for COMB (46% to 68%), compared to CBT (20% to 46%) and SRT (34% to 46%), which did not differ (Ginsburg, et al., 2011). Further research will help to identify particular subsets of youth who are at greater risk to be nonresponders.

Studies that have examined principal anxiety diagnosis and baseline anxiety severity as a predictor or moderator of treatment outcome have generally yielded non-significant results (Barrett et al., 1996; Cobham et al., 1998; Hedtke et al., 2009; Kendall et al., 1997; Legerstee et al., 2010; Ollendick et al., 2009; Panichelli-Mindel et al., 2005; Puleo & Kendall, 2011; Shortt et al., 2001). Despite this, some studies have found some effects. Ost and colleagues (2001) found that more children with animal phobia were clinically improved compared to children with other types of specific phobia after a

single-treatment session procedure. Another study found that the rate of change rate was higher for children with GAD than for children with specific phobia and SAD based on mother reported MASC, but not according to other outcome measures (Manassis et al., 2002). Another study found that treatment outcomes for children with principal SoP were worse compared to children with principal GAD or SAD (Crawley et al., 2008). With regard to baseline severity of anxiety as a predictor of treatment *outcome*, several studies have not found significant relations (Berman et al., 2000, Hedtke et al., 2009; Legerstee et al., 2009; Puleo & Kendall, 2011). Of importance, a more recent examination of treatment *response* found that high baseline severity predicted poorer symptom change (Liber et al., 2010; also see Southam-Gerow et al., 2001). In this study, Liber and colleagues (2010) examined symptom reduction using the Reliable Change index in parent-reported internalizing and externalizing symptoms. Such studies highlight the need to examine treatment *response* using change indices, as it may allow for greater variability in response scores. Overall, a number of studies that have examined treatment *outcome* have not found significant differential effects based on the assigned principal anxiety disorder, though pretreatment anxiety disorder severity has been shown to be associated with greater treatment *response.* This leads to a central topic of this review: what presentations of comorbid psychopathology are likely to act as "suppressor" of treatment *response*.

General Link Between Comorbidity and Treatment Outcome

There is a common assumption that the existence of comorbid disorders complicates treatment and decreases treatment efficacy (Rapee et al., 2013). Within the

realm of child anxiety, a handful of studies have examined this issue empirically (Ollendick, Ost, Reuterskiold, & Costa, 2010; Ost, Svensson, Hellstrom, & Lindwall, 2001; Barrett, Duffy, Dadds, & Rapee, 2001; Kendall, Brady, & Verduin, 2001; Flannery-Schroeder et al., 2004; Rapee, 2003). In one of the first studies, Kendall and colleagues (2001) compared responses to treatment in 173 children 8 to 13 years old with primary anxiety disorders. The sample was divided into three groups for analyses: those with a single (anxiety) disorder, those with two or more anxiety disorders, and those with comorbid externalizing disorders. The authors found no significant differences as identified among the groups for treatment response. In another study of children 7 to 16 years old with primary anxiety disorders, the authors also did not find significant differences following treatment among groups in terms of treatment response using a similar group breakdown (Rapee, 2003). Overall, several studies have examined general comorbidity as a predictor of treatment response, and the majority have found equal treatment gains for anxiety disordered youths with or without different types of comorbid conditions (Beidel, Turner, & Morris, 2000; Berman, Weems, Silverman, & Kurtines, 2000; Hedtke, Kendall, & Tiwari, 2009; Cooper, Gallop, Willetts, & Creswell, 2008; Panichelli-Mindel, Flannery-Schroeder, Kendall, & Angelosante, 2005; Rapee, 2003; Rapee et al., 2013). In a comprehensive review of the extant literature, Ollendick and colleagues (2008) concluded that the existence of comorbid conditions does not appear to influence the response to treatment for children with primary anxiety disorders. As we will discuss, there are limitations to some of this research as well as some exceptions; part of the issue relates to the poor operationalizations of comorbidity that are limited in

scope (i.e., presence of ADHD) or that treat all comorbdity as the same (i.e., number of comorbid conditions). Before we review treatment outcome research on specific comorbid presentations (i.e., depressive, externalizing), we will discuss studies of *nonspecific* comorbidity operationalizations that have served as notable exceptions.

Despite some conclusions that comorbidity, in general, does not impact treatment outcome, several other studies may serve as exceptions. In one such study the authors showed that five of the seven children in their sample with comorbid depression failed to improve by the end of treatment (Berman et al., 2000). As such, Berman and colleagues (2000) concluded that comorbid depression could specifically interfere with therapies targeting child anxiety. It is important to note that, for the overall sample, scores on the Children's Depression Inventory (CDI) predicted an absolute outcome of treatment but failed to predict the change across treatment. Two more recent studies also indicated a possible influence of comorbid conditions on treatment outcome (Storch et al., 2008; Liber et al., 2010). Liber and colleagues (2010) found treatment response in 124 children 8 to 12 years old to have worse outcomes in those with comorbid disorders than in those with a single anxiety disorder. The authors found this effect remained when treatment response was assessed by endpoint determinants (i.e., diagnosis-free rates or clinically significant changes), but not when the response was assessed as a measurement of change over time (i.e., reliable change metrics). This data are also consistent with other findings that youth with comorbidity present with more severe psychopathology, but that the rate of improvement is not related to comorbidity. A problem with these conclusions is that they are based on comparisons of a total comorbidity variable to youth with a single

anxiety disorder. The nonsignificant findings suggest that, perhaps, researchers have not yet used nor identified the salient features in definitions of comorbidity.

Yet to be discussed, is an important question of whether treatment protocols targeting a principal anxiety disorder also influence comorbid conditions. A handful of studies have found that treatment for one anxiety disorder leads to beneficial results for other anxiety disorders (Ollendick et al., 2010; Ost et al., 2001; Kendall et al., 2001). Given the similarities among anxiety disorders, the beneficial effects of treatment to the principal anxiety disorder and comorbid anxiety disorders, suggests that treatments generalize to other anxiety areas. Though does treatment of anxiety also lead to improvements with nonanxiety comorbidity? Kendall and colleagues (2001) reported significant decreases in ADHD diagnosis after treatment of principal anxiety, but did not find significant decreases in ODD by the end of treatment. In a subsequent analysis by Flannery-Schroder and colleagues (2004) of the same RCT sample, only 32% of externalizing disorders had remitted at the end of treatment, although 68% had remitted by 7-year follow-up. In several studies assessing childhood posttraumatic stress disorder and psychosocial treatments, small to moderate effect size decreases were observed in *symptoms* of depression and externalizing problems, though comorbid diagnoses were not assessed (Silverman et al., 2008). In fact, one limitation in the study of comorbid disorder remission is that a number of RCTs to date have not assessed for comorbid *nonanxiety* disorder criteria at pre- and post-treatment. Although children with multiple disorders often benefit from treatment that specifically target the principal anxiety disorder, it is important to remember that, in terms of overall treatment response from CBT, about 30–

40% do not benefit (for a review, see Ollendick & King, 2011; Southam-Gerow, Kendall, & Weersing, 2001). Many of the youth who do not respond to intervention present with multiple disorders and co-occurring symptoms. In order to best address the needs of poor responders to the multitude of established treatments, some have stated the importance of tailoring treatments to these comorbid conditions (e.g., see Chu, 2012). Despite these concerns, it appears that treatment targeting only the principal anxiety disorder can be beneficial to comorbid conditions, especially when they are comorbid anxiety disorders, though less is known about beneficial effects to comorbid *nonanxiety* diagnoses. Also, how do comorbid nonanxiety disorders relate to the response to treatment for child anxiety and overall psychopathology? Exploratory analyses conducted by Brodman and Kendall (in preparation) examined different operationalizations of comorbidity in a sample of anxious youth receiving CBT. Variables that combine symptom severity ratings for comorbid disorders were calculated from diagnostician and from participant ratings gathered during the Anxiety Disorders Interview Schedule child and parent (ADIS-C/P) interview. Recursive partitioning and subsequent regression analyses revealed two variables that predicted a less favorable treatment *response*: presence of a comorbid nonanxiety disorder and worse pretreatment impairment (Brodman & Kendall, in preparation).

As discussed, the interpretation of various research depends on whether treatment outcome is assessed as the degree of change over time or purely as the endpoint attained (Rapee, et al., 2013). Investigation of change over time conveys whether the *process* of treatment for anxiety is affected by nonanxiety comorbidity. The investigation of

functioning at the treatment endpoint may be of more relevance to clinicians who are interested in whether their patient will be improved by the endpoint of treatment. Since research has rarely addressed the importance of comorbidity from both perspectives, future research should tackle such questions.

Comorbid Depression and Treatment Outcome

A number of studies have examined depressive comorbidity and have reported non-significant findings of its relation with treatment outcome (Kendall et al., 1997; Kendall et al., 2001; Legerstee et al., 2010; Ollendick et al., 2010; Rapee, 2003; Shortt, Barrett, Fox, 2001; Ost, Svensson, Hellstrom, & Lindwall, 2001). For example, a CBT trial of 91 youth (aged 8-16 years) that examined subclinical symptoms of depression at baseline (Legerstee et al., 2010) did not find that it predicted a differential treatment response. Moreover, an analysis by Shortt and colleagues (2001) did not show that presence of comorbid major depressive disorder at baseline predicted worse treatment outcomes for anxiety-disordered youth. Although the majority of studies found no link between comorbid depression and outcome, two studies in particular (Southam-Gerow et al, 2001; Berman, et al., 2000) found comorbid depression to be a statistically significant predictor of poorer treatment outcome. Southam-Gerow and colleagues (2001) found depressive and withdrawal symptoms to be predictive of poor anxiety treatment response when reported by mothers and teachers, but not by youth self-report. In a CBT trial examining 106 youth (aged 6-17) by Berman and colleagues (2000), the one study to find significant associations with actual depressive *diagnoses*, comorbid depressive disorder was found to be a significant predictor of poorer treatment outcome. Though, only 7 of

the 106 youth in the sample presented with a diagnosis of depression, which may undermine the validity of these findings.

In studies that have examined associations between depressive comorbidity, treatment format, and treatment outcome, researchers have *not* been able to find significant relationships (Berman et al., 2000; Shortt et al., 2001; Verduin & Kendall 2003). For example, Berman et al. (2000) did not find a significant moderated relationship between baseline comorbid depressive diagnostic status and treatment format (individual and group-based CBT formats) with treatment outcome (i.e., remission of principal anxiety disorder). Short and colleagues (2001) similarly did not find a moderated association between pretreatment internalizing symptom severity (from parent-reported questionnaires) and treatment condition (group-based family CBT and waitlist) with post-treatment diagnostic status. The lack of significant findings is likely due to limitations of sample size and limited diversity of the anxiety-disordered sample in such studies. In a recent review of predictors and moderators of treatment outcome in anxiety-disordered youth and comorbid depressive diagnoses, Nilsen et al. (2013) concluded that the majority of studies indicate non-significant associations between comorbid psychopathology and treatment outcome. According to Nilsen et al. (2013), these findings suggest that no consistent co-occurring depressive psychopathology factors have been associated with treatment outcome.

What are some potential explanations for lack of significant findings with regard to the role of depressive symptomatology with treatment outcome? It is possible that various CBT treatment components may generalize across both anxiety and depressive

symptomatology. Description of treatment processes in trials that address comorbid depression highlight the importance of learned skills, like cognitive restructuring, that are taught within the context of anxious self-talk and then may be applied to supplemental problem areas (e.g., depressive thoughts: “I can't cope”; “I'll never get better”) (Hudson, Krain, & Kendall, 2001). Exposure exercises for anxiety-disordered youth are generally targeted toward anxiety-provoking situations, but therapists are also able to use such opportunities to challenge depressive or negative views (Hudson et al., 2001). This explanation of individual CBT generalizability is appealing but offers few specific recommendations for implementation with specific youth (Kendall & Beidas, 2007; Nock, Goldman, Wang, & Albano, 2004).

It has been suggested that among the comorbid disorders in anxiety-disordered youth, comorbid mood disorders have been found by some to be associated with the worst overall presenting psychopathology and subsequent response to treatment (Rapee et al., 2013). Unfortunately, few previous studies have had the sample size to look at the distinct associations of comorbid mood disorders. Though, as discussed earlier, youth with principal depression have higher rates of comorbid anxiety, and CBT trials with such samples are likely to have a higher co-occurrence of these disorders. When looking at CBT trials for youth *with principal mood disorders* and comorbid anxiety, adolescents with depression evidenced worse treatment outcome when they present with comorbid anxiety disorders (Rapee, Schnierin, & Hudson, 2009). As discussed earlier, youth with co-occurring mood and anxiety disorders are more likely to be older and female. However, worse outcomes were found for this group even when these demographic

factors were statistically controlled (see Rapee et al., 2009). Although children with mood disorders are likely to be characterized by additional difficulties (e.g., negative thinking) only the endpoint of treatment has been found to be impacted by comorbid mood disorders and not the rate of change (Rapee et al., 2013). Even so, the majority of research still has not replicated these findings, especially in a sample of youth with principal anxiety disorder. It is possible that youth with comorbid mood disorders appear to be generally more severe in their clinical presentation and may be more resilient or slow to change. These inferences are also consistent with previous research that has shown youth with co-occurring mood and anxiety to have worse overall severity than children with either disorder alone (Ezpeleta & Toro, 2009). Clearly, more research is needed in this area to help elucidate how comorbid depression complicates treatment, as it may *not* relate to worse treatment endpoints, and therefore may impact the course of treatment in more subtle ways, particularly the time-course of change.

Comorbid ADHD and Treatment Outcome

Pharmacological intervention, such as stimulant medication, is the most widely used treatment for children and adolescents with ADHD and the majority of youth show favorable responses to stimulants (Solanto, Arnsten, & Castellanos, 2001). However, a sizeable portion (i.e., 20%-30%) show no response or experience side effects (Swanson, McBurnett, Christian, & Wigal, 1995). As such, some primary care physicians express concerns about prescribing medications to children and adolescents (Wilens et al., 2008). Anxiety disorders, when they are comorbid with ADHD, require new targets and needs

for pharmacological treatment (Hammerness et al., 2010). For example, children and adolescents with ADHD and comorbid anxiety disorders respond differently to treatments (Baldwin & Dadds, 2008), and a number of studies have demonstrated the diminished role of stimulants in individuals with comorbid anxiety compared with ADHD alone (Tannock, Ickowicz, & Schachar, 1995; Ter-Stepanian, Grizenko, Zappitelli, & Joober, 2010). Such research highlights the need for psychosocial intervention in cases when anxiety disorders and ADHD co-occur.

Conventional CBT interventions typically aim to provide people with insight into the roles their thoughts, feelings, and actions play in the generation and maintenance of their anxiety symptoms. CBT assists youth in identifying unhelpful thoughts that trigger symptoms and encourages them to challenge these thoughts in ways that reduce their emotional influence (Benjamin et al., 2011). Although there is evidence that CBT is efficacious for adults with ADHD (see Safren et al., 2005; Safren et al., 2010), its application with children and adolescents with ADHD, or ADHD with comorbid anxiety, has been less extensive. Of the few studies conducted, Costin and colleagues (2002) recruited five boys (aged 10-12 years) with ADHD-Combined type, Oppositional Defiant Disorder and anxiety into an 8-week CBT family-based intervention. Overall, high levels of satisfaction with the program were reported but little change in symptomatology was evident. Verreault and colleagues (2007) evaluated a 10-week CBT family-based anxiety protocol with 10 children (8 boys and 2 girls, aged 8-12 years) with ADHD and anxiety. This study also included an ADHD psychoeducational session focused on parents.

Overall, parents and children reported reductions in anxiety, but parents did not report any changes in their child's ADHD symptoms.

The Multimodal Treatment of ADHD Study (MTA Study; MTA Cooperative Group, 1999a; Molina et al., 2009) was one of the first studies to examine ADHD treatment in relation to comorbidity in a large sample of youth, using medication, behavioral treatment, their combination, and community comparison conditions. With regard to comorbid anxiety, the study found a differential response to behavioral treatment when parent-reported child anxiety was present (MTA Group, 1999b). The authors report that children with ADHD and comorbid anxiety actually responded more positively to behavioral treatment on hyperactivity/impulsivity and internalizing problems, than did children without parent-reported anxiety (MTA Cooperative Group, 1999b). The MTA Study authors explained that the behavioral treatment focused on ADHD symptoms might contribute to reducing internalizing problems related to anxiety. The authors further noted that behavioral interventions designed to treat anxiety, like CBT, might have resulted in even greater benefits, given that the MTA Study interventions were designed to target ADHD-related behaviors and not anxiety. The MTA Study offered the unique ability to examine effects of comorbidity on treatment outcome, though this study was primarily implemented to address aggregate treatment outcomes for principal ADHD. As such, little is known about individual-level response and processes of change over treatment for children with co-occurring anxiety and ADHD (Jarrett et al., 2013). Overall, few studies to date have examined individual processes of change in the psychosocial treatment of principal ADHD and anxiety. As

discussed, youth in the MTA Study showed an improved response to behavioral treatment for ADHD when anxiety was present; however, little is known about why such results were observed.

Studies that have examined psychosocial treatments for youth with principal anxiety and externalizing comorbidity (Southam-Gerow et al., 2001; Manassis et al., 2002; Kendall et al., 1997; Kendall et al., 2001; Rapee, 2000) have generally reported non-significant results when examining differential treatment outcome of youth with or without comorbid externalizing symptoms and/or disorders. More specifically, Southam-Gerow and colleagues (2001) did not find that maternal-reported externalizing symptoms in youth receiving CBT for principal anxiety diagnoses were significantly associated with treatment response based on diagnostic criteria of anxiety. Manassis and colleagues (2002) did not find any significant association of parent-reported hyperactivity symptoms or presenting comorbid diagnoses with differential treatment outcome of anxiety-disordered youth based on a clinician-rated global improvement scale. Kendall, Brady, and Verduin (2001) examined whether the presence of comorbid diagnoses (including externalizing disorders) were associated with treatment outcome measured by the presence or absence of the principal anxiety disorder at posttreatment, and they also did not find a significant association. Yet, symptoms of comorbid ADHD, as determined by questionnaires, may be reduced following treatment for child anxiety (Kendall et al., 2001; Levy, Hunt, & Heriot, 2007).

In a study of concurrent ADHD and anxiety treatment Jarrett and Ollendick (2012) examined a combination of parent management training for ADHD and family-based cognitive-behavioral therapy for anxiety. The report included eight children aged 8-12 with ADHD-Combined and at least one of three major anxiety disorders (i.e., GAD, SAD, SoP). Sessions lasted approximately 90 minutes, and the treatment consisted of 10 weekly sessions. The report of cases included weekly measures of ADHD and anxiety symptoms along with pretreatment, midtreatment, and 1-week posttreatment assessments. Children were randomly assigned to a baseline phase lasting 2, 3, and 4 weeks and then received treatment after that period; the authors used an approach for analyzing single-case data (i.e., Simulation Modeling Analysis; Borckardt et al., 2008) to examine changes in the level of symptoms in comparison to the individual baseline period. Repeated weekly measures using these analyses revealed improvements in ADHD and anxiety symptoms, although the gains were generally more limited for ADHD symptoms (Jarrett & Ollendick, 2012). Treatment gains were determined using a method for calculating "clinical significance" (as described by Jacobson & Truax, 1991) as well as a Reliable Change Index. In a secondary analysis, Jarrett (2013) examined slopes of symptom change and temporal relationships among symptom domains, again using simulation modeling analysis (Borckardt et al., 2008). They found results that generally supported declining slopes for ADHD and anxiety and greater concurrent change between anxiety and hyperactivity/impulsivity than for anxiety and inattention symptoms. Few changes were found for neurocognitive functioning, but some changes were found for parent–child relationships and family functioning (Jarrett, 2013). Although such research begins

to address important questions, the small sample size in these studies necessitates replication of these findings with an independent, and larger, sample.

A number of treatment studies for ADHD and co-occurring anxiety have been designed to address questions relating to overall outcome of groups by principal diagnosis rather than through an examination of individual-level change. As noted by some authors (Barlow & Nock, 2009; Borckardt et al., 2008), single-case designs may offer unique insights into the processes of change that occur at the individual level over the course of treatment. Overall, there has been little evidence that comorbid ADHD in anxiety-disordered youth moderate outcomes (e.g., Flannery-Schroeder et al., 2004). As noted by Ollendick et al. (2008) it seems that anxious youth with comorbid externalizing problems may even sometimes respond better to anxiety treatment than their non-comorbid peers (Costin & Chambers, 2007; Kazdin & Whitley, 2006).

In another study examining CBT treatment for ADHD, Antshel and colleagues (2012) evaluated 68 adolescents with ADHD in a 13- to 16-session CBT intervention program comprising psychoeducation, training in organization and planning, reducing distractibility, cognitive restructuring, reducing procrastination, and improving communication. It is important to note that all participants were receiving concurrent pharmacotherapy. Parental and teacher ratings indicated improvements in adolescents with ADHD only, ADHD + Anxiety disorder, and ADHD + Depression across several symptoms and domains. The participants also evidenced improvements in school grades and attendance, however many of these adolescents did not normalize their functioning and remained symptomatic or functionally impaired in one domain. The study did not

examine change in anxiety-specific symptoms, though reductions in internalizing symptoms were found in parent and adolescent reported questionnaires. Of particular importance, the authors found that adolescents with co-occurring ADHD and anxiety disorder were the subgroup that evidenced the greatest symptom improvement on parent and teacher-reported measures of symptoms and functioning (Antshel et al., 2012). As the authors state, this indicates that those with this type of comorbidity (anxiety disorders) are able to benefit from CBT. Moreover, the need for psychosocial interventions is especially important as some youth cannot tolerate stimulant medications, stimulants run the risk of poor compliance and misuse, and adolescents may resist pharmacological treatment in favor of more independence (Antshel et al., 2012). In another project by Houghton and colleagues (2013) an 8-week CBT treatment designed specifically to target comorbid anxiety in a group of adolescents with principal ADHD. Nine adolescents received weekly CBT. Participants were asked to self-record levels of anxiety at four time-points, and data at post-treatment indicated significant reductions in self-reported anxiety using the Multidimensional Anxiety Scale for Children (MASC). The authors conclude that there is potential efficacy for a CBT program used for the treatment of comorbid anxiety in adolescents with principal ADHD (Houghton et al., 2013).

In a recent group CBT trial for anxiety-disordered youth in low income communities, de Souza and colleagues (2013) found significant improvements in self- and parent-rated measures of anxiety, as well as externalizing symptoms, but did not find such changes for quality of life. It is important to note that 30% of the sample met

criteria at pretreatment for comorbid ADHD, but 0% of the sample met diagnostic criteria for depression at pretreatment. It is notable that the authors found a reduction in externalizing symptoms, but given the lack of depression in their sample at pretreatment, they did not find any changes in depressive symptoms. Although externalizing and anxiety symptom levels were both found to decrease, the authors were not able to test whether presence of pretreatment externalizing diagnosis was associated with treatment outcome (de Souza et al., 2013).

In sum, a substantial proportion of youth with ADHD also present with anxiety. CBT is recognized as an effective mode of therapy for adults and children, and recent evidence indicates favorable outcomes for youth with anxiety and co-occurring ADHD. In particular, anxiety symptoms appear more likely to improve with CBT than do ADHD symptoms. Given the scarcity of literature, future studies are needed to better understand the treatment of co-occurring anxiety and ADHD and the associated time course of change (Jarrett et al., 2013).

Comorbid Disruptive Behavior and Treatment Outcome

As discussed, studies examining treatment outcome in principal anxiety have not found significant impact with respect to comorbid disruptive behavior. This is partly due to lesser rates of comorbidity between anxiety and disruptive behavior, less overlap of symptoms, and limited sample sizes to examine such effects. Although there is scant research that has looked specifically at treating anxiety and comorbid disruptive behavior, some therapies have targeted underlying factors that may contribute to the onset and maintenance of such comorbid psychopathology (Fraire et al., 2013). Therefore our

discussion in this section will briefly highlight treatment approaches that address anxiety and co-occurring disruptive behavior.

It has been suggested that anxious children are more likely to show difficulties in managing anger and sadness, and that the regulation of a range of emotions should be a focus for treatment (Suveg et al., 2009). Emotion regulation treatments are one therapy option that have been developed for internalizing symptoms and combine emotion-focused interventions with CBT (Suveg et al., 2009). Emotion-focused CBT (ECBT) systematically integrates emotional concepts with traditional CBT methods in order to enhance emotional understanding and emotion regulation (Suveg, Kendall, Comer, & Robin, 2006). Traditional CBT for anxiety generally targets the regulation of worry, though emotion-focused interventions and can possibly address issues related to anger and sadness (Seligman & Ollendick, 2011). Emotion-focused therapies could also be particularly beneficial for anxious children with comorbid oppositionality (Fraire et al., 2013). Given the underlying transdiagnostic process of emotion dysregulation in ECBT, and the way ECBT addresses reactions to negative emotional states and subsequent maladaptive responses (Suveg & Zeman, 2004), it is an intuitive treatment choice.

CBT has been used in the treatment of oppositional children as well, particularly in managing anger (e.g., Coping Power Program: Lochman, Boxmeyer, Powell, & Wells, 2010). Problem-solving skills training targets specific information processing deficits, particularly thinking through consequences and selecting appropriate solutions (e.g., Webster-Strattion, Reid & Hammond, 2004). In the anxiety literature, research on parenting behaviors focus on parents' own anxiety and over-protectiveness, which may

impact a child's anxiety. When parenting behaviors are targeted in treatment, they are often in the context of encouraging the child to be brave and independent, which can help a parent reduce their over-protectiveness (Rapee, Schniering, & Hudson, 2009). There are also treatments designed to help parents reduce their own stress in order to help their children. For example, Kazdin and Whitley (2003) evaluated the effectiveness of applying an additional component of treatment, focused on parental stress, to an established parent management training and parent-problem solving protocol. They found that the parent stress component enhanced treatment outcome and reduced parental barriers to treatment. This type of additional intervention speaks to the associations between a child and other social–environmental factors, and can be beneficial for anxious children with comorbid ODD.

Although it is clearly important to target the child's behavior that contributes to both anxiety and ODD, children do not live in a vacuum. It is important to consider the parental influences on the child when treating such symptoms. Collaborative Problem Solving (CPS: Greene & Ablon, 2006) is a treatment approach that addresses both child and parental factors, and actively incorporates parent practices in the treatment process. CPS is designed to enhance a parent's ability to express warmth through the development of listening skills and the expression of empathy (Greene & Ablon, 2006). Additionally, as parents learn the CPS model, they are able to demonstrate for their children more adaptive ways to solve problems. However, for some children, being able to have a direct conversation with parents is a novel concept, especially for a child who experiences a great deal of emotional dysregulation and oppositionality (Fraire et al., 2013).

Issues Related to the Concept of Comorbidity

Comorbidity has been shown to be quite widespread, and yet the role of comorbid psychopathology has seldom been found to relate to CBT treatment for principal anxiety. One possible reason for this involves the limited scope and the failure to identify salient operationalizations of comorbidity for anxiety-disordered youth. The following sections consider issues related to the *concept* of comorbidity .

Definitions of Comorbidity

Lilienfield and colleagues (1994) made the argument that the term comorbidity should not be used in the psychopathology literature because it creates confusion as to what meaning is intended, particularly "co-occurrence" or "covariation." Co-occurrence is simply the presence of two diagnoses while covariation is the presence of two diagnoses occurring more often than by chance (McGee, 2007). The question of primary diagnosis is also relevant in understanding comorbidity research. Primary diagnosis can refer to the disorder that appeared first in a child's history. The term principal diagnosis refers to the diagnosis that is most salient to the child, the diagnosis that is the focus of treatment, or the diagnosis that is causing the most impairment in a child's life. This raises the question of whether treatment should be focused entirely on the principal anxiety disorder, or if it should be tailored to the comorbid issues. These questions have been raised and debated; some have developed treatments that cut across diagnostic categories (Wilamowska et al., 2010), whereas many others have tailored specific treatments for particular disorders. Lilienfield's (1994) definitions of "co-occurrence" and "co-variation" are often confused. In fact, comorbidity of anxiety disorders,

depressive, and externalizing disorders in many cases more closely resembles co-variation and not co-occurrence; this is due to the high overlap of symptoms and the influence of one disorder to exacerbate the onset of another.

The complexity and wide variability of clinical presentations and the association patterns between disparate psychopathologies do not allow for an exclusive model to explain the phenomena of comorbidity (Issler, Sant'Anna, Kapczinski, & Lafer, 2004). A complete explanation of all comorbidity theories are beyond the present scope, but a review of one explanation of comorbid operationalizations for anxiety and depressive disorders merit mention. Seligman and Ollendick (1998) proposed that frequent: (1) comorbidity between anxiety and depression in youth is due to the overlap in definitions; (2) comorbidity between anxiety and depression in youth is due to the fact that anxiety and depression represent two indicators of a single construct; (3) comorbidity between anxiety and depression in youth is due to the overlap in risk factors; (4) anxiety causes or puts youth at risk for depression. These explanations appear to have merit: we know that overlapping symptom criteria is problematic, and that anxiety and depression are more likely to represent a single construct in younger children and when anxiety/depressive symptoms co-occur at subdiagnostic levels (Ollendick et al., 2003). Moreover, much research involving longitudinal studies of disorder onset support the notion that primary anxiety puts youth at risk for later depression (e.g., Espejo et al., 2007). As such, several researchers have also begun to question and challenge the current diagnostic system. Similar to Seligman and Ollendick (1998), Lilienfeld (2003) has stated that a substantive reason for comorbidity is that one disorder causes another. As such, the presence of

anxiety may moderate the relationships between non-anxiety disorders as a result of shared common factors such as inhibitory control deficits, genetic factors, and similar symptoms (Boylan et al. 2007). For instance, negative affect explains, in part, comorbidity between anxiety and depression (Clark & Watson, 1991; Jacques & Mash, 2004). While irritability and negative affect partly explain oppositional and aggressive behavior, leading to the simultaneous occurrence of anxiety, and disruptive behavior disorders (Ezpeleta et al., 2009). Anxiety and depression are difficult to discriminate in community samples, but as symptomatology reaches diagnostic levels, they are easier to discriminate. This notion is supported by factor analyses of youth, whereby youth below diagnostic threshold for anxiety and depressive disorders were found to map onto a single dimension of anxiety and depressive symptoms (Gurley et al., 1996). Such ideas suggest the possibility that subclinical symptoms of depression (i.e., irritability, moodiness) may not be easily distinguished from anxiety.

Homotypic and Heterotypic Comorbidity

Angold, Costello, and Erkanli (1999) stressed the importance of addressing both homotypic comorbidity—concurrent disorders similar in nature such as social phobia and specific phobia, and heterotypic comorbidity—disorders that are essentially different in nature. Research that has looked into associations between anxiety disorders has found a considerable amount of homotypic and heterotypic comorbidity in youth anxiety (Ezpeleta et al., 2009; Lewinsohn et al., 1997). As discussed earlier, one nonanxiety disorder that is most commonly associated with anxiety (GAD, in particular) is depression, possibly due to the fact that they both share the core features of negative

affect (Clark & Watson, 1991). Although depression is more "heterotypic" than say other comorbid *anxiety* disorders, the possibility of depression and anxiety sharing particular features leaves room for depression to be considered as a somewhat homotypic comorbidity for certain anxiety disorders (i.e., GAD, SoP). ADHD is another heterotypic comorbidity that can be considered a common comorbid condition for principal anxiety disorders, while the relationship of other disruptive behavior disorders are varied and not as prevalent (López et al. 2004; Masi et al. 1999; Mattison & Bagnato, 1987; Verduin & Kendall, 2003). This pattern suggests that, if anything, disruptive behavior disorders and anxiety disorders may have the least in common with each other (most heterotypic) and most likely to truly co-occur rather than "co-vary," among the disorders reviewed.

Another question is whether certain principal anxiety disorders are more likely to be associated with other anxiety comorbidities (i.e., homotypic comorbidities). With regard to the nature of the big three child anxiety diagnoses, these disorders have different presentations and overall psychopathology that may (by the very nature of their disorder criteria) be more associated with more homotypic comorbid diagnoses/symptomatology. It is possible that given the nature of SAD (i.e., being away from loved ones or from home), that there is a greater likelihood of additional specific fears (e.g., the dark, cars, or animals). Similarly SoP is characterized by anxiety focused on social interactions and negative evaluation by others, and may be less associated with specific fears, but more related to general worry about future events and social performance. Last, Strauss, and Francis (1987) found that total number of concurrent diagnoses did not differ among children with principal diagnoses of overanxious disorder

(OAD), avoidant disorder, separation anxiety disorder (SAD), or major depressive disorder. Children with principal SAD were least likely to have another comorbid anxiety disorder. The authors of this study, unfortunately due to small sample sizes, were not able to examine patterns of specific disorder comorbidity. Findings from Verduin and Kendall (2003) found disparate patterns—children with primary SAD were found to have a higher number of comorbid diagnoses than those with primary GAD or SoP. Children with primary GAD and SoP had similar numbers of comorbid diagnoses. Moreover, children with primary SAD were more likely to have comorbid specific phobia than children with primary SoP. The authors were unable to find differences between SAD and GAD or between GAD and SP. The high overall rates of homotypic comorbidity within and among the anxiety disorders suggest that the big three anxiety disorders are more similar than different regarding the phenomenon of comorbidity.

Heterotypic comorbidity of anxiety disorders has been found to have both positive and negative associations with overall difficulties (Mamorstein 2007). Maughan and colleagues (2004) found that the presence of comorbid anxiety diminished the dysfunctional behavior associated with principal oppositional defiant disorder, yet (as discussed) anxiety is associated with greater rates of depression and ADHD. Mood disorders have been found to most likely occur in children with primary GAD or SoP (Essau, 2003; Masi et al., 1999). These findings are consistent with the phenomenon that GAD often precedes depression (Brady & Kendall, 1992), and more recent literature implicating SoP as a risk factor for later depression (Dalrymple & Zimmerman, 2011). Several associated questions quickly become raised—is the higher rate of mood

dysregulation in GAD children due to ruminative cognitive styles in children with GAD? Also, is this association due to age effects, whereby older children (who are more likely to experience depression) are subsequently more likely to have already been diagnosed with GAD or SoP? Does GAD or SoP in some cases cause a biological "kindling effect" whereby the experience of chronic negative affectivity, is a risk factor to increased stress reactivity and the onset of depression (as suggested by Espejo et al., 2007; Keenan et al., 2009)? Children with principal SAD have been associated with the lowest comorbid rates of mood disorders (Verduin & Kendall, 2003), which is likely due to the generally younger onset for SAD. As such, age effects should be considered before jumping to conclusions that SAD, or any other disorder for that matter, has little relation to MDD.

Overall when considering heterotypic comorbidity, the shared features and high comorbid rates between anxiety, depression, and ADHD are problematic and don't support such disorders as being truly distinct. In line with Lillienfield's (1994) criteria, these difficulties appear to "co-vary" rather than truly co-occur. The issue remains if there is a certain clinical presentation or subtype of anxiety, depression, and/or ADHD that represent a more heterotypic and true comorbidity.

Categorical and Dimensional Operationalizations

A categorical system for defining comorbidity allows for ease of communication (Bubier & Drabick, 2009) whereas a dimensional model may add important information (Drabick & Kendall, 2010; Cummings, 2010). But how best to operationalize comorbidity? What "type" or "severity" of comorbidity is predictive? We have discussed

how comorbid depressive diagnoses among youth with anxiety disorders "may" negatively impact outcome (see Berman et al., 2000; Seligman & Ollendick, 1998). Though in the same report by Berman and colleagues (2000), differences were not found between responders and non-responders in terms of total number of diagnoses, comorbidity with externalizing disorders, and comorbidity with other anxiety disorders. Although a comorbid depressive diagnosis did not predict poorer CBT outcomes for anxious youth, O'Neil and Kendall (2012) found that co-occurring depressive symptoms coded in sessions were associated with poorer outcome. Novel methods for operationalizing "dimensional" symptomatology may lead to capturing co-occurring psychopathology in a more meaningful approach.

Research has examined the relation of the *number* and *type* of comorbid diagnoses with treatment outcome, but not much is known about the role of co-occurring disorder *severity* on treatment outcome. Comorbid disorder severity, a dimensional operationalization, may impact the strength and/or direction of treatment effects. Comorbid severity may inform "for whom" (after Kiesler, 1966) treatments work best (Kendall & Comer, 2011; Kraemer, Wilson, Fairburn, & Agras, 2002). Considering severity of comorbid disorders as a moderator is important because "comorbid severity" may be a patient characteristic existing prior to intervention that influences whether CBT targeting the principal anxiety will produce improvement.

Identification of subclinical psychopathology, as noted by Meehl (2001), could help identify differential treatment response. Subclinical distress may be important in childhood and adolescence because symptoms can vary from transient to full-blown

disorders (Beesdo, Knappe, & Pine, 2009). Unfortunately, very little research has examined the effect of co-occurring *subclinical* psychopathology on treatment outcome for anxious youth.

Differences in how outcome is defined in treatment studies also raise important questions. Some prior research has examined improvement using the diagnosed principal disorder. As discussed, comorbid diagnoses have often been examined as categorical variables (i.e. presence of comorbid disorders) despite many overlapping features between disorders (Brown & Barlow, 2009). In fact a large number of early studies examined comorbidity as simply the "number" of comorbid conditions, which was not likely to be associated with a differential treatment response. Other measures of improvement and outcome have varied across studies: some have examined the percentage of participants who are diagnosis-free at posttreatment, others have used clinician global ratings or parent, teacher, and self-report measures (Ollendick et al., 2008) as dimensional variables of improvement. These strategies are reasonable, but variability in findings may depend on how outcome is defined (Ollendick et al., 2008). Also problematic, is the fact that informant discrepancies in the assessment of child psychopathology often exist between different reporters (De Los Reyes & Kazdin, 2005). Although the use of global improvement as a primary outcome measure in an RCT can be questioned (e.g., De Los Reyes, Alfano, & Beidel, 2011), assessment of global functioning, from an independent evaluator, may be especially appropriate when considering the impact of comorbid conditions on treatment outcome. Global functioning measures (a broad dimensional measure like the CGAS) when used in conjunction with

categorical measures (diagnosis/remission of diagnostic criteria) may prove to best capture comorbid psychopathology and its relation to treatment outcome.

Few studies have yet to compare different methods of operationalizing comorbidity for predicting improvement following treatment. One study (Brodman & Kendall, in preparation) hypothesized that dimensional operationalizations of comorbidity would best predict a less favorable treatment response for anxiety-disordered youth. Exploratory modeling yielded surprising results. The categorical presence of a non-anxiety disorder at baseline predicted worse treatment response, than all other dimensional measures of comorbidity that were tested. Though, the presence of a comorbid nonanxiety disorder was only impactful for youth with more than mild overall psychopathology. Additionally, youth with both a comorbid non-anxiety disorder combined with severe comorbid anxiety were found to be the worst performing subset of youth in the treatment. This study shows the potential utility of combined categorical and dimensional approaches when considering treatment outcome research. Moreover, combined categorical-dimensional approaches may better capture comorbid psychopathology during assessment.

Time-Course of Change

The time-course of change is an important consideration in treatment outcome research. For example, *when* do symptom reductions of principal anxiety occur in relation to reductions in heterotypic or homotypic comorbidities? Such time-course information can be valuable in understanding the impact of comorbidity on treatment outcome.

(Jarrett & Ollendick, 2013). With regard to co-occurring ADHD and anxiety disorder, some evidence suggests that decreasing symptom slopes for ADHD and anxiety are significantly associated with greater concurrent change between anxiety and hyperactivity/impulsivity than for anxiety and inattention symptoms (Jarrett & Ollendick, 2013). In other studies of anxiety disorders and concurrent ADHD, it has been suggested that psychosocial treatment had an earlier impact on anxiety, which in turn helped with ADHD symptoms (Antshel et al., 2012). Moreover, there is evidence, as found by Rapee and colleagues (2013) that the endpoint of treatment response was significantly impacted by comorbid mood disorders, though no other researchers to our knowledge have substantiated this finding in anxiety-disordered youth receiving CBT.

Gaps in the literature with regard to the impact of comorbidity on treatment time-course remain. For example, how might heterotypic comorbidities be related to a concurrent change in symptoms—perhaps when ADHD/depression and anxiety symptoms are affected by a shared influence (e.g., dysfunctional parent–child relationships), a change in that influencing factor may result in concurrent symptom change (Jarrett & Ollendick, 2013). In such scenarios, categorical operationalizations of heterotypic comorbidity appear less meaningful, whereas dimensional/contextual measures of family burden and dysfunction may be the more salient "co-occurring difficulty" with regard to the time-course of treatment response.

Flexibility of Treatments

When addressing comorbid conditions in an anxiety treatment, flexibility is typically encouraged. The phrase "flexibility within fidelity" (Kendall & Beidas, 2007) has been used to emphasize flexibility and judgment in the treatment of complex cases within manual-based therapy. In this approach, a therapist chooses an empirically supported treatment manual designed to address a target disorder and then uses judgment to adapt treatment strategies to meet the individualized needs of each client. Although Chu and colleagues (2012)noted that the flexibility literature often fails to specify how much flexibility is ideal or when flexibility is most appropriate, guidelines have been proposed (Kendall et al, 2008) indicating that CBT for anxiety must include homework and exposure tasks. Further, if a clinician accommodates or reinforces a child's anxiety, or fails to acknowledge a completed homework task and apply rewards, that clinician would be departing from the essential CBT principles and be outside flexibility. Research that has studied flexibility using observational methods, has demonstrated that high levels of therapist flexibility can be obtained within high levels of treatment fidelity, yet little evidence directly links such flexibility with improved treatment outcomes (Chu & Kendall, 2009; Kendall & Chu, 2000).

Family and Interpersonal Factors

Parent–child relationships and family functioning is most certainly an important contextual factor that may be related to worse treatment outcomes. Children with comorbid anxiety conditions are significantly more psychologically distressed (Essau, 2003) but only a few families seek treatment for their problems (Essau, Conrado, &

Petermann 2000). The attenuating or aggravating role of anxiety when it co-occurs with others disorders could facilitate or hinder families from seeking professional help for a child's problems and a physician's decision to prescribe medication. Although a large literature has documented difficulties in the parent–child relationship for ADHD (e.g., see Johnston & Mash, 2001), subsequent researchers have found additional family relationship difficulties for children with comorbid ADHD and anxiety (Jarrett & Ollendick, 2008; Kepley & Ostrander, 2007; Pfiffner & McBurnett, 2006). For example, Kepley and Ostrander (2007) found that children with ADHD and anxiety exhibited similar levels of family conflict as children with only ADHD, but that greater impairment (i.e., lacking independence and an overly controlling environment) were exhibited in families of children with ADHD and co-occurring anxiety. Pfiffner and McBurnett (2006) found that parents of children with ADHD and anxiety also exhibited diminished positivity in parenting style and greater over-protectiveness than families of children with ADHD only. Overall, the literature in this domain suggests that comorbid conditions (particularly ADHD and anxiety) may be associated with greater family dysfunction. Further research should examine how family dynamics and conflict change over time or as a result of successful treatment for comorbid conditions.

Summary and Future Directions

Examination of the literature yields important areas where the collective knowledge of comorbidity and its role on treatment is either inconsistent or non-existent. Most research that has examined the role of comorbidity on treatment response by evaluating changes across time on continuous measures did not demonstrate that

comorbid conditions decreased treatment efficacy for anxious youth. Of note, homotypic anxiety comorbidity has not been found to negatively impact treatment compared to anxious youth with only one anxiety disorder. The only studies that found a relationship of heterotypic comorbidity with treatment outcome may have been idiosyncratic, due to a small sample of youth with heterotypic comorbidity (as in Berman et al., 2000). In cases where heterotypic comorbidity was found to be associated with treatment outcome (e.g., Liber et al., 2010; Rapee, (2013), the findings indicated that comorbidity related to differential outcome when assessed by endpoint determinants (i.e., diagnosis-free rates); though such studies also found an association of heterotypic comorbidity with worse overall pretreatment severity, which is an important confound in the examination of "endpoint determinants." Studies that find an association of comorbidity with regard to treatment "response" or rates of change over time may be more meaningful. As such, it *is* possible, and likely, that heterotypic comorbidity is associated with worse pretreatment overall severity, but it remains unclear if comorbidity is associated with *slower* improvement. Furthermore, questions remain for the effects of anxiety-targeted treatments on nonanxiety comorbid conditions. Although a number of psychosocial treatment studies indicate minimal (if any) relation of CBT with clinical *remission* of comorbid externalizing diagnoses, several studies support reduction in associated externalizing symptoms. Given reductions in externalizing *symptoms* over the course of CBT, it is possible that treatment addresses other contextual factors that result in improvements in some externalizing symptoms (i.e., impulsivity). Treatment (CBT) may

be less effective for other externalizing symptoms (i.e., inattentiveness) (as in Jarrett, 2013).

Currently, research that delves into these practical issues are impacted by important limitations. First, very few studies have examined comorbidity and treatment response with respect to both rate of change and treatment endpoint (Rapee et al., 2013). In addition to testing associations of comorbidity with differential outcomes, it is important to know if comorbidity is differentially associated with the time-course and rate of change. Second, sample sizes in a many of the reviewed studies were underpowered to effectively examine comorbidity as a moderator of outcomes. Without a properly powered sample of anxiety-disordered youth with comorbid psychopathology, a more detailed analysis of heterotypic comorbidity and the influence of clinical-level depressive/externalizing disorder severity has not been possible. Last, a number of studies were further restricted by age, and did not include adolescents which limits the number of youth with possible comorbidities, especially comorbid mood disorders.

Future research, using properly powered samples, should examine a multitude of factors that could impact comorbid psychopathology and treatment outcome. With regard to comorbid depression, questions remain as to the role of age and how anxiety with depression may be associated with differential treatment outcome. Furthermore, research has indicated that, specifically, depressive symptoms may be an important factor in its association with anxiety. Analyses that combine categorical and dimensional approaches may be especially important in capturing the relation of these complex presentations. With regard to comorbid externalizing problems, further study of anxious youth with co-

occurring impulsivity and disruptive behavior is needed, as these youth may be quite distinct (truly heterotypic) from anxious youth with only co-occurring inattentiveness. Further analysis should examine individual-level change, rather than simply examining aggregate outcomes, as many have done. Lastly, parenting behaviors and the child-parent relationship may serve as a further co-occurring issue that resolves over the course of treatment or serves as a predictor of differential outcome.

CHAPTER 3

RESULTS

Power Analyses

No previous evaluations of the relationships between comorbidity and treatment condition on the time-course to treatment response have been conducted. As such, no specific estimates of the effect size are available. However, data regarding *overall* survival rates by treatment condition are available. Survival analysis can be used to examine change over time in relation to achieving an "event" (Maki, 2006), and in this analysis the event will correspond to the time-point that participants achieve treatment response as measured by the CGI-I. In the first report of CAMS outcomes, Walkup and colleagues (2008) reported that, 80.7% of youth receiving COMB, 59.7% of youth receiving CBT, and 54.9% of youth receiving SRT achieved this event after their 12-week treatment as measured by independent evaluators. With regard to trajectories of treatment response, an analysis of CAMS data suggests that substantial improvements for youth who received CBT do not occur until after moderate level exposure tasks (Peris et al., in preparation), which is toward the end (i.e., ~week 10) of CBT. With regard to SSRI treatment, there is reason to believe that treatment response occurs earlier than for CBT. Medication RCTs have observed that anxiety symptoms become significantly improved by the 6th week (e.g., Liebowitz et al., 2003).

A power analysis (as described by Maki, 2006; Schoenfeld & Richter, 1982; calculated using PS Version 3.0 retrieved from

http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize) assessed the estimated power of our sample. Our planned analysis has 139 participants in the CBT condition and 133 participants in the SRT condition, an accrual interval of 2 weeks, and a time interval following the accrual interval of 12 weeks. Estimates of the median survival time of the CBT condition is 10 weeks. If the true median survival times of the CBT and SRT condition are 10 and 6 weeks, respectively, then we will be able to reject the null hypothesis that the survival curves are equal with probability (power) 0.933. The Type I error probability associated with the test of this null hypothesis is 0.05.

Preliminary Analyses

Examination of demographic factors and child characteristics indicated that female participants were associated with faster treatment response time-course than males (B = -.244, SE = .113, Wald χ^2 = 4.66, p = .031, Exp(B) = .78, N = 488; Table 1; Figure 1).

Table 1

Descriptive Information for Study Participants in Relation to Tx Response Time-Course

Variable	*n*	(%)	Significance Test for Relationship with Tx Response Time-Course
Child age in years	$M = 11.17$	$SD = 2.81$	$\chi = .22$, $p > .05$
Gender			
Females	242	50	$\chi = 4.6$, $p = .031$
Race			
Caucasian	385	78.9	
Black	44	9.0	
Asian	12	2.5	$\chi = 4.77$, $df = 5$, $p > .05$
Pacific Islander	2	.4	
American Indian	6	1.2	
Other	39	8.0	
Principal Anxiety Diagnosis			
GAD[a]	236	48.4	$\chi = 3.5$, $p > .05$
Social Phobia[a]	247	50.6	$\chi = 1.3$, $p > .05$
SAD[a]	144	29.5	$\chi = .62$, $p > .05$
Comorbid Externalizing Dx			
ADHD	49	10.0	
ODD	46	9.4	
Total SES Score[b]			
08 to 19	8	1.6	
20 to 29	33	6.8	
30 to 39	62	12.7	$\chi = .57$, $df = 4$, $p > .05$
40 to 54	218	44.7	
55 to 66	167	34.2	

Note. GAD = Generalized Anxiety Disorder, SAD = Separation Anxiety Disorder, OCD = Obsessive Compulsive Disorder, AD-NOS = Anxiety Disorder, Not Otherwise Specified
[a]Significance test for severity of disorder based on Clinician Severity Rating (CSR) in relation to treatment response time-course. [b]Socioeconomic status based on the Hollingshead's (1975) Four-Factor Index of Social Status.

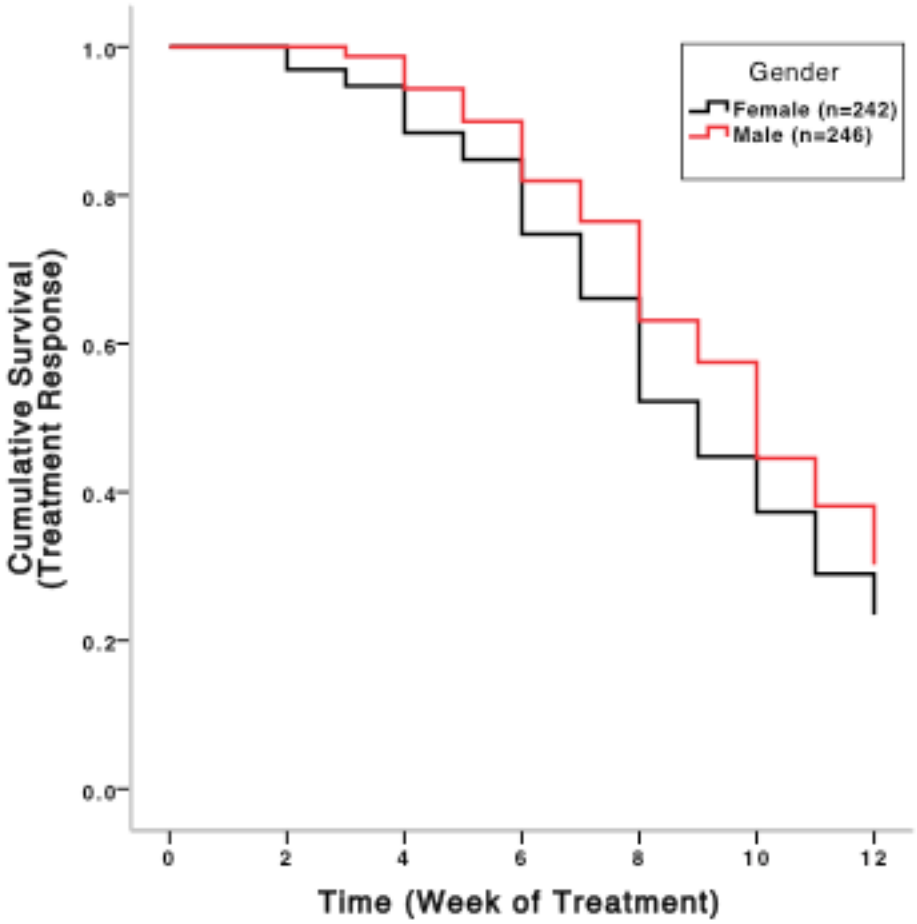

Figure 1. Gender and Treatment Response Time-Course. Y-axis described as proportion of participants ongoing in study before achieving treatment response.

Age was significantly associated with baseline child depressive symptom severity reported by child (β = .17 $p < .001$, n = 486) and reported by parents (β = .17, $p < .001$, N = 488); age was also associated with baseline externalizing symptom severity reported by parents (β = -.14, $p = .003$, N = 488). Given the relation of age with baseline symptom severity and gender with treatment response time-course, "Age" and "Gender" were included as covariates in the following analyses. No other demographic factors or child

characteristics examined were included as covariates given that no other factors were associated with dependant or independent variables.

Condition and Treatment Response Time-Course

As expected, treatment condition was associated with differential treatment response trajectories over time, as (Breslow $\chi^2 = 37.09$, $p < .001$, N = 488, see Figure 2).

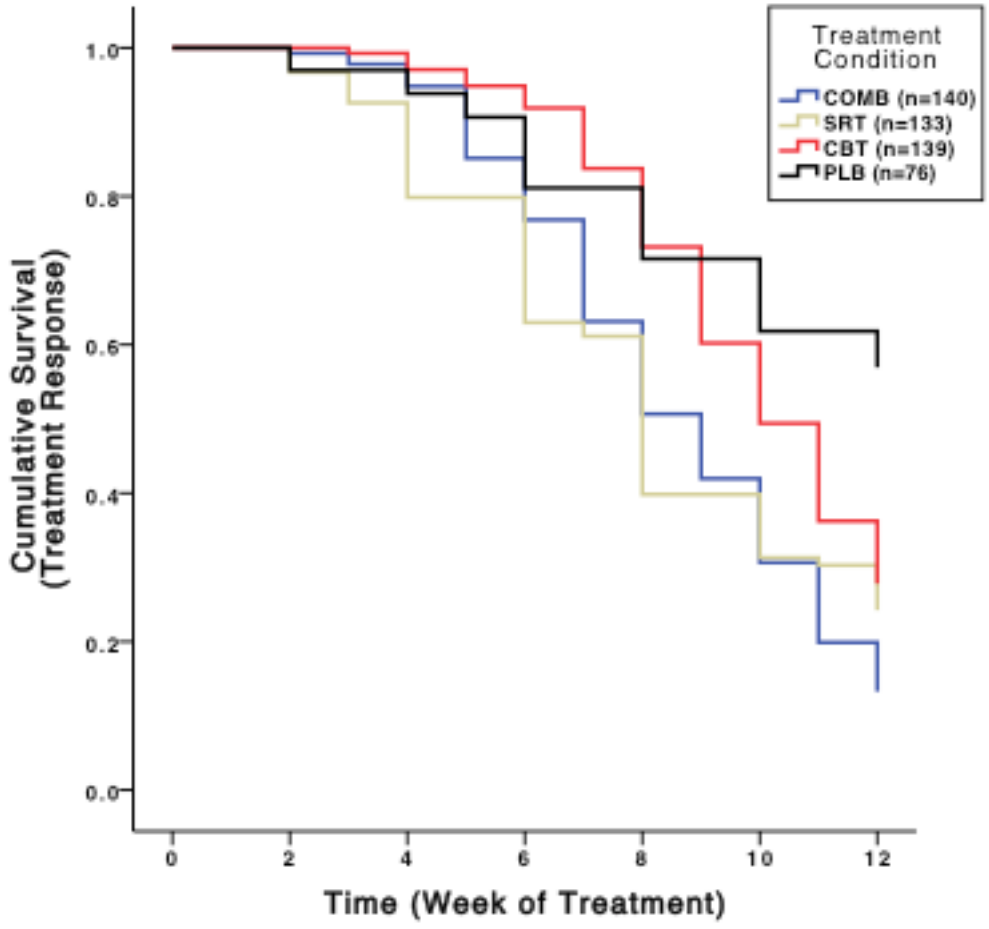

Figure 2. Treatment Condition and Treatment Response Time-Course.
Y-axis described as proportion of participants ongoing in study before achieving treatment response.

Analyses of contrasts indicated that participants in the CBT condition were associated with significantly different treatment response time-course compared to participants in the SRT condition (B = -.385, SE = .151, Wald χ^2 = 6.49, p = .011, Exp(B) = .68, N = 272). Subsequent contrasts also indicated significant differences when comparing the CBT condition to the COMB condition in treatment response time-course (B = -.499, SE = .141, Wald χ^2 = 12.49, p < .001, Exp(B) = .607, N = 279). Of note, when comparing the SRT condition to COMB condition there is no significant association with differential treatment response time-course (B = -.071, SE = .145, Wald χ^2 = .237, p = .626, Exp(B) = .932, N = 273).

Aim 1: The Role of Comorbid Psychopathology in Relation to Treatment Response Time-Course Between Youth Receiving CBT and SRT.

In comparison of CBT to SRT, baseline externalizing disorder comorbidity was not significantly associated with differential treatment response time-course (Wald χ^2 = .56, p = .45, N = 272; Table 2), such that presence of a comorbid externalizing disorder was not significantly associated with more rapid time-course to treatment response for youth in the CBT condition compared to the SRT condition.

Table 2

Cox Regression for Comorbid Externalizing Diagnosis predicting Treatment Response Time Course, for youth in CBT compared to SRT condition

	B	**SE B**	**Wald χ**
Step 1			
Male	-.90	.15	1.15
Age	-.003	.002	1.60
Step 2			
Male	-.2.4	.15	2.59
Age	-.003	.002	2.11
CBT Tx Condition	-.43	.15	8.00**
Comorbid Externalizing Dx	-.10	.20	.269
Step 3			
Male	-.26	.15	2.80*
Age	-.003	.002	1.68
CBT Tx Condition	-.38	.17	5.05**
Comorbid Externalizing Dx	-.05	.28	.03
CBT Tx * Externalizing Dx	-.31	.41	.56

Note. $n = 272$. $\chi^2 = 3.18$ for Step 1 ($p = .20$); $\Delta \chi^2 = 8.13$, for Step 2 ($p = .017$); $\Delta \chi^2 = .057$ for Step 3 ($p = .45$). *$p < .1$, **$p < .05$.

Among youth in monotherapy conditions (i.e., CBT and SRT), presence of a baseline comorbid externalizing disorder did not predict a significant difference in the time-course of treatment response (Breslow $\chi^2 = .001$, $p = .973$, N = 272).

In comparison of SRT to CBT, severity of child-reported baseline depressive symptoms was not significantly associated with differential treatment response time-course ($B = -.01$, $SE = .01$, Wald $\chi^2 = .86$, $p = .35$, N = 272; Table 3).

Table 3

Cox Regression for Comorbid Child-reported Depressive Symptoms predicting Treatment Response Time Course, for youth in SRT compared to CBT condition

	B	**SE B**	**Wald χ**
Step 1			
Male	-.19	.15	1.59
Age	-.003	.002	1.60
Step 2			
Male	-.25	.15	2.66
Age	-.003	.002	1.79
SRT Tx Condition	-.43	.15	7.97**
Child-reported Depressive Sx	-.001	.007	.012
Step 3			
Male	-.25	.15	2.71*
Age	-.003	.002	1.81
SRT Tx Condition	-.66	.29	5.28**
Child-reported Depressive Sx	.004	.009	.25
SRT Tx * Child-reported Depressive Sx	-.01	.01	.86

Note. n = 272. SRT Tx Condition is dummy coded '1' for SRT and '0' for CBT. χ^2 = 3.19 for Step 1 (p = .20); $\Delta\ \chi^2$ = 7.86, for Step 2 (p = .02); $\Delta\ \chi^2$ = .86 for Step 3 (p = .35). *p < .10, **p < .05.

Similarly, when comparing SRT to CBT, severity of parent-reported depressive symptoms was also not significantly associated with differential treatment response time-course (B = .001, SE = .015, Wald χ^2 = .001, p = .99, N = 272). As such, severity of baseline depressive symptoms did not significantly predict more rapid time-course to treatment response for youth in the SRT condition compared to the CBT condition (Table 4).

Table 4

Cox Regression for Comorbid Parent-reported Depressive Symptoms predicting Treatment Response Time Course, for youth in SRT compared to CBT condition

	B	SE B	Wald χ
Step 1			
Male	-.19	.15	1.59
Age	-.003	.002	1.60
Step 2			
Male	-.25	.15	2.70
Age	-.003	.002	1.79
SRT Tx Condition	-.43	.15	7.90**
Parent-reported Depressive Sx	-.002	.008	.072
Step 3			
Male	-.25	.15	2.70*
Age	-.003	.002	1.79
SRT Tx Condition	.43	.26	2.67
Parent-reported Depressive Sx	-.002	.011	.04
SRT Tx * Parent-reported Depressive Sx	.001	.015	.001

Note. n = 272. SRT Tx Condition is dummy coded '1' for SRT and '0' for CBT. χ^2 = 3.19 for Step 1 (p = .20); $\Delta\ \chi^2$ = 7.93, for Step 2 (p = .02); $\Delta\ \chi^2$ = .001 for Step 3 (p = .99). *p < .10, **p < .05.

Among youth in monotherapy conditions (i.e., CBT and SRT), severity of child- and parent-reported depressive symptoms did not predict a significant difference in the time-course of treatment response (B = -.003, SE = .007, Wald χ^2 = .14, p = .70, Exp(B) = .99; B = -.004, SE = .008, Wald χ^2 = .001, p = .996, Exp(B) = 1.00, N = 272, respectively).

Aim 2: Examination of Dimensional and Categorical Externalizing Comorbidity in Relation to Treatment Response Time-Course

Severity of co-occurring parent-reported externalizing symptoms was not significantly associated, above and beyond the association of externalizing comorbid

diagnosis, with improved treatment response time-course (Chi Square $\chi^2 = .056$, $df = 1$, $p = .813$; Table 5).

Table 5

Cox Regression Analysis for Externalizing Symptom Severity predicting Treatment Response Time Course, above and beyond externalizing diagnosis

	B	SE B	Wald χ
Step 1			
Age	-.16	.15	1.15
Male	-.003	.002	2.14
Step 2			
Age	-.004	.002	2.29
Male	-.16	.15	1.11
Comorbid Externalizing Dx	-.12	.19	.356
Step 3			
Age	-.004	.002	2.35
Male	-.16	.15	1.14
Comorbid Externalizing Dx	-.10	..212	..227
CBCL Externalizing Total	-.002	..008	.056

Note. $n = 272$. CBCL = Child behavior checklist, Parent report. $\chi^2 = 3.3$ for Step 1 ($p = .193$); $\Delta \chi^2 = .365$, for Step 2 ($p = .55$); $\Delta R^2 = .056$ for Step 3 ($p = .813$). *$p < .05$.

In fact, the main effect of parent-reported externalizing symptom severity was also not significantly associated with treatment response time-course ($B = -.003$, $SE = .007$, Wald $\chi^2 = .191$, $p = .662$, Exp(B) = .99, N = 272). As such, neither dimensional nor categorical measures of externalizing severity significantly predicted the rate of treatment response.

Aim 3: The Role of Caregiver Burden in Relation to Treatment Response Time-Course between youth receiving CBT and SRT.

In comparison of CBT to SRT, severity of parent-reported baseline caregiver burden was not significantly associated with differential treatment response time-course (B = -.003, SE = .012, Wald χ^2 = .062, p = .804, N = 272; Table 6).

Table 6

Cox Regression for Parent-reported caregiver burden predicting Treatment Response Time Course, for youth in CBT compared to SRT condition

	B	**SE B**	**Wald χ**
Step 1			
Male	-.19	.15	1.59
Age	-.003	.002	1.60
Step 2			
Male	-.25	.15	2.64
Age	-.003	.002	1.97
CBT Tx Condition	-.43	.15	7.73**
BAS Total	-.001	.006	.010
Step 3			
Male	-.25	.15	2.69
Age	-.003	.002	1.94
CBT Tx Condition	-.30	.55	.29
BAS Total	.001	.009	.014
CBT Tx * BAS Total	-.003	.012	.062

Note. n = 272. CBT Tx Condition is dummy coded '1' for CBT and '0' for SRT. BAS Total = Family Burden Assessment Scale Total Score. χ^2 = 3.19 for Step 1 (p = .20); Δ χ^2 = 7.86, for Step 2 (p = .02); Δ χ^2 = .062 for Step 3 (p = .80). *p < .10, **p < .05.

Among youth in monotherapy conditions (i.e., CBT and SRT), severity of caregiver burden associated with having a child with a mental health disorder did not predict a significant difference in the time-course of treatment response (B = -.002, SE = .006, Wald χ^2 = .176, p = .675, Exp(B) = .99, N = 272).

In comparison of CBT to SRT, severity of child-reported baseline family dysfunction was not significantly associated with differential treatment response time-course (B = .003, SE = .018, Wald χ^2 = .037, p = .848, N = 272; Table 7).

Table 7

Cox Regression for Child-reported Family Dysfunction predicting Treatment Response Time Course, for youth in CBT compared to SRT condition

	B	**SE B**	**Wald χ**
Step 1			
Male	-.18	.15	1.47
Age	-.003	.002	1.69
Step 2			
Male	-.24	.15	2.50
Age	-.003	.002	2.08
CBT Tx Condition	-.44	.15	8.26**
Child-Reported BFAMG Total	.001	.009	.001
Step 3			
Male	-.24	.15	2.32
Age	-.003	.002	2.10
CBT Tx Condition	-.60	.87	.48
Child-Reported BFAMG Total	-.002	.013	.022
CBT Tx * Child-Reported BFAMG	.003	.018	.037

Note. n = 272. CBT Tx Condition is dummy coded '1' for CBT and '0' for SRT. BFAMG Total = Brief Family Assessment Measure General Scale Total Score. χ^2 = 3.16 for Step 1 (p = .21); $\Delta\ \chi^2$ = 8.17, for Step 2 (p = .02); $\Delta\ \chi^2$ = .037 for Step 3 (p = .85). *p < .10, **p < .05.

Similarly, when comparing CBT to SRT, severity of parent-reported baseline family dysfunction was also not significantly associated with differential treatment response time-course (B = -.014, SE = .015, Wald χ^2 = .861, p = .353, N = 272; Table 8). As such, severity of baseline family dysfunction did not significantly predict more rapid time-course to treatment response for youth in the CBT condition compared to the SRT condition.

Table 8

Cox Regression for Parent-reported Family Dysfunction predicting Treatment Response Time Course, for youth in CBT compared to SRT condition

	B	SE B	Wald χ
Step 1			
Male	-.17	.15	1.31
Age	-.003	.002	1.40
Step 2			
Male	-.23	.15	2.28
Age	-.003	.002	1.72
CBT Tx Condition	-.45	.16	8.44**
Parent-Reported BFAMG Total	.001	.007	.017
Step 3			
Male	-.23	.15	2.18
Age	-.003	.002	1.57
CBT Tx Condition	.166	.686	.059
Parent-Reported BFAMG Total	.009	.011	.608
CBT Tx * Parent-Reported BFAMG	-.014	.015	.861

Note. n = 272. CBT Tx Condition is dummy coded '1' for CBT and '0' for SRT. BFAMG Total = Brief Family Assessment Measure General Scale Total Score. $\chi^2 = 2.69$ for Step 1 ($p = .26$); $\Delta \chi^2 = 8.51$, for Step 2 ($p = .014$); $\Delta \chi^2 = .86$ for Step 3 ($p = .35$). *$p < .10$, **$p < .05$.

Among youth in monotherapy conditions (i.e., CBT and SRT), severity of child- and parent-reported family dysfunction did not predict a significant difference in the time-course of treatment response (B = -.002, SE = .009, Wald χ^2 = .05, p = .82, Exp(B) = .99; B = -.004, SE = .007, Wald χ^2 = .36, p = .55, Exp(B) = .99, N = 272, respectively).

Exploratory Aim: Comorbidity and Family Functioning in Relation to Treatment Response Time-Course between youth receiving COMB and Monotherapy.

In comparison of COMB to Monotherapy (CBT/SRT), baseline externalizing disorder comorbidity was not significantly associated with differential treatment response time-course (Wald χ^2 = .55, p = .46, Exp(B) = 1.27, N = 412), such that presence of a comorbid externalizing disorder was not significantly associated with more rapid time-

course to treatment response for youth in the CBT condition compared to the SRT condition. In comparison of COMB to Monotherapy, severity of child-reported baseline depressive symptoms was not significantly associated with differential treatment response time-course (Wald χ^2 = .39, p = .53, Exp(B) = 1.01, N = 412). Similarly, when comparing COMB to Monotherapy, severity of parent-reported depressive symptoms was also not significantly associated with differential treatment response time-course (Wald χ^2 = .112, p = .74, Exp(B) = 1.00, N = 412). In comparison of COMB to Monotherapy, severity of parent-reported baseline caregiver burden was not significantly associated with differential treatment response time-course (Wald χ^2 = .012, p = .91, Exp(B) = .99, N = 412). In comparison of COMB to Monotherapy, severity of child-reported baseline family dysfunction was not significantly associated with differential treatment response time-course (Wald χ^2 = .27, p = .60, Exp(B) = .99, N = 412). Similarly, when comparing COMB to Monotherapy, severity of parent-reported baseline family dysfunction was also not significantly associated with differential treatment response time-course (Wald χ^2 = .21, p = .65, Exp(B) = .99, N = 412). As such, the baseline factors of comorbid externalizing disorder, depressive symptoms severity, or baseline family functioning was not significantly associated with more rapid time-course to treatment response for youth in the COMB condition compared to the Monotherapy conditions.

In additional exploratory analyses comparing CBT to SRT, baseline parental treatment assignment reactions were significantly associated with differential treatment response time-course (Wald χ^2 = 7.97, p = .005, N = 272). This is a significant interaction, such that parents with more enthusiastic treatment assignment reaction to

CBT were associated with more favorable treatment response time-course, while more enthusiastic treatment assignment reaction to SRT was associated with less favorable treatment response time-course (Table 9; Figure 3).

Table 9
Cox Regression for Parental Treatment Assignment Reaction predicting Treatment Response Time Course, for youth in CBT compared to SRT condition

	B	**SE B**	**Wald χ**
Step 1			
Male	-.20	.15	1.77
Age	-.003	.002	1.25
Step 2			
Male	-.26	.15	2.81
Age	-.003	.002	1.54
CBT Tx Condition	-.43	.17	6.79**
Parent TAR	.018	.083	.045
Step 3			
Male	-.28	.15	3.39
Age	-.002	.002	1.12
CBT Tx Condition	-2.1	.62	11.45**
Parent TAR	-.22	.12	3.34
CBT Tx * Parent TAR	.49	.17	7.97**

Note. $n = 272$. CBT Tx Condition is dummy coded '1' for CBT and '0' for SRT. Parent TAR = Parental Treatment Assignment Reaction. $\chi^2 = 3.04$ for Step 1 ($p = .22$); $\Delta \chi^2 = 7.42$, for Step 2 ($p = .024$); $\Delta \chi^2 = 8.20$ for Step 3 ($p = .004$). *$p < .05$, **$p < .01$.

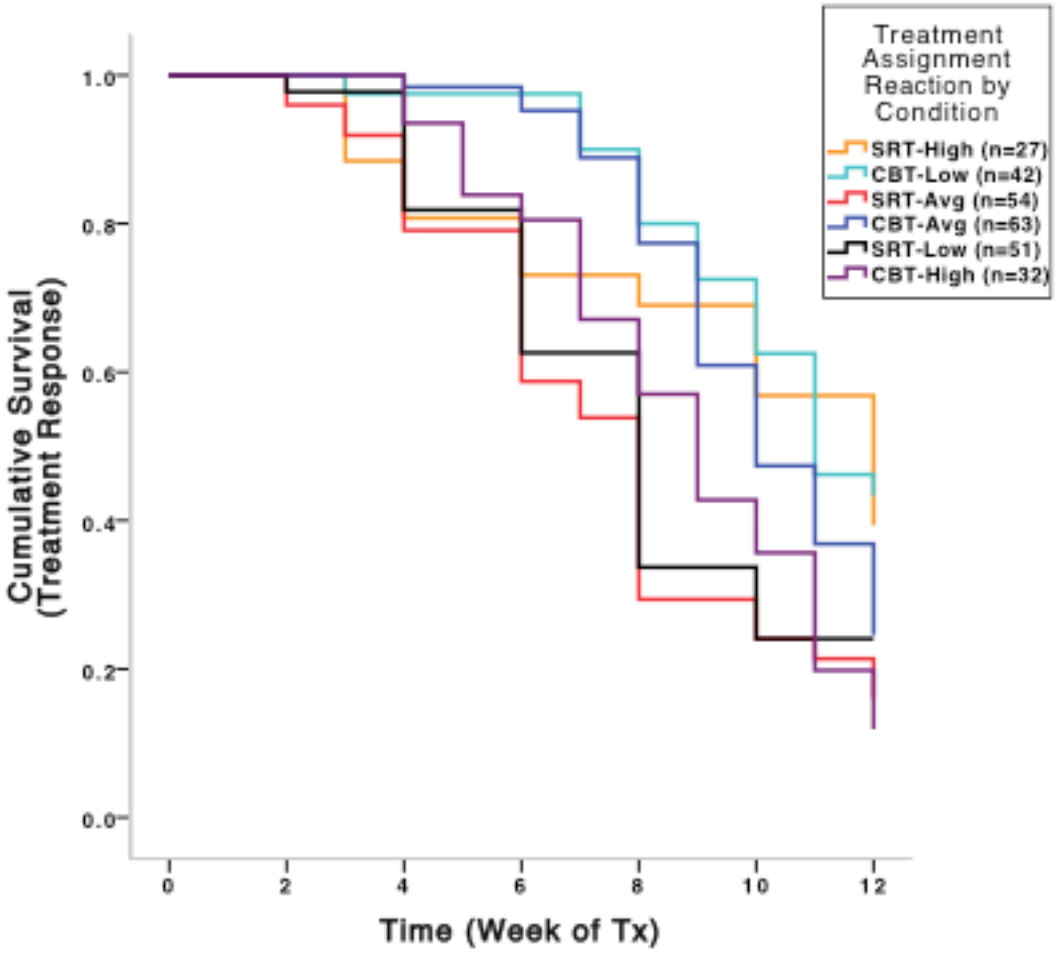

Figure 3. Interaction of Diagnostician-Rated Parental Treatment Assignment Reaction predicting Treatment Response Time Course, for youth in CBT and SRT condition. Y-axis described as proportion of participants ongoing in study before achieving treatment response. Treatment Assignment Reaction categories include Extremely Disappointed = 1, Disappointed = 2, Neutral = 3, Pleased = 4, Extremely Pleased = 5; Categories were combined for parsimony and visual simplicity as follows, SRT-High=4,5; SRT-Avg=3; SRT-Low=1,2; CBT-High=5; CBT-Avg=4; CBT-Low=1,2,3.

Among youth in monotherapy conditions (i.e., CBT and SRT), the main effect of parental treatment assignment reaction did not predict a significant difference in the time-course of treatment response (B = -.065, SE = .077, Wald χ^2 = .71, p = .40, Exp(B) = .94, N = 272). There is a significant simple main effect for CBT but not a significant effect for SRT, such that for CBT more enthusiastic parental treatment assignment reaction

predicted more favorable treatment response time course (B = .31, SE = .13, Wald χ^2 = 6.00, p = .014, Exp(B) = 1.37, N = 139), while for SRT no significant association was found for parental treatment assignment reaction with treatment response time-course (B = -.16, SE = .12, Wald χ^2 = 1.67, p = .20, Exp(B) = .86, N = 133).

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