# WHO GETS BETTER AND WHY? PREDICTING THE DEVELOPMENT OF A WORKING ALLIANCE AND ITS SUBSEQUENT ROLE IN PHARMACOTHERAPY FOR SOCIAL ANXIETY DISORDER

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## ABSTRACT

Social anxiety disorder (SAD) is highly prevalent and associated with high levels of impairment and distress. Therapies for SAD leave many patients symptomatic at the end of treatment, and little is known about predictors of treatment response or the mechanisms by which these variables exert their influence on treatment outcome. This study investigated whether levels of depression, social anxiety, submissive behavior, childhood maltreatment, and suppression of anger predicted response to pharmacotherapy for SAD and whether the working alliance mediated these relationships. One hundred thirty-eight treatment-seeking individuals with a primary diagnosis of SAD received 12 weeks of open treatment with the selective serotonin reuptake inhibitor paroxetine. Higher levels of depression predicted higher levels of social anxiety symptoms at the end of treatment and higher levels of submissive behavior and childhood emotional maltreatment predicted a higher probability of attrition from treatment. The working alliance mediated response to pharmacotherapy for individuals who self-reported a history of emotional maltreatment. These results identify variables that predict pharmacotherapy treatment outcome and emphasize the importance of the psychiatrist-assessed working alliance as a mechanism of treatment response for those with a history of emotional maltreatment. Implications for person-specific treatment selection are discussed.

This dissertation is dedicated to

my parents, Dori and Lloyd, and

my brother, Avi,

for their boundless love

that made it so I never once had to question

whether I could pursue the things that I love.

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# CHAPTER 1

## INTRODUCTION

Social anxiety disorder (SAD) is highly prevalent in the population, with lifetime prevalence rates as high as 12.1% (Kessler et al., 2005). SAD is associated with significant social, occupational, and educational impairment (Aderka et al., 2012; Kessler, 2003; Schneier et al., 1994). Although several empirically supported treatments exist for SAD (e.g., Heimberg & Magee, 2014; Schneier, Bruce, & Heimberg, 2014), many patients still fail to adequately respond to treatment or relapse after treatment cessation. One study suggested that 42% of patients receiving group cognitive behavioral therapy (GCBT) either dropped out of treatment or did not respond (Heimberg et al., 1998), and response rates for selective serotonin reuptake inhibitors (SSRIs) are similar (e.g., Liebowitz, Gelenberg, & Munjack, 2005; M. Stein et al., 1998; Van Ameringen et al., 2001).

The National Institute of Mental Health has called for the study of personalized mental health care in its Strategic Plan (NIMH, 2015) as a way to augment the efficacy of currently available empirically supported treatments. This call for personalization research echoes Donald Kiesler's (1966) discussion about the myths of uniformity in psychotherapy research and Gordon Paul's (1969) subsequent call for a collaborative project investigating "what treatment, by whom, is most effective for this individual with that specific problem, and under what set of circumstances" (p. 111). To date, treatment personalization research has focused on identifying baseline variables that predict the degree to which a patient responds to a given treatment across a range of psychological concerns including mood (e.g., Cuijpers, et al, 2014) and anxiety (e.g., Schneider, Arch, & Wolitzky-Taylor, 2015) disorders.

Numerous studies have investigated predictors of outcome of treatment for SAD (for reviews, see Hofmann, 2000; Mululo et al., 2002). More rigorous personalization studies have only been conducted recently, and these have focused on CBT or Acceptance and Commitment Therapy (see Niles et al., 2013; Craske et al., 2014). Despite the rapid proliferation of psychotropic medications in the United States (Medco Health Solutions, 2011) there is a paucity of personalization research on pharmacotherapy for SAD.. The extant literature has largely focused on older monoamine oxidase inhibitors (e.g., Slaap, van Vliet, Westenberg, & Den Boer, 1996; Versiani et al., 1997), although a few studies have examined personalization questions relating to selective serotonin reuptake inhibitors. For example, early childhood onset of SAD (Van Ameringen, Oakman, Mancini, Pipe, & Chung, 2004), duration of SAD (Van Ameringen et al., 2004), and presence of the minor allele polymorphism of gene RGS2 (M. Stein et al., 2014) predicted poorer response to treatment with sertraline. Bruce, Heimberg, Blanco, Schneier, and Liebowitz (2012) found that a history of emotional maltreatment predicted attrition from paroxetine pharmacotherapy.

Researchers have also recently explored variables that account for (i.e., mediate) improvements during the course of particular treatments, another line of inquiry pertaining to treatment personalization. Studies that focus on SAD have recently undergone rapid proliferation. Although no study has examined mechanisms of change in pharmacotherapy for SAD, recent studies have explored mechanisms of change in CBT and acceptance-based interventions (for a review of studies prior to 2000, see Hoffmann, 2000). Decreases in maladaptive interpersonal beliefs (Boden et al., 2012) and increases in cognitive reappraisal success (Golden et al., 2014) and reappraisal self-efficacy (Goldin et al., 2012) all mediate the effect of CBT on social anxiety outcome. In a meta-analysis, Gu, Strauss, Bond, and Cavanagh

(2015) suggest that cognitive and emotional reactivity mediate outcome for mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy. Goldin and colleagues (2016) examined psychological characteristics that account for positive psychological change experienced in GCBT versus MBSR and found that increases in cognitive reappraisal frequency, mindfulness skills, attention focusing, attention shifting and decreases in subtle avoidance behaviors and cognitive distortions mediated outcome for both GCBT and MBSR, whereas increases in cognitive reappraisal self-efficacy and decreases in avoidance behaviors mediated outcome for GCBT, but not MBSR.

However, only one study of the treatment of any psychological disorder has, to our knowledge, combined the statistical approaches of prediction and mediation (Newman & Fisher, 2013), and no study has undertaken this approach in relation to any modality of treatment for SAD. In Newman and Fisher's study, individuals with a longer duration (i.e., the baseline predictor) of generalized anxiety disorder demonstrated greater benefit from cognitive therapy and self-control desensitization than from combined treatment (i.e., CBT) whereas individuals with a shorter duration of GAD responded better to CBT than the component treatments (i.e., cognitive therapy or self-control desensitization). Further, decreases in rigidity during treatment mediated the moderating effect of GAD duration.

Research designs that examine both baseline predictor variables and the associated mechanisms through which such variables exert their influence provide a richer and more comprehensive picture of the subtleties of treatment personalization. Such models permit the understanding of (a) who is most likely to respond to a given treatment and (b) why individuals with these particular traits are more (or less) likely to respond to treatment. Given the prevalence of SAD and the impairment associated with it, treatment personalization for SAD is an important

area of research. Further, comparatively little research has focused on personalization of pharmacologic interventions for SAD. Thus, this study sought to fill these gaps in the literature by identifying baseline predictors of treatment outcome and an associated mechanism of action in pharmacotherapy for SAD.

**Baseline Interpersonal Predictors of the Outcome of Treatment for SAD**

Given the centrality of interpersonal concerns in the phenomenology of SAD (Alden & Taylor, 2010; Heimberg, Brozovich, & Rapee, 2014), this study focused on variables that have been shown to be related to deficits in interpersonal functioning and which have been associated with SAD and/or with the outcome of treatment for SAD, regardless of treatment modality. Below, we review depression, childhood maltreatment, anger suppression, submissive behavior, and severity of social anxiety as putative predictors of outcome of pharmacotherapy for SAD.

*Depression*

Individuals with SAD have a two-fold increase in risk for developing depression compared to those without SAD, and the risk is three-fold when compared to individuals without any anxiety disorder (Beesdo et al., 2007). Further, compared to individuals without a mental disorder, individuals with SAD were 3.5 times more likely to develop a depressive disorder during a follow-up period of 34-50 months (M. Stein et al., 2001), and the onset of SAD precedes the onset of major depressive disorder (MDD) in approximately 70% of individuals (Kessler, Stang, Wittchen, Stein, & Walters, 1999). Higher levels of depression have been associated with poorer response to CBT for SAD across multiple trials (Chambless et al., 1997; Collimore & Rector, 2012; Hedman et al., 2012; Scholing & Emmelkamp, 1999). Although studies have examined baseline differences in depression between treatment groups (e.g., Kasper, Stein, Loft, & Rico, 2005; M. Stein, Fyer, Davidson, Pollack, & Wiita, 1999), no

research to our knowledge has examined depression as a predictor of the outcome of pharmacotherapy for SAD.

*Childhood maltreatment*

Childhood maltreatment has been reliably associated with SAD and treatment outcome in various studies. In one study, 9% percent of treatment-seeking patients with SAD endorsed prior physical and/or sexual abuse (Safren, Gershuny, Marzol, Otto, & Pollack, 2002). Simon and colleagues (2009) examined a broader range of types of maltreatment, including emotional abuse and neglect and found that 70% of a treatment-seeking sample of patients with SAD met criteria for at least one type of childhood maltreatment. A history of childhood parental abuse predicted poorer response (smaller reductions in depression and severity of social anxiety symptoms) to GCBT for SAD (Alden, Taylor, Laposa, & Mellings, 2006) and a history of emotional maltreatment predicted higher rates of attrition from pharmacotherapy (Bruce et al., 2012).

*Anger suppression*

Individuals with SAD report higher levels of anger relative to individuals without SAD (Erwin, Heimberg, Schneier, & Liebowitz, 2003) and they spend more time during the day experiencing anger than non-anxious individuals (Kashdan & Collins, 2010). Yet, despite the intensity and frequency of anger experience, individuals with SAD suppress the expression of anger more than their non-anxious counterparts (Erwin et al., 2003; Moscovitch, McCabe, Antony, Rocca, & Swinson, 2008). The suppression of anger appears to be particularly relevant to SAD given the fear of negative evaluation and rejection experienced by socially anxious individuals (Breen & Kashdan, 2011). In a recent study, a latent class analysis examined the anger profiles of individuals with SAD and found that the class with elevated trait anger and the greatest tendency to suppress the expression of anger was characterized by the most distress and

impairment (Versella, Piccirillo, Potter, Olino, & Heimberg, 2016). Although anger has not been examined in relation to medication treatment, individuals with SAD who suppress their anger tend to have poorer treatment response and higher rates of attrition from GCBT (Erwin et al., 2003).

*Submissive behavior*

According to several ethological and psychobiological models (e.g., Gilbert, 2014), social anxiety occurs to attenuate competition for social status between people. Engaging in submissive behavior is one way in which this competition-attenuating process is enacted (reviewed in Weeks, Heimberg, & Heuer, 2011). Examples of submissive behaviors related to social anxiety include body collapse and vocal pitch peak elevation (Weeks et al., 2011), and such submissive behavior has a negative impact in the eyes of others (Gilbert, 2014; Weeks et al., 2011). However, to date, no research has examined the association of submissive behavior to treatment outcome.

*Social anxiety severity*

Higher clinician ratings of impairment and severity at baseline predict poorer outcome in trials of GCBT (Kawaguchi et al., 2013; Scholing & Emmelkamp, 1999). However, severity of social anxiety was unrelated to treatment outcome in a study that examined the efficacy of paroxetine for SAD (D. Stein, Stein, Goodwin, Kumar, & Hunter, 2002).The association of baseline social anxiety severity and pharmacotherapy treatment outcome needs further study.

Overall, the reviewed predictors have all been shown to be associated with SAD and many of these predictors have been shown to influence the outcome of treatment. Given the deficits in interpersonal function associated with SAD, we review the therapeutic relationship as a putative mediator of pharmacotherapy outcome for SAD.

**The Working Alliance and Response to Treatment for SAD**

The research on the role of the working alliance in the treatment of SAD is somewhat mixed and lacking well-designed methodology, a particularly meaningful gap in the literature given that interpersonal difficulties dominate the clinical picture of SAD. Compared to patients with panic disorder, individuals with SAD report having working alliances of poorer quality (Haug et al., 2016). Mörtberg (2014) found that individuals with SAD demonstrated stronger working alliances with their therapists in individual versus GCBT but the strength of the alliance was not related to outcome in either modality. However, this study only examined treatment completers (25% of the sample attrited from treatment), so it is possible that failure to develop an alliance led to withdrawal from the study, a limitation acknowledged by the author. Moreover, the study examined only 54 participants and included only one (self-report) outcome measure. Other studies have also failed to find a relationship between the alliance and treatment outcome for SAD, but these studies have examined either group or internet-based interventions (Andersson et al., 2012; Kashdan & Roberts, 2012)—treatment modalities that involve the practitioner to a lesser degree than individual treatment.

One well-designed study of the working alliance in individual CBT for SAD found that there was a positive association between ratings of the alliance and ratings of session helpfulness (Hayes, Hope, VanDyke, & Heimberg, 2007). Interestingly, moderate (rather than high) levels of the working alliance were associated with the greatest levels of anxiety habituation during exposures to feared social situations, suggesting the existence of important subtleties in the relationship between the alliance and outcome. It may be that a weak working alliance impedes the patient's full engagement in treatment, whereas a strong working alliance makes the patient feel overly comfortable, negating opportunities for exposure to uncomfortable situations that

may lead to treatment change (e.g., Longmore & Worrell, 2007). Furthermore, recent studies have found that lower ratings of working alliance in CBT are associated with treatment failure (Haug et al., 2016; Weck, Grikscheit, Jakob, Höfling, & Stangier, 2015).

No study to date has examined the role of the working alliance in pharmacotherapy for SAD. However, studies have shown that the working alliance is associated with outcome of pharmacotherapy for adults with MDD (Krupnick et al., 1996), bipolar disorder (Gaudiano & Miller, 2006), substance dependence (Dundon et al., 2008), and schizophrenia and other psychotic disorders (Montreuil et al., 2012; Wykes, Rose, Williams, & David, 2013).

**Working Alliance as a Mediator Between Predictors and Response to Pharmacotherapy**

Given that the interpersonal realm is central in SAD, the working alliance may be one pathway by which the aforementioned interpersonal characteristics may influence the outcome of treatment. More specifically, in socially anxious individuals, the interpersonal deficits engendered by childhood maltreatment, anger suppression, depression, submissive behavior, and severity of social anxiety may negatively affect the development of a therapeutic alliance, thereby leading to poorer therapy outcomes. Below, we review the associations between our putative predictors and related deficits in interpersonal functioning, both generally and as they relate to the quality of a working alliance.

*Depression*

Individuals with depression have poorer quality parental relationships, less optimal peer relationships, and fewer friends (Field, Diego, & Sanders, 2001). Individuals with MDD report fewer positive interactions and more negative interactions with their romantic partners than individuals without a mood disorder and without any psychiatric disorder (Zlotnick, Kohn, Keitner, & Della Grotta, 2000). Coyne (1976), in his interpersonal theory of depression, posited

that depressed individuals interact with others in a way that elicit feelings of rejection and the need for reassurance, ultimately leading to an increase in depressive symptoms. In one study of individuals seeking CBT for depression, the working alliance mediated the relationship between interpersonal functioning at baseline and the alleviation of depressive symptoms (Howard, Turner, Olkin, & Mohr, 2006). The working alliance also mediated the association between higher levels of certain personality traits (i.e., agreeableness, extraversion, and openness) and better outcomes for individuals with MDD treated with interpersonal therapy, CBT, or antidepressant medication (intervention-specific mediation analyses were not conducted, Kushner, Quilty, Uliaszek, McBride, & Bagby, 2016). These studies suggest that interpersonal variables exert their influence via the working alliance.

*Childhood maltreatment*

A history of childhood maltreatment is associated with a diversity of interpersonal difficulties. For example, individuals with a history of emotional abuse have higher levels of paranoid ideation and interpersonal sensitivity (Dias, Sales, Hessen, & Kleber, 2014). Moreover, children with a history of maltreatment display less intimacy, more conflict, and more negative and less positive affect in relationships (Parker & Herrera, 1996). Of interest, a greater frequency and severity of childhood maltreatment has been associated with a lower quality of the therapeutic alliance in a sample of hospitalized adolescent inpatients (Eltz, Shirk, & Sarlin, 1995) and, notably, in a sample of patients with SAD (Alden et al., 2006).

*Anger suppression*

Anger suppression can have deleterious effects on the quality of interpersonal relationships. Higher levels of anger suppression have been associated with greater distrust of others and lower quality of life (QOL; Erwin et al., 2003). Additionally, Sperberg and Stabb

(1988) found higher levels of anger suppression to be associated with reduced interest in other people and a decrease in the amount that one expresses his or her own feelings, thoughts, and needs. Anger has also been shown to be negatively related to the quality of the working alliance in patients with chronic pain (Burns, Higdon, Mullen, Lansky, & Wei, 1999).

*Submissive behavior*

The relationship between submissive behavior, the working alliance, and treatment outcome is less clear and has not been explicitly studied. However, Gilbert (2014) posits that social anxiety is elicited in circumstances in which individuals view themselves as low on the social hierarchy. Psychological or psychiatric treatment may be precisely such a circumstance. Socially anxious individuals may interpret treatment as containing an implicit power dynamic between therapist and patient. Indeed, patient perceptions of this power dynamic exist regardless of clinical population (Reandeau & Wampold, 1991). Moreover, this research suggests that patients who are able to form a strong working alliance with their practitioner regardless of the power differential do so by being highly involved in their treatment. Thus, socially individuals may be more sensitive to this power dynamic and engage in submissive behavior as a way to counter social competition, thereby participating less and negatively affecting the working alliance. This dynamic may be particularly pronounced in medication management, as the psychiatrist-patient relationship is one of strong power differential.

*Severity of social anxiety*

The presence and severity of social anxiety is associated with an array of interpersonal difficulties. Individuals with social anxiety have problems both in initiating and maintaining close relationships across the lifespan (Alden & Taylor, 2004; Rodebaugh, 2009). Moreover, romantic relationships (Darcy, Davila, & Beck, 2005; Sparrevohn & Rapee, 2009; Wenzel,

2002) and close relationships more generally (Davila & Beck, 2002) of socially anxious individuals are marked by lower amounts of social and emotional intimacy and difficulties expressing emotion. The working alliance has been shown to predict end-state social anxiety within an exposure (Hayes et al., 2007) and in one session of CBT combined with virtual reality (Moldovan & David, 2014); however, these studies did not examine the alliance as a mediator of change.

**Current Study**

Given the high prevalence and disabling nature of SAD, the frequency with which medication is used as a treatment for SAD, and the sensitivity of patients with SAD to their interpersonal environment, research that assesses the working alliance in the pharmacotherapy of SAD is needed. This study examined various interpersonally-oriented predictors of response (i.e., depression, childhood maltreatment, anger suppression, submissive behavior, and severity of social anxiety) to pharmacotherapy and further examined whether these predictors exerted their effect through the working alliance, a relationship-centric variable, in an open trial of pharmacotherapy for SAD. We sought to evaluate outcomes of pharmacotherapy not limited to typical measures of symptom reduction, but also including clinically significance change (CSC) and changes in quality of life.

Our study design enabled us to test two primary hypotheses. We examined the prospective association between self-reported depression, childhood maltreatment, anger suppression, submissive behavior, severity of social anxiety, and treatment outcome, hypopthesizing that higher levels of these baseline predictors would be related to significantly higher levels of post-treatment social anxiety, lower probability of achieving treatment responder status, greater attrition, and lower QOL (**Hypothesis 1)**. We also examined the mediating role of

the working alliance in the relationship between the predictor variables and treatment outcome, hypothesizing that the association between the putative predictors and treatment outcome (levels of social anxiety, responder status, attrition, QOL) in an open trial of pharmacotherapy for SAD would be mediated by the working alliance (**Hypothesis 2).**

# CHAPTER 2

## METHOD

### Participants

Data for this study were obtained from treatment-seeking outpatients with a principal diagnosis of generalized SAD. Individuals were recruited to participate in a randomized controlled trial of the treatment of SAD with paroxetine (with or without augmentation with CBT for patients who evidenced only a partial response to paroxetine). Due to a substantially smaller sample size after randomization, only the open treatment portion of the trial was considered part of the present study. Forty-six patients from the Adult Anxiety Clinic of Temple University and 92 patients from the Anxiety Disorders Clinic of the New York State Psychiatric Institute participated. In total, 138 patients (37.7% female) received pharmacological intervention.

Individuals were excluded if they had current psychotic symptoms, a current or past diagnosis of bipolar disorder or major depressive disorder, suicidal ideation, clinically significant or currently unstable medical pathology, psychological disorder due to medical origins, past paroxetine or CBT treatment for SAD, pregnancy or strong likelihood of becoming pregnant, current or past diagnosis of a seizure disorder, unwillingness to discontinue other psychotropic medications, inability or refusal to undergo a drug-free period before commencement of treatment, or current psychotherapeutic intervention. Individuals who failed to follow the prescribed medication course, missed three (or more) visits with the prescribing psychiatrist, failed to take paroxetine for 7 consecutive days or a total of 10 days, or requested to terminate treatment were classified as attritors (Heimberg et al., 2016).

### Procedure

Individuals who met inclusion criteria after preliminary screening underwent a structured diagnostic interview by an independent evaluator trained to reliability. Those patients meeting DSM-IV (American Psychiatric Association [APA], 1994) criteria for generalized SAD and not meeting any exclusionary criteria underwent a comprehensive medical evaluation and then were consented to treatment. Patients met with a study psychiatrist once a week for the first 6 weeks during titration and then every other week, for a total of 9 visits over 12 weeks. Psychiatrists varied between sites and both the Psychiatric Institute and Temple employed multiple psychiatrists over the course of the study. Patients received paroxetine treatment at no charge. Patients started at 10 mg of paroxetine per day and were increased to a therapeutic dose on an individual basis (from 20 - 60 mg). The psychiatrist offered general encouragement and support while monitoring clinical progress. The psychiatrist instructed patients to expose themselves to emotionally adverse or feared situations to help overcome avoidance behaviors and explained that the role of paroxetine was to make such exposure easier. No other instructions were offered. Pill counts were taken to ensure treatment adherence. Treatment response was assessed by an independent evaluator.

**Measures**

*Diagnostic interviews*

At the New York State Psychiatric Institute, individuals were administered the Structured Clinical Interview for DSM-IV, Patient Edition with Psychotic Screen (SCID-I/P; First, Spitzer, Gibbon, & Williams, 2002). At the Adult Anxiety Clinic of Temple, individuals were administered the Anxiety Disorders Interview Schedule for the DSM-IV: Lifetime Version (ADIS-IV-L; Di Nardo, Brown, & Barlow, 1994). In New York, because the reliability of SAD is lower when based on the SCID-I/P (Zanarini & Frankenburg, 2001; Zanarini et al., 2000) than

on the ADIS-IV-L, the social phobia module of the ADIS was used to supplement the SCID-I/P social phobia module. The full interviews were used for inclusion and exclusion criteria.

The ADIS-IV-L is a semi-structured interview that provides psychometrically sound diagnostic information for past and current Axis I disorders, with a focus on anxiety, mood, somatoform and substance abuse/dependence. The ADIS-IV-L provides a 0-8 rating of the severity of each diagnosis and its associated impairment. A kappa coefficient of .77 for a principal diagnosis of SAD was found in two independent ADIS-IV-L interviews in a sample of 362 individuals (Brown, Di Nardo, Lehman, & Campbell, 2001). The ADIS-IV-L has also been shown to have strong construct validity (Brown, Campbell, Lehman, Grisham, & Mancill, 2001; Brown, Di Nardo et al., 2001).

The SCID-I/P is a clinician-administered semi-structured interview that is designed to assess Axis I disorders according to the DSM-IV (APA, 1994). Both novice and experienced clinicians have good to excellent agreement on Axis I disorders when administering the SCID-I/P, with an overall kappa coefficient of .85 (Ventura, Liberman, Green, Shaner, & Mintz, 1998). The ADIS-IV-L and the SCID-I/P were only administered by one independent evaluator at one time point; thus no reliability statistics are available.

*Baseline predictors*

The Beck Depression Inventory, second edition (BDI-II; Beck, Steer, & Brown, 1996) is a 21-item self-report measure intended to assess affective, cognitive, and somatic symptoms of depression. The BDI-II has demonstrated good internal consistency (Beck, Steeer, Ball, & Ranieri, 1996; Riskind, Beck, Berchick, Brown, & Steer, 1987) and convergent and divergent validity (Beck, Steer, Ball & Ranieri, 1996). At baseline, internal consistency of the BDI-II was excellent ($\alpha = .92$).

The Childhood Trauma Questionnaire, Short Form (CTQ-SF; Bernstein et al., 2003) is a self-report questionnaire with 3 validity items and 25 clinical items subdivided into five different subscales with five items each: sexual abuse, physical abuse, physical neglect, emotional abuse, and emotional neglect. Studies suggest that histories of emotional abuse and emotional neglect (rather than sexual abuse, physical abuse, and physical neglect) are most strongly related to SAD at pre-treatment and post-treatment (Bruce, Heimberg, Goldin, & Gross, 2013; Kuo et al., 2011). For the purposes of this study, we created an "emotional maltreatment" subscale, used for all childhood trauma analyses, by adding together the emotional abuse and emotional neglect subscales. The CTQ-SF has good test-retest reliability ($r$ = .79-86), internal consistency ($\alpha$ = .66-.92) (Scher et al., 2001), and convergent validity (Spinhoven et al., 2014). The CTQ-emotional maltreatment subscale was administered at baseline and had good internal consistency ($\alpha$ = .87).

The State-Trait Anger Expression Inventory, Second Edition (STAXI-2; Spielberger, 1999) assesses both state and trait anger and how individuals express and control their anger. The anger expression-in (e.g., "I boil inside, but I don't show it") subscale was used for this study. The anger expression-in subscale measures a person's tendency to suppress the expression of angry emotions. Factor analysis supports using individual subscales (Spielberger & Reheiser, 2009), and previous research on the association between the STAXI subscales and SAD treatment outcome supports using the anger expression-in subscale (Erwin et al., 2003; Breen & Kashdan, 2011). In previous studies, the anger expression-in subscale has demonstrated good reliability ($\alpha$ = .83; Versella et al., 2016) and convergent and discriminant validity (Spielberger, 1999). At baseline, the STAX-2 anger expression-in subscale displayed adequate internal consistency ($\alpha$ = .75).

The Submissive Behavior Scale (SBS; Allan & Gilbert, 1997) is a 16-item self-report scale intended to measure submissive social behaviors. The SBS has good internal consistency (α = .85; Allan & Gilbert, 1997) and convergent validity (O'Connor, Berry, Weiss, & Gilbert, 2002). At baseline, the SBS displayed good internal consistency (α = .93).

The Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) and the Clinician Global Impression scale, as modified for SAD by Zaider, Heimberg, Fresco, Schneier, and Liebowitz (2003) were used to assess social anxiety symptom severity. These scales were also used as outcome measures and are described below.

*Outcome measures*

The LSAS was administered by an independent evaluator to patients at weeks 0, 4, 8, and 12, but for the purposes of this study, only weeks 0 and 12 were considered. The LSAS is a 24-item clinician-administered scale that assesses social anxiety and avoidance in performance and social interaction situations. The LSAS has been found to be sensitive to change in studies of psychotropic medication and cognitive behavioral interventions (e.g., Heimberg et al., 1998). The LSAS has demonstrated excellent reliability (Cronbach's α > .90; Heimberg et al., 1999), convergent validity with other well validated measures of social anxiety (Heimberg et al., 1999), and known-groups validity (Heimberg & Holaway, 2007). Internal consistency in this study was good at baseline (α = .85) and excellent at post-treatment (α = .93).

The Clinician Global Impression (CGI) scale is a 2-item clinician-administered scale (in the present study, it was administered by an independent evaluator) designed to assess severity of symptoms (CGI-S) and improvement in response to treatment (CGI-I). A version of the CGI specifically developed for SAD (Zaider et al., 2003) was used as an outcome measure in the current study. This version of the CGI, which has specifically developed anchor points related to

SAD, was administered at baseline (only the CGI-S was administered at this time point), week 4, week 8, and post-treatment, but for the purposes of this study, only weeks 0 and 12 were considered. The CGI-S uses a Likert-type scale from 1 (not ill) to 7 (extremely ill). A score of 3 or greater indicates that an individual meets criteria for SAD. The CGI-I uses a Likert-type scale from 1 (markedly improved) to 7 (markedly worse). A score of 4 indicates no change. Participants were considered to be treatment responders if they had a CGI-I score of 1 or 2 at post-treatment (week 12). The CGI has been shown to have strong convergent and discriminant validity (Berk et al., 2008; Zaider et al., 2003). The CGI was only administered by one independent evaluator; thus no reliability statistics are available.

The Quality of Life Inventory (QOLI; Frisch, 1994) is a self-report measure intended to assess subjective contentment in 16 life domains (e.g., health, self-esteem, goals and values). Participants rate how important each domain is to their happiness on a three-point scale, ranging from 0 (Not Important) to 2 (Extremely Important) and then rate how satisfied they are with each domain on a six-point scale from -3 (Very Dissatisfied) to 3 (Very Satisfied). The satisfaction ratings for each domain are weighted by the importance to the individual, creating a score from -6 to 6. Global QOL is evaluated by calculating the mean of the weighted satisfaction ratings. Frisch, Cornell, Villanueva, and Retzlaff (1992) reported internal consistency coefficients for the total QOLI score in three clinical and three non-clinical samples ($\alpha$ = .77 to .89), and test-retest coefficients ranging from $r$ = .80 to .91. The QOLI has shown good convergent validity (Cohen, Jensen, Dryman, & Heimberg, 2015) and had excellent reliability in this study at baseline ($\alpha$ = .96) and good reliability at post-treatment ($\alpha$ = .82).

*Working alliance*

The Working Alliance Inventory (WAI) was administered at baseline and week 8. The 12-item version of the WAI was used in this study (Tracey & Kokotovic, 1989). Scores on this short form (Busseri & Tyler, 2003) are interchangeable with the original 36-item version (Horvath & Greenberg, 1989). Hovarth and Greenberg designed the WAI to be appropriate across all domains of therapeutic interventions. In this study, the WAI was completed by the pharmacotherapist and reflected his/her perceptions of the alliance. Each of the 12 items is rated 1-7, with higher scores representing a better alliance. The WAI has been shown to have good internal consistency ($\alpha > .80$) and good convergent validity with other alliance questionnaires (Munder, Wilmers, Leonhart, Linster, & Barth, 2010; Stiles et al., 2002). In the present study, internal consistency was good at baseline ($\alpha = .86$) and at week 8 (mid-treatment, $\alpha = .83$).

**Statistical Analyses**

*Outcomes*

All statistical analyses were performed with MPlus Version 7.11 (Muthén and Muthén, 1998-2014) and SPSS Version 21.0 (International Business Machines Corporation, 2012). All results were analyzed using an intention-to-treat approach and participants who received any amount of intervention were included in all analyses. Full Information Maximum Likelihood (FIML) Estimation was used to handle missing data (Enders & Bandalos, 2001; Graham, 2009). FIML uses all available data to estimate model parameters but does not impute values, permitting participants with missing data to be included in model estimations (Enders, 2001).

We first examined whether baseline levels of social anxiety, post-treatment levels of social anxiety, responder status, and working alliance measures differed between study sites. We also examined whether any of the demographic variables were significantly related to treatment outcome. Variables that were significantly associated were added as covariates in all models.

Second, we investigated whether pharmacotherapy for SAD was efficacious. Structural equation models were estimated, and each model contained a pair of variables (a variable evaluated at two given time points) and tested whether the difference between the two variables differed significantly from zero based on the estimated models (a test of parameter constraints that yields a Wald $\chi^2$ value). These models allowed us to estimate pairwise differences.

*Prediction*

Multiple regression was used to investigate the association between baseline predictors and outcomes. We entered all of the study's predictors (i.e. depression, childhood maltreatment, anger suppression, submissive behavior, and social anxiety) and covariates in the same model to examine the unique variance associated with each variable. These analyses were conducted for CGI-S at week 12, LSAS at week 12, and QOL at week 12. Severity of social anxiety at baseline was controlled for with the CGI-S administered at baseline except in analyses that examined treatment outcome with the LSAS. In these analyses the LSAS at baseline was used instead. The CGI was selected due to its sensitivity to both social anxiety symptoms and impairment (Zaider et al., 2003). All analyses that examined QOL as an outcome also controlled for baseline levels of QOL. In addition, we used probit multiple regression to examine the association of the predictor variables with treatment responder status (CGI-I), attrition, and clinically significant improvement

To determine clinically significant improvement we computed reliable change and CSC based on LSAS scores. Reliable change was computed as 1.96 x the standard error of the difference, which indicated that a reduction in LSAS score greater than 18.45 was needed (Jacobson & Truax, 1991). Reliable change is necessary although not sufficient for CSC; CSC is defined as both meeting the threshold for reliable change and as shifting from the dysfunctional

to the functional range (Jacobson & Truax, 1991). The CSC criterion was determined as a LSAS score lower than the halfway point (34.6) between two standard deviations above the mean of a non-anxious healthy adult sample (35.81, $M$ = 13.61, $SD$ = 11.1; Fresco et al., 2001) and two standard deviations below the baseline LSAS mean in this sample (33.39, $M$ = 74.45, $SD$ = 21.03). Given that CSC is a more conservative assessment of change than symptom change alone, CSC analyses for hypotheses one and two were only conducted when one symptom outcome (i.e., LSAS, CGI-S, or CGI-I) was also significant for the corresponding hypothesis.

For analyses with a continuous dependent variable, the standardized estimate for each predictor variable (β) and Cohen's $f^2$ for the overall model were included as measures of effect size. For analyses with a categorical dependent variable, effect sizes were calculated using Nagelkerke's $R^2$. For both Cohen's $f^2$ and Nagelkerke's $R^2$, effect sizes of .02, .15, and .35 are considered small, medium, and large, respectively.

*Mediation*

To examine the preconditions for mediation, we used zero-order correlations to examine the strength of the relationships between our predictor variables and our outcome variables. We then examined the correlations between the five baseline predictors and the working alliance. We checked for multicollinearity among the five predictor variables using the standard Variance Inflation Factor (VIF) with a critical value of 10 (Tabachnik & Fidell, 2007). Depression, childhood maltreatment, anger suppression, submissive behavior, and social anxiety served as the predictors in mediation models (entered separately), working alliance assessed at week 8 was the hypothesized mediator, and post-treatment social anxiety (CGI-S and LSAS), response to treatment (CGI-I) and QOL were the outcome variables. To demonstrate treatment response, baseline levels of social anxiety and any necessary demographic variables were controlled.

Statistical significance was determined at $p < .05$ if the 95% bootstrapped confidence interval (5,000 resamples) of the indirect effect did not contain zero (see Preacher & Hayes, 2004, 2008). Effect sizes for the indirect effect of analyses with a continuous outcome variable were calculated using kappa-squared ($k^2$). For $k^2$, Preacher and Kelley (2011) suggest that 0.01, 0.09, and 0.25 represent small, medium, and large effect sizes, respectively. Effect sizes for mediation models with a dichotomous outcome variable should be considered with caution, given that they are only recently being developed and subjected to scrutiny (e.g., Iacobucci, 2012; MacKinnon, Fairchild, & Fritz, 2007; Preacher & Kelley, 2011). Instead, the indirect effect can suffice in communicating effect size and the mediator's relative importance in these models (Preacher & Kelley, 2011).

*Exploratory analyses*

Prior research has found quadratic associations between the working alliance and decreases in anxiety (Hayes et al., 2007) and that a strong working alliance early in treatment positively predicted outcome (Zuroff & Blatt, 2006). Thus, we examined whether quadratic, rather than linear, models of the working alliance predicted outcome by regressing a working alliance quadratic term and a working alliance linear term on end-state social anxiety (LSAS and CGI-S). In addition, we also regressed working alliance after session 1 on these outcomes.

# CHAPTER 3

## RESULTS

### Preliminary Analyses

There were no significant site differences between baseline or post-treatment levels of social anxiety symptoms (CGI-S and LSAS), responder status, or mid-treatment working alliance (all *p*s > .05). Participants who responded to paroxetine did not differ from those who did not on any demographic characteristics, with the exception of sex (greater proportion of male non-responders; β = -1.114, Wald $\chi^2$ = -2.305, OR = 0. 328, *p* = .021, 95% CI = 0.127-0.846) and age (greater proportion of older non-responders; β = .047, Wald $\chi^2$ = 2.441, OR = 1.048, *p* = .015, 95% CI = 1.009-1.089). Sex and age were added as covariates in all analyses. There were no significant differences (all *p*s > .05) in demographic variables among completers and non-completers on sex, age, years of education, marital status, or income. Demographic characteristics are displayed in Table 1 and correlations between study variables are displayed in Table 2.

Table 1
Demographic Characteristics of Sample

| | |
|---|---|
| Females, No. (%) | 52 (37.7) |
| Age, mean (*SD*), years | 32.74 (11.36) |
| Years of education (*SD*) | 15.38 (2.32) |
| Race, No. (%) | |
| Caucasian | 64 (46.4) |
| Asian or Pacific Islander | 18 (13.0) |
| Black | 30 (21.7) |
| Other | 26 (18.9) |
| Hispanic, No. (%) | 20 (14.5) |
| Marital Status No. (%) | |
| Single (never married) | 99 (71.7) |
| Married | 21 (15.2) |
| Divorce-Separated | 14 (10.2) |
| Widowed | 1 (0.72) |
| Other | 2 (1.5) |
| Not reported | 1 (0.72) |
| Yearly Income No. (%) | |
| <$10,000 | 10 (7.2) |
| $10,000-$19,999 | 22 (15.9) |
| $20,000-$39,999 | 30 (21.7) |
| $40,000-$59,999 | 20 (14.5) |
| $60,000-$79,999 | 16 (11.6) |
| $80,000-$99,000 | 6 (4.3) |
| >$100,000 | 5 (3.6) |
| Not reported | 29 (21.0) |

Table 2

*Descriptive Statistics and Correlations Between Study Varibles at Baseline and Mid-Treatment Working Alliance*

| *Variable* | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| 1. Emotional Maltrreatment | - | | | | | | | |
| 2. LSAS Total Score | .243** | - | | | | | | |
| 3. CGI - Severity | .225* | .392** | - | | | | | |
| 4. Submissive Behavior Scale | .119 | .474** | .255* | - | | | | |
| 5. Anger Suppression | .068 | .198* | .142 | .474** | - | | | |
| 6. Beck Depression Inventory - II | .268** | .466** | .362** | .350** | .244** | - | | |
| 7. Mid-Treatment Working Alliance | -.266* | -.061 | -.001 | .107 | .107 | -.181 | - | |
| 8. Baseline Working Alliance | -.180 | -.132 | -.110 | .092 | -.054 | -.309** | .546** | - |
| *Mean* | 23.640 | 75.450 | 5.260 | 35.390 | 20.410 | 16.520 | 66.078 | 53.040 |
| *Standard Deviation* | 9.130 | 21.030 | .720 | 9.650 | 4.530 | 12.230 | 12.866 | 13.87 |

*Note.* * $p < .05$; ** $p < .01$. LSAS = Liebowitz Social Anxiety Scale. CGI = Clinician Global Impression Scale.

**Treatment Effects on Social Anxiety Symptoms**

Overall, there was a significant difference between LSAS scores at baseline ($M$ = 76.337, $SD$ = 20.064) and post-treatment ($M$ = 37.728, $SD$ = 21.304), Wald $\chi^2$ = 193.13, $p < .001$, and 36.7% of the sample experienced CSC. There was also a significant difference in CGI-S scores at baseline ($M$ = 5.324, $SD$ = 0.721) and post-treatment ($M$ = 3.509, $SD$ =1.223), Wald $\chi^2$ = 175.22, $p < .001$. In addition, 67.9% of individuals who completed treatment were classified as treatment responders. Overall, paroxetine treatment was an efficacious intervention for SAD.

**Predictors of Outcome**

Consistent with our hypotheses, higher levels of depression predicted poorer response to pharmacotherapy, indicated by higher scores of the CGI-S at week 12 (β = 0.03, $p$ = .003) and the LSAS at week 12 (β = 0.388, $p$ = .032). Being female predicted better response to pharmacotherapy as measured by severity of social anxiety (LSAS and CGI severity) and quality of life.

A history of emotional maltreatment (β = 0.248, $p$ = .029) predicted whether patients dropped out of treatment. Contrary to hypotheses, higher levels of submissive behavior at baseline predicted a reduced likelihood of attrition (β = 0.223, $p$ = .041). Other statistical analyses probing the association between predictor variables and pharmacotherapy outcome were

non-significant. Lower levels of quality of life at baseline were associated with lower levels of quality of life at post-treatment. All predictor results are displayed in Tables 3 and 4.

Table 3
*Linear Regressions with Predictors*

| | | LSAS-12 | | | | CGI Severity-12 | | | | QOLI-12 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Step | *Predictors* | β | *t* | *p* | $\Delta f^2$ | β | *t* | *p* | $\Delta f^2$ | β | *t* | *p* | $\Delta f^2$ |
| | Model | | | | .079 | | | | .101 | | | | .923 |
| 1 | Age | .165 | 1.757 | .082 | | .145 | 1.549 | .124 | | -.008 | -.112 | .911 | |
| | Sex | .191 | 2.041 | .044* | | .248 | 2.643 | .009** | | -.161 | -2.247 | .027* | |
| | QOLI - Baseline | - | - | - | | - | - | - | | .648 | 8.718 | <.001** | |
| | Model | | | | .410 | | | | .113 | | | | .050 |
| 2 | Emotional Maltreatment | -.242 | 1.064 | .287 | | .025 | 1.869 | .069 | | -.309 | 1.178 | .239 | |
| | Submissive Behavior Scale | .254 | .943 | .346 | | .015 | 1.023 | .307 | | .139 | .514 | .607 | |
| | Anger Suppression | -.316 | -.637 | .524 | | .005 | .164 | .870 | | .134 | .229 | .819 | |
| | BDI- II | .388 | 2.150 | .032* | | .030 | 2.921 | .030** | | -.074 | -.301 | .763 | |
| | CGI - Severity | - | - | - | | .203 | 1.209 | .227 | | 3.242 | 1.037 | .300 | |
| | LSAS Total Score | .302 | 2.365 | .018* | | - | - | - | | - | - | - | |

*Note.* * $p < .05$; ** $p < .01$. LSAS = Liebowitz Social Anxiety Scale. CGI = Clinician Global Impression Scale. QOLI = Quality of Life Inventory BDI-II=Beck Depression Inventory-II.

Table 4
*Probit Regressions with Predictors*

| | | Attrition | | | | CGI-Improvement | | | | Clinically Significant Improvement | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Step* | *Predictors* | *B* | *SE B* | *p* | $\Delta f^2$ | *B* | *SE B* | *p* | $\Delta f^2$ | *B* | *SE B* | *p* | $\Delta f^2$ |
| | Model | | | | .009 | | | | .150 | | | | .030 |
| 1 | Age | .015 | .017 | .382 | | .042 | .020 | .032* | | - | - | - | |
| | Sex | .177 | .018 | .675 | | 1.002 | .492 | .042* | | .589 | .407 | .148 | |
| | Model | | | | .106 | | | | .041 | | | | .030 |
| 2 | CGI - Severity | .240 | .163 | .141 | | - | - | - | | - | - | - | |
| | Emotional Maltreatment | .028 | .013 | .029* | | .008 | .015 | .592 | | - | - | - | |
| | Submissive Behavior Scale | .024 | .012 | .041* | | -.006 | .019 | .762 | | - | - | - | |
| | Anger Suppression | .002 | .027 | .947 | | -.022 | .038 | .559 | | - | - | - | |
| | BDI- II | .005 | .011 | .645 | | -.012 | .013 | .338 | | .008 | .011 | .465 | |

*Note.* * $p < .05$; CGI = Clinician Global Impression Scale. BDI-II = Beck Depression Inventory-II.

## Mediators of Outcome

VIF values for all predictor variables (BDI = 1.29; Emotional Maltreatment = 1.07; SBS = 1.63; Anger Suppression = 1.377; LSAS Baseline = 1.440; CGI-S Baseline = 1.468) were under 10, suggesting no significant multicollinearity among variables. Given that age and sex were significantly associated with outcome, *post hoc* mediation analyses were conducted for both variables.

Consistent with our hypotheses, the psychiatrist-assessed working alliance significantly mediated the relationship between emotional maltreatment and response to pharmacotherapy, indexed by the CGI-S-12 and LSAS-12 (controlling for baseline levels of social anxiety) and QOL (controlling for baseline levels of QOL). All other mediation relationships between predictors and outcomes of pharmacotherapy were non-significant (Table 5).

Table 5

*Mediation Analyses with Working Alliance Mid-Treatment Mediating Associations Between Baseline Predictors and Outcomes*

| Independent Variable (IV) | Dependent Variable (DV) | Effect of IV on Mediator | Effect of Mediator on DV | Direct Effect of IV on DV | Indirect effect | CI of indirect effect | $K^2$ |
|---|---|---|---|---|---|---|---|
| LSAS | LSAS-12 | -.044 | -.308 | .450 | .014 | [-.023, .097] | .015 |
| | Attrition | -.040 | -.023 | -.004 | .001 | [-.001, .006] | |
| | CGI-Improvement-12 | .216 | -.016 | -.082 | -.003 | [-.091, .068] | |
| | QOLI | -.034 | .534 | -.344 | -.018 | [-.127, .050] | .013 |
| CGI - Severity | CGI-Severity-12 | -.225 | -.017 | .323 | .004 | [-.051,.113] | 0.01 |
| | Attrition | .216 | -.022 | .219 | -.005 | [-.094, .097] | |
| | CGI-Improvement-12 | .216 | -.016 | -.082 | -.003 | [-.091, .068] | |
| | QOLI | -.068 | .607 | -4.580 | -.041 | [-2.921, 1.782] | .001 |
| Emotional Maltreatment | LSAS-12 | -.392 | -.380 | -.441 | .149 | **[.015, .433]*** | .063 |
| | CGI-Severity-12 | -.381 | -.024 | -.029 | .009 | **[.001, .025]*** | .084 |
| | Attrition | -.396 | -.019 | .014 | .008 | [-.003, .025] | |
| | CGI-Improvement-12 | -.396 | -.016 | -.003 | .007 | [-.002, .021] | |
| | QOLI | -.379 | .446 | -.108 | -.169 | **[-.493, -.011]*** | .053 |
| | Clinical Significant Improvement | -.374 | .027 | -.002 | -.010 | [-.031, .032] | |
| Submissive Behavior Scale | LSAS-12 | .128 | -.426 | .639 | -.054 | [-.239, .030] | .021 |
| | CGI-Severity-12 | .127 | -.017 | .007 | -.002 | [-.011, .001] | .017 |
| | Attrition | .111 | -.021 | -.020 | -.002 | [-.011, .002] | |
| | CGI-Improvement-12 | .111 | -.015 | -.008 | -.002 | [-.011, .001] | |
| | QOLI | .115 | .622 | -.411 | .097 | [-.032, .376] | .035 |
| Anger Suppression | LSAS-12 | .272 | -.417 | .568 | -.113 | [-.580, .098] | .026 |
| | CGI-Severity-12 | .270 | -.017 | .028 | -.005 | [-.029, .004] | .018 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Attrition | .220 | -.220 | -.014 | -.005 | [-.03, .007] | |
| | CGI-Improvement-12 | .220 | -.015 | -.028 | -.003 | [-.027,.004] | |
| | QOLI | .305 | .631 | -1.372 | .193 | [-.0162, .812] | .034 |
| Beck Depression Inventory - II | LSAS-12 | -.207 | -.349 | .413 | .072 | [-.005, .270] | .042 |
| | CGI-Severity-12 | -.024 | -.015 | .022 | .003 | [-.001, .012] | .031 |
| | Attrition | -.176 | -.023 | -.005 | .004 | [-.001, .015] | |
| | CGI-Improvement-12 | -.195 | -.006 | -.002 | .001 | [0.0, .005] | |
| | QOLI | -.196 | .449 | -.970 | -.088 | [-.270, .001] | .040 |
| Age | LSAS-12 | -1.397 | -.405 | 2.812 | .565 | [-.225, 2.946] | .030 |
| | CGI-Severity-12 | -1.543 | -.017 | .132 | .027 | [-.010, .142] | .024 |
| | Attrition | -1.337 | -.022 | .061 | .030 | [-.021, .135] | |
| | CGI-Improvement-12 | -1.337 | -.016 | .255 | .021 | [-.013, .137] | |
| | QOLI | -1.802 | .635 | .753 | -1.145 | [-4.143, .217] | .045 |
| Sex | LSAS-12 | 4.431 | -.412 | -6.779 | -1.826 | [-6.172, .045] | .042 |
| | CGI-Severity-12 | 4.525 | -.018 | -.556 | -.080 | [-.276, .008] | .033 |
| | Attrition | 4.157 | -.022 | .202 | -.092 | [-.330, .020] | |
| | CGI-Improvement-12 | 4.156 | -.016 | -.544 | -.066 | [-.272, .029] | |
| | QOLI | 4.748 | .453 | 8.808 | 2.150 | [.245, 5.951] | .036 |

*Note.* * $p < .05$; ** $p < .01$. LSAS = Liebowitz Social Anxiety Scale. CGI = Clinician Global Impression Scale. QOLI = Quality of Life Inventory.

## Exploratory Analyses

To examine whether a quadratic relationship would present a better fit than a linear model, we entered both linear and quadratic terms as predictors in a model and LSAS-12 as the outcome. The mid-treatment working alliance, modeled quadratically ($\beta$ <.001, $t$ = -0.275, $p$ = .783) did not predict outcome, suggesting that a quadratic relationship did not model the results better than a linear one. In addition, the therapeutic relationship at the end of session 1 was unrelated to end-state social anxiety (LSAS-12, $\beta$ = -0.177, $t$ = -.983, $p$ = .325; CGI-S-12, $\beta$ = -0.012, $t$ = -1.181, $p$ = .238) or attrition (Wald $\chi^2$ = 33.808, $p$ = .734).

# CHAPTER 4

## DISCUSSION

The aims of this study were to investigate predictors of pharmacotherapy outcome for individuals with SAD and to test whether the quality of the patient-clinician relationship was a pathway through which these predictors exerted their influence. The results of the present analyses indicate that patients with SAD who had high levels of depression did not respond to pharmacotherapy as well (i.e., they demonstrated higher end-point social anxiety) as individuals with SAD and lower levels of depression. In addition, individuals with SAD who had experienced high levels of emotional maltreatment and individuals with SAD who displayed lower levels of submissive behavior had a higher likelihood of dropping out of treatment. Finally, individuals who reported higher levels of emotional maltreatment formed a comparatively weaker relationship with their psychopharmacologist, thereby leading to a poorer response to treatment (i.e. higher end-point social anxiety and lower end-point QOL).

The finding that females responded better than males is consistent with studies of pharmacotherapy for depression (Baca, Garcia-Garcia, & Porras-Chavarino, 2004; Khan, Brodhead, Schwartz, Kolts, & Brown, 2005; Kornstein et al., 2000). However, our study is the first to find a significant association between gender and outcome for individuals with a primary diagnosis of SAD for any treatment modality. Some researchers speculate that sex-specific biological differences in serotonergic systems may, at least in part, explain differences in treatment response (e.g., Young et al., 2009). Yet, given that emotional maltreatment predicts social anxiety and interpersonal dysfunction, it is also worth considering a psychological explanation. Although we did not examine whether gender moderated the mediating role of working alliance, it is possible that gender differentially influenced the working alliance, a

speculation consistent with research associating increased interpersonal sensitivity to interpersonal experiences for women as opposed to men (Stroud, Salovey, & Epel, 2002). The results of our study also indicate that younger patients responded better to treatment compared to their counterparts. However, when other covariates were added into the model, age became non-significant, suggesting that the variance shared by age and outcome was accounted for by other variables.

**The Association Between Predictor Variables and Outcome**

For our first hypothesis, we conjectured that higher levels of depression, emotional maltreatment, anger suppression, submissive behavior and social anxiety would be associated with poorer response to pharmacotherapy. Support for our first hypothesis was mixed.

We found that higher levels of depression among patients with SAD predicted a poorer response to pharmacotherapy, extending previous research that has investigated this relationship for group (Chambless et al., 1997; Scholing & Emmelkamp, 1999), individual (Collimore & Rector, 2012), and internet-based (Hedman et al., 2012) CBT. Our study is the first to investigate this question in relationship to pharmacotherapy for SAD. Future research should focus on better understanding possible explanatory mechanisms for this finding, considering that our study suggested that the working alliance did not mediate the association.

We also found that higher social anxiety at baseline was associated with higher social anxiety at the end of treatment. This finding is consistent with other studies that found an effect for patients with SAD treated with brofaromine and fluvoxamine (Slaap et al., 1996) as well as GCBT (Kawaguchi et al., 2013; Scholing & Emmelkamp, 1999). However, our finding is at odds with D. Stein and colleagues' (2002) investigation of three separate trials of paroxetine for SAD in which baseline levels of social anxiety were not associated with treatment response. Yet, our

results did not indicate that baseline levels of social anxiety predicted responder status, a metric that factors into the clinical status of a particular patient at the beginning of treatment. Therefore, it may be that individuals who had higher social anxiety symptoms at baseline had the same magnitude of improvement as individuals with a lower severity of social anxiety symptoms, but still had comparatively higher end-point severity of symptoms.

Emotional maltreatment predicted a greater probability of attrition from pharmacotherapy, a finding consistent with our hypothesis and one that replicates existing research for the treatment of disorders other than SAD. Our results are consistent with a previous analysis of this dataset which found a similar relationship with a different analytic approach (Bruce et al., 2012). Although a better working alliance significantly mediated the relationship between high levels of emotional maltreatment and higher end-point social anxiety, the working alliance did not mediate the relationship between emotional maltreatment and probability of attrition. It is certainly possible that the working alliance does not influence the relationship between emotional maltreatment and attrition from treatment; but it is also worth considering the possibility that many of the patients dropped out before session eight, when the working alliance was assessed, precluding a thorough investigation of this question.

Higher levels of submissive behavior predicted a lower probability of dropping out of treatment, a direction of effect counter to our hypothesis. Our study is the first to examine the role of submissive behavior on treatment outcome, although animal models have indicated that SSRI medications (i.e., fluoxetine) reduce submissive behavior in rats (Malatynska, Rapp, Harrawood, & Tunnicliff, 2005). We hypothesized that submissive behavior would predict a higher probability of treatment attrition as submissive behavior would impede the development of a strong therapeutic relationship. However, it is possible that such individuals were more

treatment compliant, given the speculation that individuals behave submissively as a means of attenuating interpersonal competition (Gilbert, 2014), in turn making it less likely that patients would enact behaviors that would cause a rift in the therapeutic relationship.

Although previous studies have found higher levels of baseline anger suppression (Erwin et al., 2003) to be associated with poorer response to CBT, our results suggest that the same influence may not be present in connection with pharmacotherapy. This finding is also consistent with a study that found that, among socially anxious people, relationship closeness was enhanced over time for those more likely to withhold negative emotions, whereas for individuals with less social anxiety relationship closeness was enhanced when emotions were openly expressed (Kashdan, Volkmann, Breen, & Han, 2007).

**The Working Alliance as a Mediator Between Predictor Variables and Outcome**

Our second hypothesis was partially supported. The working alliance did not mediate the relationship between submissive behavior, social anxiety, depression, or anger suppression and outcome. However, consistent with our hypothesis, individuals with a history of greater self-reported emotional maltreatment had a poorer response to pharmacotherapy, and this comparatively muted change was at least partially explained by a lower quality therapeutic relationship. Thus, SAD patients with a history of emotional maltreatment have a lower likelihood of completing pharmacotherapy and, should they complete the trial, will likely have more severe social anxiety and a more impaired quality of life. Effect sizes pertaining to the influence of the working alliance on treatment outcome were in the small to moderate range, a finding consistent with literature suggesting that the therapeutic relationship explains approximately 30% of the variance in therapy outcome (Hubble, Duncan, & Miller, 1999).

The mediating role of the working alliance for the socially anxious patient who experienced emotional maltreatment is consistent with the cognitive behavioral conceptualization of SAD etiology. This model posits that SAD is often a result of a biological vulnerability that acts in conjunction with negative learning experiences, forming social threat schemata. These schemata are then activated by social interaction due to attention and cognitive biases that maintain social anxiety and reinforce the threat schemata (Heimberg et al., 2014). Within the framework of emotional maltreatment, this model is also consistent with literature suggesting that harsh discipline and abuse are linked to threat-salient attributions about others' behaviors (Taylor & Alden, 2005; Weiss, Dodge, Bates, & Pettit 1992), a finding that illustrates how early life experiences could engineer and maintain social anxiety.

These results speak to the importance of the therapeutic relationship, a psychosocial construct, to a biologically-based intervention. The finding that the working alliance, an inherently interpersonal construct, significantly mediated the association between self-reported emotional maltreatment and higher social anxiety symptoms at post-treatment, suggests that pharmacotherapy did not adequately address the interpersonal deficits that arise from a history of emotional maltreatment. It may be that such patients need a longer duration of treatment, an adjunctive treatment, or a treatment that focuses on their longstanding interpersonal difficulties to achieve a more robust treatment response.

Integrating components of interpersonally focused, evidence-based therapies with pharmacotherapy for patients with SAD and a history of emotional maltreatment is a notion that merits consideration given the results of this study. Individuals with high levels of self-reported emotional maltreatment experience a large range of significant interpersonal difficulties (Parker & Herrera, 1996), and thus an intervention that, at least in part, targets these difficulties would be

indicated. This recommendation is consistent with the American Psychiatric Association's practice guidelines for recommending psychodynamic psychotherapy for individuals with panic disorder and comorbid Cluster C personality disorders (APA, 2009) as an adjunct to pharmacotherapy.

Several evidence-based, interpersonally-centric, treatments for SAD exist. Integrated interpersonal cognitive-behavioral group treatment (IICBT; Alden & Taylor, 2011) has shown promise as an efficacious treatment for SAD. IICBT has three primary components: standard CBT interventions and techniques, attention to interpersonal habits with behavioral experiments, and exercises that aim to identify core interpersonal patterns and their social developmental origins. In addition to IICBT, interpersonal therapy for SAD (IPT; Lipsitz, Markowitz, Cherry, & Fyer 1999) has been shown to be significantly superior to a waitlist control group (although it does not perform as well as cognitive therapy; Stangier, Schramm, Heidenriech, Berger, & Clark, 2011). IPT strives to help patients form and maintain close relationships through the exploration of their social roles. Finally, at its theoretical core, short-term psychodynamic psychotherapy (STPP) focuses on interpersonal difficulties and how such difficulties interact with the patient-therapist relationship (Shedler, 2010), a reality consistent with the dynamically-informed roots of the theory of the working alliance (Bordin, 1979). STPP for SAD aims to identify a patient's core habits of relating (i.e., the "core conflictual relationship theme"; Luborsky, 1984). In STPP, earlier interpersonal learning experiences (e.g., emotional maltreatment) are believed to be played out in the consulting room with the clinician, providing a rich opportunity for therapeutic intervention. One randomized controlled trial showed no differences between STPP and CBT (Bögels, Wijts, Oort, Sallaerts, 2014), although STPP required quite a few more sessions to achieve a similar effect. Another study showed higher rates of remission (but not response) in

favor of CBT, although STPP was still superior to a waitlist control group (Leichsenring et al., 2013). Furthermore, a meta-analysis (Leichsenring, Rabung, & Leibing, 2004) indicated that STPP is an efficacious treatment for SAD.

**Clinical Implications**

This study has several findings that may offer heuristic guidance for clinical care. First, clinicians should consider assessing patients with SAD for depression, higher levels of submissive behavior, and a history of emotional maltreatment, as all of these predict a poorer response to pharmacotherapy. As already discussed, clinicians may wish to consider increased attention to interpersonal dysfunction, particularly for those patients who have experienced emotional maltreatment, and consider how such interpersonal presentations may impact the therapeutic relationship, play themselves out in therapy, and ultimately negatively influence response to treatment. To this end, clinicians may wish to consider employing IICBT, IPT, or STPP as adjuncts to pharmacotherapy.

In addition, this study sought to evaluate outcomes of treatment beyond the typical focus on symptom reduction, an aim consistent with prior recommendations for treatment outcome research (e.g., Kendall, Holmbeck, & Verduin, 2004). We are aware of only one other study (Zuroff & Blatt, 2006) that examined the impact of the working alliance on outcomes beyond symptom reduction. The finding that emotional maltreatment led to lower levels of QOL, significantly mediated by the therapeutic relationship, indicates the scope of outcomes in which the working alliance is negatively impactful. However, none of our analyses predicted clinically significant improvement, underscoring the need for augmenting treatments with scientifically-informed clinical approaches such as treatment personalization.

Finally, this study was the first to show that the working alliance is influential for a particular set of patients receiving pharmacotherapy for SAD, extending the findings from the psychotherapy literature for SAD specifically (Alden et al., 2006). Yet, psychiatry training of late is increasingly centered on understanding the neurobiological and pharmokinetic underpinnings of psychotropic medications, to the relative exclusion of factors such as the alliance. Our findings highlight the importance of training emerging clinicians in the development, maintenance, and change-inducing properties pertaining to the therapeutic relationship (an argument made by others as well, e.g., Norcross, 2002). Psychiatry training programs should offer didactics in non-specific skills (a similar argument can be made for psychology training programs, but that is beyond the scope of the paper), in addition to continuing to offer the much needed training in evidence-based interventions. Research indicates that clinical supervision positively influences therapists' ability to form an alliance (Bambling, King, Raue, Schweitzer, & Lambert, 2006) and that there are identifiable and modifiable therapist traits that positively influence the development of a strong therapeutic relationship (Horvath, 2001).

**Limitations and Future Directions**

Although this study benefited from the use of a clinical sample and several other methodological strengths including independent evaluators and the proper dosing of paroxetine, several limitations need to be acknowledged. First, all predictor variables in this study were assessed by self-report (a potential problem of common method variance) and emotional maltreatment was assessed retrospectively. Future research would benefit from assessing these variables via additional methodologies such as clinician-interview and corroborative report. In addition, only the psychiatrist-rated, rather than patient-rated, alliance was assessed. Previous

research has suggested that therapist-rated and patient-rated working alliances are significantly but only moderately correlated (Guadiano & Miller, 2006, $r$ =.38; Tryon, Blackwell, & Hammel, 2007, $r$ = .36). Future research should probe whether the patient-rated alliance is also positively associated with pharmacotherapy outcome among individuals with SAD.

In addition, the clinician was not blind to the clinical improvement status of the patient (although they did not fill out the CGI or LSAS, they still had an impression of clinical status). Thus, it is possible that ratings of the therapeutic relationship were merely epiphenomenal and clinical improvements were driving the positive perception of the working alliance. Although some research is consistent with this finding (e.g., Webb, Beard, Auerbach, Menninger, & Björgvinsson, 2004), other research (e.g., Zuroff & Blatt, 2006) suggests that, independent of intervention and early clinical improvement, the working alliance contributes directly to positive outcome. Nonetheless, no research to our knowledge has examined the temporal relationships between the working alliance and clinical improvement in pharmacotherapy, an important line of future research. Future research should also collect data from individuals who have dropped out of treatment and ask them about reasons for their attrition. We also did not assess the characteristics (pertaining to personality and treatment approaches) of the psychiatrists in this study and thus were unable to evaluate how clinician and patient characteristics may interact, an important avenue for future investigation. Furthermore, baseline levels of social anxiety were controlled for by using the CGI-S at baseline for the majority of analyses. Although the LSAS and the CGI-S were significantly correlated at baseline, it is possible that the results would have changed had the LSAS been selected as the primary control variable.

Additionally, this study was an open trial of paroxetine for SAD and thus did not include a control group, precluding a determination of whether the findings in this study are specific to

this particular sample and/or treatment. Nonetheless, given that personalization research is a burgeoning area of research, hypothesis-generating studies that examine several putative predictors are necessary. Furthermore, future research should continue to investigate other mediators of treatment, given that depression seemed to exert its influence through mechanisms distinct from the therapeutic relationship. Our study also lacked the capacity to precisely examine the manner in which a history of emotional maltreatment negatively influenced the development of a working alliance and future investigations should examine this relationship in further detail. Finally, given that the working alliance accounts for only approximately 30% of the change experienced in treatment (Hubble et al., 1999), the analyses (and, in particular, the effect sizes) reported here may have been tempered by ceiling effects.

**Conclusions**

In accord with the movement toward personalized mental healthcare, this study investigated predictors of response to pharmacotherapy for patients with SAD and examined whether these predictors exerted their influence through an influence on the working alliance. Higher depression, emotional maltreatment, and lower submissive behavior predicted a poorer response to pharmacotherapy. Further, the working alliance significantly mediated the relationship between emotional maltreatment and pharmacotherapy response. This was the first study to investigate the therapeutic relationship in pharmacotherapy for SAD and also the first to investigate a putative mechanism (i.e., the therapeutic relationship) through which various baseline predictors may exert their influence. Given the high prevalence of SAD, its associated impairment and distress, and the frequency of SSRI pharmacotherapy, this study provides meaningful clinical implications and identifies important areas of future inquiry.

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