HHS Public Access

Author manuscript

J Anxiety Disord. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

J Anxiety Disord. 2017 December ; 52: 79–87. doi:10.1016/j.janxdis.2017.10.004.

Pharmacotherapy for Social Anxiety Disorder: Interpersonal Predictors of Outcome and the Mediating Role of the Working Alliance

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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 or mechanisms of treatment outcome. Given the interpersonal dysfunction fundamental to SAD, this study investigated whether prominent interpersonal features of SAD (submissive behavior, childhood maltreatment, suppression of anger, and depression) predicted attrition and response to pharmacotherapy and whether the working alliance mediated these relationships. This is the first study to examine the role of the working alliance in pharmacotherapy for SAD. One hundred thirty-eight treatment-seeking individuals with a primary diagnosis of SAD received 12 weeks of open treatment with paroxetine. Higher levels of depression predicted greater severity of SAD at the end of treatment, and higher levels of submissive behavior and childhood emotional maltreatment predicted a greater probability of attrition from treatment. The psychiatrist-assessed working alliance mediated response to pharmacotherapy for individuals who reported a history of emotional maltreatment. These results

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Conflicts of Interest: Dr. Cohen, Dr. Drabick, and Dr. Heimberg have no financial disclosures nor conflicts of interest to report. Dr. Blanco reports ownership of stock in General Electric, Sanofi, and Eli Lilly, Inc. Dr. Schneier reports receiving research funding from Forest Labs. Dr. Liebowitz reports the following: (1) equity ownership: Pherin Pharmaceutical, Liebowitz Social Anxiety Scale; (2) consulting: Astra Zeneca, Pfizer, Takeda, Pherin, Otsuka, Eisai, Avera, Tikvah, Wyeth, Lilly, Concert, J and J, Forest, Sunovion; (3) licensing software: GSK, Pfizer, Avera, Tikvah, Endo, Lilly, Indevus, Servier, Janssen; (4) speaking or presentation fees: Wyeth, Pfizer, Pherin, Forest; (5) recent or current clinical trial contracts: Pfizer, GSK, Astra Zeneca, Forest, Tikvah, Avera, Eli Lilly, Novartis, Sepracor, Horizon, Johnson and Johnson, Allergan, PGX Health, Abbott, Jazz, MAP, Takeda, Wyeth, Cephalon, Indevus, Endo, Ortho-McNeil, Grunenthal, Purdue Pharma, Lundbeck, Otsuka, Naurex, Shionogi, Teva, Cerecor, MSI, Pherin, Alkermes, Sunovion, Roche Genentech, Enzymotec, Alcobra, Aztherapies; and (6) recent or current investigator-initiated trial support: Pfizer, Forest, Takeda.

identify variables that predict pharmacotherapy outcome and emphasize the importance of the working alliance as a mechanism of treatment response for those with a history of emotional maltreatment. Implications for person-specific treatment selection are discussed.

Keywords

working alliance; pharmacotherapy; social anxiety disorder; treatment predictor; treatment mechanism; paroxetine

1. Introduction

Social anxiety disorder (SAD) is highly prevalent, with lifetime rates as high as 12.1% (Kessler et al., 2005), and is associated with significant social, occupational, and educational impairment (Aderka et al., 2012; Kessler, 2003; Schneier et al., 1994). Although several evidence-based treatments exist for SAD (Schneier, Bruce, & Heimberg, 2014), many patients fail to adequately respond. In one study, 42% of patients receiving group cognitive behavioral therapy (CBT) either dropped out of treatment or did not respond (Heimberg et al., 1998), and response rates for selective serotonin reuptake inhibitors (SSRIs) are similar (Liebowitz, Gelenberg, & Munjack, 2005; Van Ameringen et al., 2001). Furthermore, in studies of SSRI pharmacotherapy, only three of four patients complete the trial (Liebowitz et al., 2005; Van Ameringen et al., 2001), indicating that attrition rates, in addition to response rates, are problematic.

The National Institute of Mental Health Strategic Plan (2015) called for the study of personalized mental health care to augment the efficacy of evidence-based treatments. Numerous studies have investigated predictors of outcome of psychological treatments for SAD (e.g., Craske et al., 2014; Mululo, Menezes, Vigne, & Fontenelle, 2012). However, only a few studies have identified baseline predictors of pharmacotherapy outcomes. Early childhood onset of SAD, duration of SAD (Van Ameringen, Oakman, Mancini, Pipe, & Chung, 2004), and presence of the minor allele polymorphism of gene RGS2 (M. Stein et al., 2014) predicted poorer response to treatment with sertraline. In a previous analysis of the dataset which forms the basis of the current paper, a history of emotional maltreatment predicted attrition from paroxetine pharmacotherapy (Bruce, Heimberg, Blanco, Schneier, & Liebowitz, 2012).

Furthermore, researchers have recently explored variables that account for (i.e., mediate) improvements, another line of inquiry pertaining to treatment personalization. Although no study has examined mechanisms of change in pharmacotherapy for SAD, recent studies (e.g., Goldin et al., 2016; Gu, Strauss, Bond & Cavanagh, 2015) have explored mechanisms of change in CBT and acceptance-based interventions. Only one study has jointly considered prediction and mediation (Newman & Fisher 2013), although this study focused on GAD rather than SAD.

Research designs that examine baseline predictors and the associated mechanisms through which such variables exert their influence permit the understanding of (a) who is most likely to respond to a given treatment and (b) why individuals with these particular characteristics

are more (or less) likely to respond to treatment. Given the centrality of interpersonal concerns to SAD (Heimberg, Brozovich, & Rapee, 2014), the current study focused on interpersonally-focused variables (depression, childhood maltreatment, anger suppression, submissive behavior) that are routinely and robustly associated with SAD and/or with the outcome of pharmacotherapy for SAD and examined whether they exert their influence through the therapeutic relationship.

1.2 The Role of the Working Alliance in Social Anxiety Treatment

The working alliance (WA) is the therapeutic bond and agreement between patient and clinician on tasks and goals (Bordin, 1979). Compared to patients with panic disorder, individuals with SAD have poorer WAs (Haug et al., 2016). The WA predicted end-state social anxiety in an exposure to a feared social situation (Hayes, Hope, VanDyke, & Heimberg, 2007) and in one session of CBT combined with virtual reality therapy (Moldovan & David, 2014). However, these studies did not examine the alliance as a mediator of change.

WA is associated with outcome of pharmacotherapy for adults with major depressive disorder (MDD; Zilcha-Mano, Roose, Barber, & Rutherford, 2015), bipolar disorder (Gaudiano & Miller 2006), substance dependence (Dundon et al., 2008), and psychotic disorders (Wykes, Rose, Williams, & David, 2013). Importantly, no study to date has examined the role of WA in pharmacotherapy for SAD.

1.3 Interpersonal Variables Associated with SAD

A large number of studies examining predictors of therapeutic outcome in SAD have tended to examine variables only marginally related to core features of the disorder. For example, studies have focused on SAD subtype (e.g., Slaap, van Vilet, Westenberg, & Den Boer, 1996), age of onset (Van Ameringen et al., 2004), and duration of illness (D. Stein, Stein, Pitts, Kumar, & Hunter, 2002). Still further, although the studies mentioned above indicate predictive utility of the identified variables, other studies contradict their findings (Chen et al., 2007; Lincoln et al., 1996; Slaap et al., 1996), leaving a mixed and mostly inconclusive picture. We believe that when examining variables that may inform treatment selection and treatment process for patients grouped by diagnosis (e.g., SAD), studies should select variables that are central to the diagnostic picture rather than more peripheral. For these reasons we selected interpersonally-oriented variables relevant to SAD as both our predictor variables and our mediating variable (i.e., the therapeutic relationship).

Below, we review the evidence for several interpersonal predictors that have been consistently associated with social anxiety. We briefly discuss 1) the co-occurrence of these predictors and social anxiety, 2) the interpersonal disruption associated with these predictors, and 3) the evidence of their influence on social anxiety treatment outcome. We hypothesize that the interpersonal difficulties associated with these predictors may negatively impact the working alliance and thus pharmacotherapy outcome overall.

1.3.1 Depression—Individuals with SAD have a two-fold increase in risk for developing depression compared to those without SAD (Beesdo et al., 2007), and compared to

individuals without a psychiatric disorder, individuals with SAD were 3.5 times more likely to develop a depressive disorder during a period of 34–50 months (M. Stein et al., 2001). Individuals with depression have poorer quality parental relationships, less optimal peer relationships, and fewer friends (Field, Diego, & Sanders, 2001).

Higher levels of depression are associated with poorer response to CBT for SAD (Chambless, Tran, & Glass, 1997; Collimore & Rector, 2012; Hedman et al., 2012). No research to our knowledge has examined depression as a predictor of the outcome of pharmacotherapy for SAD. The WA mediated the relationship between interpersonal functioning and depressive symptoms in CBT for depression (Howard, Turner, Olkin, & Mohr, 2006). The WA also mediated the association between personality traits and better outcomes for depressed individuals treated with interpersonal therapy, CBT, or antidepressant medication (Kushner, Quilty, Uliaszek, McBride, & Bagby, 2016).

1.3.2 Childhood maltreatment—Simon and colleagues (2009) found that 70% of a treatment-seeking sample of patients with SAD experienced at least one type of childhood maltreatment. Interpersonally, children with a history of maltreatment display less intimacy, more conflict, and more negative and less positive affect in relationships (Parker & Herrera, 1996). A greater frequency and severity of childhood maltreatment has been associated with a lower quality of the therapeutic alliance in a sample of hospitalized adolescents (Eltz, Shirk, & Sarlin, 1995) and, notably, in a sample of patients with SAD (Alden, Taylor, Laposa, & Mellings, 2006). A history of parental abuse during childhood predicted poorer response to CBT for SAD (Alden et al., 2006), and a history of emotional maltreatment predicted higher rates of attrition from paroxetine pharmacotherapy (Bruce et al., 2012).

1.3.3 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). They also suppress the expression of anger more than their non-anxious counterparts (Erwin et al., 2003; Moscovitch, McCabe, Antony, Rocca, & Swinson, 2008). Among individuals with SAD, those with both high trait anger and the tendency to suppress the expression of anger demonstrated the most distress and impairment (Versella, Piccirillo, Potter, Olino, & Heimberg, 2016). Anger suppression is associated with reduced interest in other people and a decrease in the frequency with which one expresses his or her own feelings, thoughts, and needs (Sperberg & Stabb, 1988). Furthermore, individuals with SAD who suppress their anger have poorer treatment response and higher rates of attrition from CBT (Erwin et al., 2003).

1.3.4 Submissive behavior—According to ethological models, submissive behavior attenuates competition for social status between people (Weeks, Heimberg, & Heuer, 2011). Examples of submissive behaviors include body collapse and vocal pitch peak elevation (Weeks et al., 2011). No research has examined the association of submissive behavior to treatment outcome. Interestingly, animal models have indicated that fluoxetine reduces submissive behavior in rats (Malatynska, Rapp, Harrawood, & Tunnicliff, 2005). Although submissive behavior has a negative impact in the eyes of others (Gilbert, 2014; Weeks et al., 2011), no research to date has examined the influence of submissive behavior on the WA.

1.4 Current Study

This study examined various interpersonally-oriented predictors of response to pharmacotherapy and further examined whether these predictors exerted their effect through the WA, a relationship-centric variable, in an open trial of pharmacotherapy for SAD.

We hypothesized that higher levels of childhood maltreatment, depression, anger, and submissive behavior would be related to the following outcomes: smaller reductions in social anxiety, lower probability of achieving responder status, greater attrition, and lower quality of life (QOL). We also hypothesized that that the association between the predictors and outcome would be mediated by the WA.[1]

2. Materials and Methods

2.1 Participants

Treatment-seeking outpatients with a primary diagnosis of generalized SAD received open-label paroxetine in the first phase of a trial that later randomized patients to continuation of paroxetine with or without augmentation with CBT (clinicaltrials.gov identifier NCT00074802). Forty-six patients from the Adult Anxiety Clinic of Temple University (AACT) and 92 patients from the Anxiety Disorders Clinic of the New York State Psychiatric Institute (NYSPI) participated. Informed consent was obtained from all participants after procedures were explained. Individuals were excluded from the trial 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.

2.2 Procedure

Individuals underwent a structured diagnostic interview by an independent evaluator trained to reliability. Those patients meeting DSM-IV (American Psychiatric Association, 1994) criteria for generalized SAD underwent a medical evaluation and then met with a psychiatrist for a total of 9 visits over 12 weeks. Each patient was treated by a single psychiatrist, although multiple psychiatrists were employed across sites. Patients started at 10mg of paroxetine and were increased to a therapeutic dose (20–60mg) as tolerated. Psychiatrists offered encouragement, suggested that exposure to feared situations may be beneficial, and explained that paroxetine made such exposure easier. Pill counts were taken for treatment adherence.

[1]The current study aims were not part of the primary aims of the larger trial. However, all hypotheses were made on an *a priori* basis.

2.3 Measures

2.3.1 Diagnostic interviews—At NYSPI, 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 AACT, individuals were administered the Anxiety Disorders Interview Schedule for the DSM-IV: Lifetime Version (ADIS-IV-L; Di Nardo, Brown, & Barlow, 1994). At NYSPI, 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 supplemented the SCID-I/P social phobia module. The ADIS-IV-L and the SCID-I/P were administered by independent evaluators.

2.3.2 Baseline predictors—The Beck Depression Inventory, second edition (BDI-II; Beck, Steer, & Brown, 1996b) is a self-report measure of depression. The BDI-II has demonstrated good internal consistency and convergent and divergent validity (Beck, Steer, Ball, & Ranieri, 1996a). At baseline, internal consistency of the BDI-II was excellent (α=.92).

The Childhood Trauma Questionnaire, Short Form (CTQ-SF; Bernstein et al., 2003) is a self-report questionnaire with five subscales: sexual, physical, and emotional abuse, and physical and emotional neglect As emotional abuse and emotional neglect are most strongly related to SAD (Bruce, Heimberg, Goldin, & Gross, 2013; Kuo, Goldin, Werner, Heimberg, & Gross, 2011), we created an “emotional maltreatment” scale by summing the emotional abuse and neglect subscales. The CTQ-SF has good test-retest reliability (Scher, Stein, Asmundson, McCreary, & Forde, 2001) and convergent validity. The CTQ-emotional maltreatment scale had good internal consistency at baseline (α=.87).

The State-Trait Anger Expression Inventory, Second Edition (STAXI-2; Spielberger, 1999) assesses state and trait anger and how individuals express and control their anger. The anger expression-in subscale, which measures a person’s tendency to suppress the expression of anger, was used. Previous research supports its use (Breen & Kashdan, 2011; Erwin et al., 2003) and demonstrates its strong psychometric properties (Spielberger, 1999; Versella et al., 2016). At baseline, the anger expression-in subscale displayed adequate internal consistency (α=.75).

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

2.3.3 Outcome measures—The Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) was administered by an independent evaluator to patients at weeks 0, 4, 8, and 12, but given that we were chiefly interested in the effect on overall outcome, only weeks 0 and 12 were considered. The LSAS assesses social anxiety and is sensitive to change in studies of psychotropic medication and CBT (e.g., Heimberg et al., 1998). The LSAS has demonstrated excellent psychometric properties (Heimberg et al., 1999). 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 clinician-administered and 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, Heimberg, Fresco, Schneier, & Liebowitz, 2003) was used in the current study. This version of the CGI was administered at baseline (CGI-S only), week 4, week 8, and post-treatment, but for the purposes of this study, only weeks 0 and 12 were considered. The CGI-S is rated from 1 (not ill) to 7 (extremely ill). The CGI-I is rated 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. The CGI has strong convergent and discriminant validity (Berk et al., 2008; Zaider et al., 2003).

The Quality of Life Inventory (QOLI; Frisch, 1994) is a self-report measure intended to assess life satisfaction or QOL. The QOLI has good reliability (Frisch, Cornell, Villanueva, & Retzlaff, 1992) and convergent validity (Cohen, Jensen, Dryman, & Heimberg, 2015). The QOLI had excellent reliability at baseline (α=.96) and good reliability at post-treatment (α=.82).

2.3.4 Working Alliance—The Working Alliance Inventory (WAI) was administered at week 8. The 12-item version of the WAI (Busseri & Tyler 2003) used in this study is psychometrically equivalent to the original 36-item version (Horvath & Greenberg 1989). The WAI was completed by the pharmacotherapist. The measure has good internal consistency and convergent validity (Munder, Wilmers, Leonart, Linster, & Barth, 2010). Internal consistency was good (α=.83).

2.4 Statistical Analyses

2.4.1 Outcomes—Statistical analyses were performed with MPlus 7.11 (Muthén & Muthén, 1998–2014) and SPSS 21.0 (International Business Machines Corporation, 2012) using an intention-to-treat approach. Full Information Maximum Likelihood (FIML) estimation was used to handle missing data (Enders & Bandalos, 2001; Graham, 2009).

We first examined baseline site differences and whether any demographic variables were related to treatment outcome. Variables that were significantly associated were added as covariates. To investigate whether pharmacotherapy for SAD was efficacious, structural equation models were estimated. These analyses tested whether the difference between two variables differed significantly from zero (a test of parameter constraints that yields a Wald χ^2 value), allowing estimation of pairwise differences.

2.4.2 Prediction—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). Multiple regression was used to investigate the association between baseline predictors and outcomes. We entered all predictors and covariates in the same model. Severity of social anxiety at baseline was controlled for with the CGI-S except in analyses that examined treatment outcome with the LSAS, in which the LSAS was used. Thus, analyses predicted change in social anxiety over treatment.

2.4.3 Mediation—Statistical significance was determined at $p<.05$ if the 95% bootstrapped confidence interval (5,000 resamples) of the indirect effect did not contain zero (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 (Iacobucci, 2012; MacKinnon, Fairchild, & Fritz, 2007; Preacher & Kelley, 2011). Instead, the indirect effect can communicate the mediator's relative importance in these models (Preacher & Kelley 2011).

3. Results

3.1 Demographic Analyses

There were no significant site differences between baseline or post-treatment levels of social anxiety, responder status, or WA (all ps>.05). Responders did not differ from non-responders on any demographic characteristics, with the exception of sex (greater proportion of males were non-responders) and age (modeled continuously, greater proportion of older non-responders). Being female predicted greater change in social anxiety (LSAS and CGI-S) and QOL. There were no significant differences (ps>.05) in demographic variables between completers and non-completers. One hundred five participants (76.1%) completed the full course of pharmacotherapy. Twenty-two participants dropped out prior to week 8 when working alliance was assessed (66.67% of total attritors) and 11 (33.33% of total attritors) participants dropped out at week 8 or after. Demographic characteristics are displayed in Table 1 and correlations between study variables are displayed in Table 2.

3.2 Overall Treatment Effects on Social Anxiety Symptoms

There was a significant difference between LSAS scores at baseline (M=76.34, SD=20.06) and post-treatment (M=37.78, SD=21.30), Wald χ^2=193.13, $p<.001$. There was also a significant difference in CGI-S scores at baseline (M=5.32, SD=0.72) and post-treatment (M=3.51, SD=1.22), Wald χ^2=175.22, $p<.001$. Additionally, 67.9% of individuals who completed treatment were classified as treatment responders using the CGI-I.

3.3 Predictors of Response and Attrition

VIF values for all predictor variables suggested no significant multicollinearity among variables (BDI=1.29; Emotional Maltreatment=1.07; SBS=1.63; Anger Suppression=1.38; LSAS=1.44; CGI-S=1.47). Patients with higher levels of depression at baseline exhibited a poorer response to pharmacotherapy, indicated by smaller reductions in social anxiety (CGI-S and LSAS). Patients with higher levels of emotional maltreatment had an increased likelihood of dropping out of treatment, whereas patients who had higher levels of submissive behavior had a reduced likelihood of attrition. Lower levels of QOL at baseline were associated with lower levels of QOL at post-treatment. All other associations between predictor variables and pharmacotherapy outcomes were non-significant. All predictor results are displayed in Tables 3 and 4.

3.4 Outcomes Mediated by WA

Patients with higher levels of emotional maltreatment had a poorer response to pharmacotherapy (indexed by changes in CGI-S and LSAS and QOLI), and this effect was a function of the WA. All other mediational relationships between predictors and outcomes of pharmacotherapy were non-significant (Table 5).

4. Discussion

This study examined predictors of pharmacotherapy outcome for individuals with SAD and tested whether WA was a pathway through which these predictors exerted their influence.

Higher levels of depression (subthreshold for MDD) among patients with SAD predicted a poorer response to pharmacotherapy, extending previous findings for group (Chambless et al., 1997; Scholing & Emmelkamp 1999), individual (Collimore & Rector 2012), and internet-based (Hedman et al., 2012) CBT. Higher levels of submissive behavior predicted a lower probability of attrition. It is possible that individuals who exhibited submissive behavior were more treatment compliant, given the hypothesis that individuals behave submissively to attenuate interpersonal competition (Gilbert, 2014).

Although previous studies have found an association between higher anger suppression and poorer response to CBT (Erwin et al., 2003), our results suggest that the same association is not present in pharmacotherapy. In Erwin and colleagues' study, CBT targeted social anxiety, and no attention was specifically devoted to issues of anger management. However, there is some evidence that paroxetine is an efficacious treatment for anger (e.g., Cherek, Lane, Pietras, & Steinberg, 2002) as well as SAD. Thus, anger (and the need to suppress one's anger) may have been more effectively treated in pharmacotherapy with paroxetine.

Emotional maltreatment predicted a greater probability of attrition. These results are consistent with a previous analysis of this dataset using a different analytic approach (Bruce et al., 2012). Although WA significantly mediated the relationship between emotional maltreatment and change in social anxiety symptoms, WA did not mediate the relationship between emotional maltreatment and attrition. Because many patients dropped out before session eight, when WA was assessed, investigation of this dissociation is precluded.

Individuals with a history of greater emotional maltreatment demonstrated less reduction in social anxiety symptoms, and this was partially explained by a lower quality WA. 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. Given that only the indirect effect (and not the direct effect of emotional maltreatment on outcomes) was significant, results such as ours are likely to be observed only when the working alliance is poor.

The finding that women responded better than men is consistent with studies of pharmacotherapy for depression (e.g., Khan, Brodhead, Schwartz, Kolts, & Brown, 2005). However, our study is the first to find a significant association between gender and outcome for individuals with SAD. Sex-specific biological differences in serotonergic systems

(Young et al., 2009) or sex-specific relational differences may partially explain differences in treatment response.

The results of this study speak to the importance of the therapeutic relationship, a psychosocial construct, to a biologically-based intervention. Speculatively, it may be that paroxetine operated on different neurobiological systems as a function of the various interpersonal predictors examined. For instance, particular neurobiological correlates such as reduced hippocampal volume and amygdala hyper-reactivity are more consistently observed in individuals with a history of maltreatment than those without (Teicher & Samson, 2013). Alternatively, it is possible that a strong working alliance positively influenced the placebo response that is inherent in pharmacotherapy above and beyond the pharmacologic action of the agent. A stronger working alliance may exert its influence by increasing medication adherence or by increasing engagement with exposure to feared situations. It is also possible that stronger working alliances permit the possibility of a generative relational experience in which a person with SAD and emotional maltreatment is able to experience a safe and intimate environment, a circumstance that runs counter to their threat-salient attributions about others' behaviors (Weiss, Dodge, Bates, & Pettit, 1992; Taylor & Alden 2005).

4.1 Limitations and Future Directions

This study was the first to look at a variety of interpersonal predictors and an interpersonal mediator in the pharmacotherapy of SAD, a disorder in which the hallmark characteristic is interpersonal disruption. Furthermore, this study benefited from a relatively large clinical sample with a single treatment and independent evaluators of outcome. However, several limitations need to be acknowledged.

Although several outcome measures were clinician-administered, all predictor variables were assessed by self-report (a potential problem of common informant and method variance). Emotional maltreatment was assessed retrospectively, and inter-rater reliability for the ADIS-IV-L, LSAS, and CGI, within and across sites, was not assessed. Importantly, only psychiatrist-rated alliance was assessed. Previous psychotherapy research has suggested that therapist-rated and patient-rated WAs are significantly but only moderately correlated (Guadiano & Miller, 2006, r=.38; Tryon, Blackwell, & Hammel, 2007, r=.36). Furthermore, in psychotherapy, patient-reported alliance is thought to predict outcomes more robustly than therapist-assessed alliance (Constantino, Castonguay, & Schut, 2002). Nevertheless, therapist-assessed alliances are routinely predictive of outcome (e.g., Klein et al., 2003) and may provide a more conservative estimate of the relationship between alliance and outcome. Research on the relationship psychiatrist- and patient-assessed alliance in pharmacotherapy is scant. Yet, in one study, both psychiatrist- and patient-assessed working alliances were predictive of outcome (De Bolle, Johnson, & Fruyt, 2010). Future pharmacotherapy research should use both patient and psychiatrist assessments of alliance to further tease apart whether there may be differences between the two modes of assessment.

In this study, the alliance was assessed at week 8, after sufficient time for pharmacotherapy to demonstrate a therapeutic effect. Thus, it is possible that ratings of the therapeutic relationship were epiphenomenal and clinical improvements were driving the positive perception of the WA. Although some research is consistent with this speculation (Webb et

al., 2014), other research (Zuroff & Blatt, 2006; Zilcha-Mano et al., 2015) suggests that, independent of intervention and early clinical improvement, the WA contributes directly to positive outcome. In addition, two-thirds of patients dropped out prior to the assessment of WA, providing an incomplete evaluation of the association between various predictor variables, WA, and attrition. Furthermore, patients whose WA was assessed were more likely to finish the full treatment and were thus perhaps more likely to have a favorable response to pharmacotherapy. This possibility may have contributed to the results of the mediation analyses.

This study did not include a control group receiving placebo or another active treatment, precluding a determination of the extent to which the findings in this study are specific to this particular treatment. Nonetheless, hypothesis-generating studies that examine several putative predictors are necessary for improving personalization of treatment.

Finally, this study examined a relatively circumscribed number of interpersonal predictors that have been robustly associated with SAD. Future research should consider evaluating the effect of other interpersonal predictors. In addition, this study excluded patients with comorbid MDD, limiting the generalizability of the findings. Although to our knowledge there are no meta-analyses of pharmacotherapy outcomes that investigate the variance accounted for by the WA, given that the WA accounts for approximately 30% of the change experienced in psychotherapy (Hubble et al. 1999), the results may have been tempered by ceiling effects.

4.2 Conclusions

This was the first study to investigate the therapeutic relationship in pharmacotherapy for SAD and also the first to investigate the WA as a putative mechanism through which various interpersonal predictors may exert their influence. Given the high prevalence of SAD and its associated impairment, this study has meaningful clinical implications and identifies important areas of future inquiry.

Acknowledgments

The authors would like to thank Jonathan P. Stange, Ph.D., for his statistical consultation.

Funding: Portions of this study were supported by grants from the National Institute of Mental Health to Richard G. Heimberg (R01MH064481) and to Michael R. Liebowitz (R01MH040121) as well as grants to each of these investigators from GlaxoSmithKline Pharmaceuticals, Inc. The funding sources had no involvement in study design, collection, analysis, data interpretation, writing of the report, or the decision to submit the article for publication.

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Highlights

- Higher levels of depression associated with worse pharmacotherapy response.
- Higher submissive behavior associated with greater probability of attrition.
- Higher emotional maltreatment associated with greater probability of attrition.
- Alliance mediated pharmacotherapy response for those with emotional maltreatment.

Table 1

Demographic Characteristics of Overall Sample (N=138)

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 Variables at Baseline and Mid-Treatment Working Alliance

Variable	1	2	3	4	5	6	7
1. Emotional Maltreatment	-						
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	-
Mean	23.64	75.45	5.26	35.39	20.41	16.52	66.08
Standard Deviation	9.13	21.03	0.72	9.65	4.53	12.23	12.87

Note.

*$p < .05$;

**$p < .01$.

LSAS = Liebowitz Social Anxiety Scale. CGI = Clinician Global Impression Scale.

Table 3

Linear Regressions with Predictors

		LSAS-12				CGI Severity-12				QOLI-12			
Step	***Predictors***	***B***	***t***	***p***	**Δf^2**	***B***	***t***	***p***	**Δf^2**	***B***	***t***	***p***	**Δf^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	8.71	<.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	
	Beck Depression Inventory - 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.

Table 4

Probit Regressions with Predictors

		Attrition				CGI-Improvement			
Step	***Predictors***	***B***	***SE B***	***p***	**Δf^2**	***B***	***SE B***	***p***	**Δf^2**
	Model				.009				.150
1	Age	.015	.017	.382		.042	.020	.032*	
	Sex	.177	.018	.675		1.002	.492	.042*	
	Model				.106				.041
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	

Note.

* $p < .05$.

CGI = Clinician Global Impression Scale. BDI-II = Beck Depression Inventory-II.

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
Emotional Maltreatment	LSAS	−.392	−.380	−.441	.149	[.015, .433]*	.063
	CGI-Severity	−.381	−.024	−.029	.009	[.001, .025]*	.084
	Attrition	−.396	−.019	.014	.008	[−.003, .025]	
	CGI-Improvement	−.396	−.016	−.003	.007	[−.002, .021]	
	QOLI	−.379	.446	−.108	−.169	[−.493, −.011]*	.053
Submissive Behavior Scale	LSAS	.128	−.426	.639	−.054	[−.239, .030]	.021
	CGI-Severity	.127	−.017	.007	−.002	[−.011, .001]	.017
	Attrition	.111	−.021	−.020	−.002	[−.011, .002]	
	CGI-Improvement	.111	−.015	−.008	−.002	[−.011, .001]	
	QOLI	.115	.622	−.411	.097	[−.032, .376]	.035
Anger Suppression	LSAS	.272	−.417	.568	−.113	[−.580, .098]	.026
	CGI-Severity	.270	−.017	.028	−.005	[−.029, .004]	.018
	Attrition	.220	−.220	−.014	−.005	[−.03, .007]	
	CGI-Improvement	.220	−.015	−.028	−.003	[−.027,.004]	
	QOLI	.305	.631	−1.372	.193	[−.0162, .812]	.034
Beck Depression Inventory - II	LSAS	−.207	−.349	.413	.072	[−.005, .270]	.042
	CGI-Severity	−.024	−.015	.022	.003	[−.001, .012]	.031
	Attrition	−.176	−.023	−.005	.004	[−.001, .015]	
	CGI-Improvement	−.195	−.006	−.002	.001	[0.0, .005]	
	QOLI	−.196	.449	−.970	−.088	[−.270, .001]	.040

Note.

*p<.05;

**p<.01.

LSAS = Liebowitz Social Anxiety Scale. CGI = Clinician Global Impression Scale. QOLI = Quality of Life Inventory.