



Treatment of social anxiety with paroxetine: mediation of changes in anxiety and depression symptoms

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Abstract

Investigation of relationship patterns between co-occurring symptoms has greatly improved the efficacy of psychiatric care. Depression and anxiety often present together, and identification of primary vs secondary psychiatric symptoms has implications for treatment. Previous psychotherapy research investigating the relationship between social anxiety and depression, across social anxiety treatment, found that severity of social anxiety accounted for most of the change in depression severity across time. Conversely, severity of depression accounted for little variation in severity of social anxiety. The current investigation was conducted to extend these findings by examining this mediational relationship in a pharmacologic trial comparing paroxetine ($n = 20$) and placebo ($n = 22$). Social anxiety and depression severity were assessed weekly for 16 weeks. Consistent with the previous study, results indicated that social anxiety severity mediated most of the variance in depression severity, with little variance accounted for by a test of the reverse mediation. Surprisingly, this same pattern was also found in the placebo group. These findings suggest that this pattern of mediational relationships may be fundamental to social anxiety, rather than specific to treatment modality or secondary comorbidity.

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1. Introduction

A statistical test of mediation is an invaluable tool long used to help understand how one variable exerts influence on another and the extent to which a third variable may influence this relationship. Essentially, mediation is determined by the degree to which the following 5 conditions are met (see Fig. 1): (1) the predictor must significantly predict the outcome variable independently (path c); (2) the predictor variable must significantly predict the mediator variable (path a); (3) the mediator must significantly predict the outcome variable (path b); (4) when both the predictor and the mediator simultaneously predict the outcome variable, the mediator must continue to demonstrate a significant relationship with the outcome variable; and (5) the strength of the predictor variable on the outcome variable will be significantly

decreased when both the predictor (now path c') and mediator variable simultaneously predict the outcome variable. If path c' is significantly lowered in strength, in comparison with path c , but still maintains a significant relationship with the outcome variable, this is consistent with partial mediation. If path c' is significantly lowered in strength, in comparison with path c , and path c' fails to show a significant relationship with the outcome variable, this is consistent with full mediation.

In examining the influence of cognitive behavioral group therapy for social anxiety, Moscovitch and colleagues [1] found that improvement in depression over time was fully mediated by social anxiety symptoms, explaining 91% of session-to-session variation. However, only 6% of the improvement in social anxiety symptoms was accounted for by changes in depression, with depression being a partial mediator. These results suggest that depressive symptoms co-occurring with social anxiety (also known as *social phobia*) may best be conceptualized as a function of the social anxiety, rather than being mutually independent. This interpretation would be congruent with related areas of research that find that most

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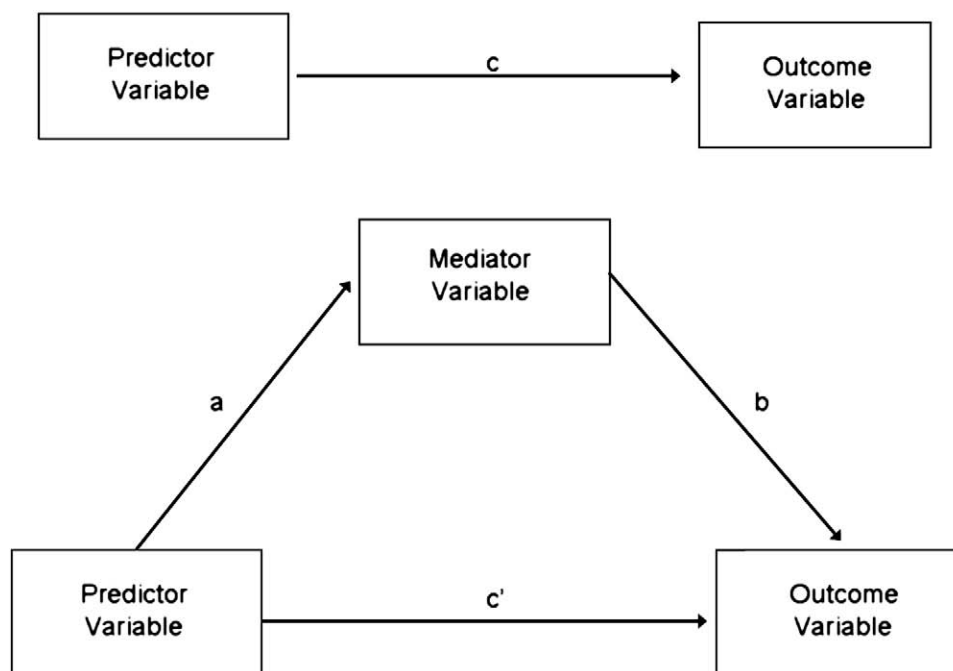


Fig. 1. Mediational relationship with paths identified.

anxiety disorders are primary in nature but increase the risk for secondary depression [2]; treating anxiety disorders may prevent the development of subsequent depression [3]; and, among this comorbid population, interpersonal rejection may be a fundamental aspect of depression symptoms [4].

Moscovitch and colleagues [1] are the first to report a unidirectional mediational relationship between temporal changes in social anxiety and depressive symptoms and the first to use hierarchical linear modeling statistical procedures [5] to examine this relationship. However, it is unclear whether these results are specific to cognitive behavioral group therapy. The current investigation was conducted to determine if this relationship is evident after pharmacologic treatment of social anxiety with paroxetine, a selective serotonin reuptake inhibitor. Although one could argue that the same pattern of mediational relationships should be seen regardless of the treatment modality, it is relevant that Moscovitch and colleagues used a form of group psychotherapy specific to the treatment of social anxiety only (ie, psychotherapy did not target symptoms of depression). Paroxetine is an effective treatment of both major depressive disorder and social anxiety, independently [6]. It is plausible that paroxetine would decrease both social anxiety and depressive symptoms without one symptom type mediating changes in the other.

The present investigation also includes a placebo group. This is particularly important because many individuals show improvement in psychiatric symptoms with placebo treatment or wait-list control [7,8], a point raised by Moscovitch and colleagues [1]. Assessment of the

mediational relationships in question, with placebo treatment, will help determine if this phenomenon is fundamental to amelioration of social anxiety symptoms, regardless of treatment type, or specific to a particular modality of treatment.

2. Methods

The present investigation is a secondary analysis of a clinical trial of paroxetine in the treatment of social anxiety among individuals with a co-occurring alcohol use disorder [9]. The study was approved by the hospital's Humans Subjects Review Committee; and subjects participated with informed, voluntary, written consent. Complete participant inclusion/exclusion criteria and greater detail on procedures can be found in that article. For brevity, only methodological information relevant to the current investigation is included. All participants in the current investigation met diagnostic criteria for an alcohol use disorder (alcohol abuse or dependence) in addition to social anxiety, a distinct difference from the sample used by Moscovitch and colleagues [1].

2.1. Participants

Participants were randomized to either placebo ($n = 22$) or paroxetine group ($n = 20$). Participants in the paroxetine and placebo groups did not statistically differ in age (mean [M] = 25 [$SD = 6.5$], 30 [$SD = 8.3$]), sex (male = 55%, 50%), ethnicity (white = 100%, 82%), or proportion of current *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, major depressive disorder ($n = 2, 2$), respectively.

Participants were recruited through community advertisement for an investigation of pharmacologic treatment of social anxiety. These advertisements did not mention the inclusion requirement of an alcohol use disorder, and none of the participants were seeking treatment of an alcohol problem. Participants were initially screened by telephone, and those likely meeting the criteria for both social anxiety disorder and an alcohol use disorder were invited to a comprehensive in-person screening. Diagnoses of social anxiety and alcohol use disorders were completed with the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* [10]; and additional inclusion/exclusion criteria were assessed.

2.2. Procedures

Eligible participants were then enrolled in a double-blind, placebo-controlled trial of paroxetine. Treatment was provided for 16 weeks. Initial dosage of paroxetine was 10 mg and was titrated to a maximum of 60 mg at 4 weeks. Participants were assessed weekly for compliance using pill count and biomarkers and completed assessments of functioning (psychologic and medical).

Participants were compensated \$50.00 for participation at week 16. Of particular relevance to the current investigation, every week, participants completed the Beck Depression Inventory (BDI) [11] to assess severity of depressive symptoms and the Liebowitz Social Anxiety Scale (LSAS) [12] to assess severity of social anxiety symptoms. The BDI [11] is a 21-item self-report measure, is widely used in both research and clinical purposes, and has demonstrated good psychometric properties [13,14]. Scores range from 0 to 63. The LSAS is a psychometrically validated, standardized questionnaire widely used in research studies to quantify social anxiety severity and treatment response [12]. The LSAS total score ranges from 0 to 144. Inclusion criteria included a baseline total score of at least 60 on the LSAS.

2.3. Statistical analyses

The Baron and Kenny (1986) method of testing mediation has been adapted for multilevel analyses [15–18].¹

¹ Kenny et al [17] described the analysis of level 1 mediation in a hierarchical model and pointed out that the Sobel test of the significance of the indirect path (eg, time to BDI to LSAS) required the covariance of the 2 regression coefficients. More recently, Bauer et al [15] detailed a method of obtaining the covariance by simultaneous estimation of the entire model via “stacking the data set” and indicating (with dummy-coded indicator variable) which variable (ie, mediator or final dependent variable) was the dependent variable for each row in the data set. Their method was employed in the current investigation’s analyses. Thus, the strength of the indirect (mediator) path was assessed by using a Sobel test [19] as well as by calculating the percentage variance accounted for by the mediational path [17], taking into account the amount of covariance between paths *a* and *b* [15]. Essentially, the percentage of variance accounted for by the mediational path is calculated by $([ab + c' + \text{covariance of } a \text{ and } b] - c') / (ab + c' + \text{covariance of } a \text{ and } b)$.

Similar to Moscovitch and colleagues [1], this adapted mediation test was applied to examine whether changes in depression were mediated by changes in social anxiety. Consistently, the reverse was examined, assessing whether changes in social anxiety were mediated by changes in depression. The predictor variable in the current investigation was time (temporal fluctuation across weeks). Mediation was assessed separately for each group (paroxetine and placebo). Thus, 4 multilevel mediation analyses were conducted, depression mediating social anxiety and social anxiety mediating depression, for the paroxetine and placebo groups separately, with time as the predictor for all analyses.

Data were analyzed as a multilevel or hierarchical linear model (HLM) in which the repeated observations are nested within subjects. Conceptually, HLM models can be thought of as 2 simultaneous regressions: level 1 and level 2. Level 1 variables change with individual observations across time (eg, week, BDI, LSAS). Level 2 variables distinguish between subjects but remain constant across observations (eg, treatment group, sex). The coefficients at level 1 (eg, BDI as a function of week) are the dependent variables of the level 2 regression (eg, treatment group). In this analysis, the level 2 regression was simply an intercept, as the treatment groups were analyzed separately.

Four multilevel mediational analyses were conducted. The first set of analyses examined whether changes in social anxiety accounted for changes in depression over time. The second set of analyses examined whether changes in depression accounted for changes in social anxiety over time. Statistical tests are shown in tables; mediational relationships (*B* values for each path) are shown in figures. Within each figure, circled *B* values reflect results from the paroxetine group; noncircled values reflect the placebo group.

3. Results

3.1. Participants

Participants in the paroxetine and placebo groups did not differ in severity of social anxiety symptoms (LSAS *M* = 87 [SD = 14.9], 93 [SD = 18.5]) or severity of depressive symptoms at baseline (BDI *M* = 17 [SD = 10.3], 17 [SD = 11.0]). Analyses of variance testing differences in baseline level of LSAS score and BDI score, by treatment group, were nonsignificant ($F_{1,41} = 1.13$, $P > .05$; $F_{1,41} = .01$, $P > .05$; respectively).

3.2. Analyses of time on depression and social anxiety

An HLM, with slopes as outcome, was conducted to determine changes in depression (BDI) and social anxiety (LSAS) over time. These relationships constitute paths *c* and *a* for all subsequent analyses. Level 1 in these analyses was BDI or LSAS predicted by time (temporal fluctuation across weeks). Subjects were nested within treatment group (paroxetine or placebo), a level 2 variable.

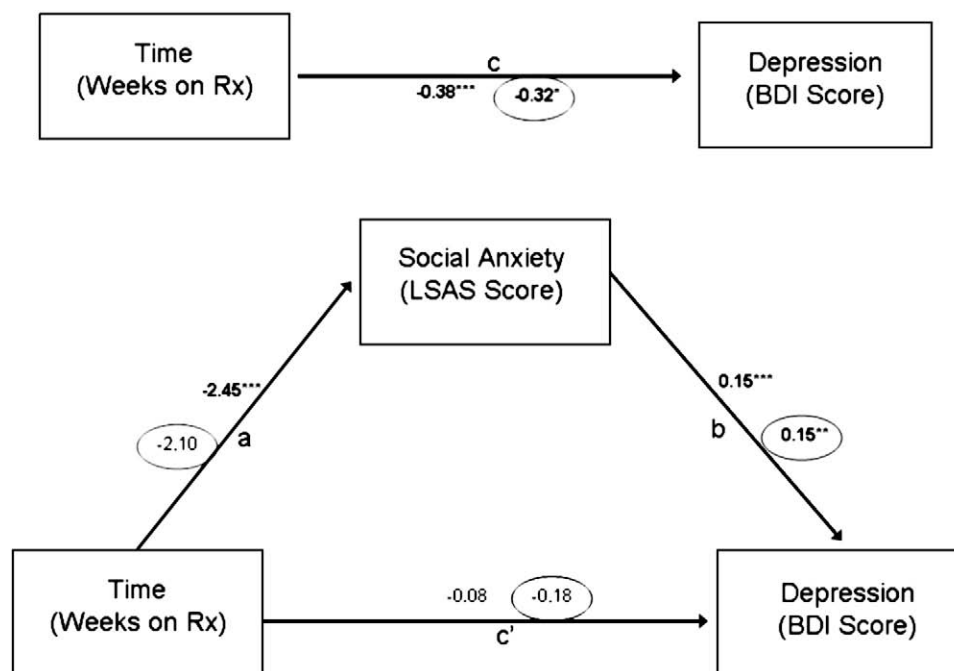


Fig. 2. Mediation of time on depression by social anxiety. Circled values represent placebo group data, and uncircled values represent paroxetine group data. * $P < .05$, ** $P < .01$, *** $P < .001$.

For depression severity, participants in both treatment groups significantly improved over time (paroxetine group: $B = -.38$, $P = .001$; placebo group: $B = -.32$, $P = .021$). For social anxiety severity, the paroxetine group showed significant reductions over time ($B = -2.45$, $P = .001$); this slope reached a trend level ($B = -2.10$, $P = .053$) for the placebo group. Although significance in paths c and a is a prerequisite for conducting a mediational analysis (Baron and Kenny, 1986), because the P value was so close to reaching significance for the placebo group in this case, analyses were continued for the placebo group to permit comparison with the paroxetine group.

3.3. Mediation analyses

3.3.1. Social anxiety mediates depression severity

Analyses to examine whether changes in depression severity (BDI scores) were mediated by changes in social anxiety severity (LSAS scores) were conducted (Fig. 2 and Table 1). Two sets of analyses were performed, one for each treatment group (paroxetine and placebo). As reported above, both treatment groups decreased in depression over time (path c in this model); and both treatment groups showed at least a trend level decrease in social anxiety over time (path a in this model).

The LSAS scores were predictive of depression scores (path b) for both treatment groups (P s $< .01$), reflecting that social anxiety and depression severity covaried within participants over time. When controlling for the effect of social anxiety, however, time was no longer a significant predictor of depression scores (ie, path c' was no longer significant for either the paroxetine or the placebo group).

The Sobel test indicated that the indirect effect of LSAS on the relationship between time and BDI was significant for both the paroxetine group ($P < .001$) and the placebo group ($P < .05$). Social anxiety severity mediated 96% and 76% of the variance of time on depression severity for the paroxetine and placebo groups, respectively.

Taken together, the results indicate that social anxiety severity was a full mediator of the relationship between time and depression severity. The results were similar regardless of whether participants received paroxetine or placebo.

3.3.2. Depression mediates social anxiety severity

Analyses to examine whether changes in social anxiety severity were mediated by changes in depression were then conducted to determine whether reverse mediation was

Table 1
Social anxiety mediating depression

Step	Path	Predictor	Outcome	B	SE B	T	P
<i>Paroxetine group</i>							
1	c	Time	Depression	-0.38	0.07	-5.31	.001
2	a	Time	Social anxiety	-2.45	0.37	-6.63	.001
3	b	Social anxiety	Depression	0.15	0.02	8.03	.001
	c'	Time	Depression	-0.08	0.08	-1.03	.318
Sobel test of indirect effect of mediator: $ab = -0.03$						-3.41	.001
<i>Placebo group</i>							
1	c	Time	Depression	-0.32	0.13	-2.50	.021
2	a	Time	Social anxiety	-2.10	1.03	-2.05	.053
3	b	Social anxiety	Depression	0.15	0.04	3.88	.001
	c'	Time	Depression	-0.18	0.12	-1.52	.144
Sobel test of indirect effect of mediator: $ab = -0.10$						-2.03	.05

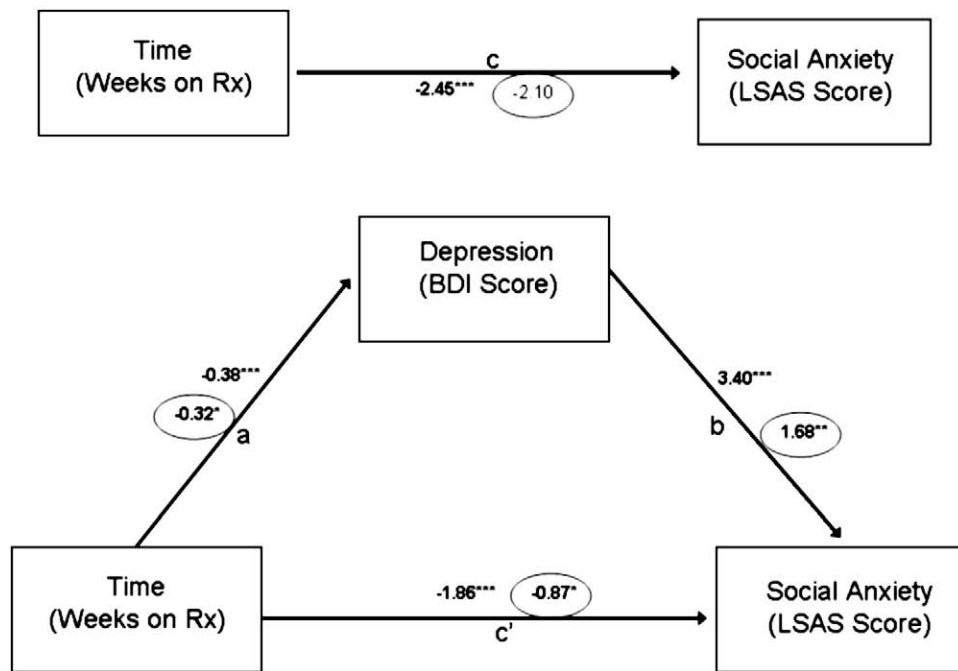


Fig. 3. Mediation of time on social anxiety by depression. Circled values represent placebo group data, and uncircled values represent paroxetine group data. * $P < .05$, ** $P < .01$, *** $P < .001$.

present (Fig. 3 and Table 2). Analyses were conducted separately for paroxetine and placebo groups. For this model, path *c* reflects whether treatment groups decreased over time in LSAS scores. As reported above, this slope was significant for the paroxetine-treated group and approached significance ($P = .053$) for the placebo group. Both the paroxetine and the placebo groups significantly decreased in depression scores over time (path *a*).

Depression severity scores were predictive of social anxiety scores (path *b*) for both treatment groups. When controlling for the effect of depression, time remained a significant predictor of LSAS score for both the paroxetine and placebo groups (path *c'*), although the strength of this relationship was diminished. The Sobel test indicated that the indirect effect of BDI on the relationship between time and LSAS scores was significant only for the paroxetine-treated group ($P < .01$); it reached a trend level ($P = .08$) for the placebo group. In the paroxetine group, depression severity mediated 23% of the variance of time on social anxiety severity.

Taken together, the results indicate that depression severity was a partial mediator of the relationship between time and social anxiety severity. The results were similar regardless of treatment group.

4. Discussion

Results from the present investigation indicate that variation in depression is tightly coupled with session-to-session variation in social anxiety. Furthermore, the results

strongly suggest that changes in depression are driven by changes in social anxiety (ie, depression variation is “mediated” by social anxiety). Results also suggest that change in social anxiety is only partially mediated by changes in depression symptoms. These results extend upon the study by Moscovitch and colleagues [1] in which they investigated mediational relationships between depression and anxiety during a course of cognitive behavioral group therapy for social anxiety. Our results are consistent with theirs, which is notable in that we examined these relationships in participants receiving a medication approved to treat social anxiety and depression, as well as in participants who received placebo.

Table 2
Depression mediating social anxiety

Step	Path	Predictor	Outcome	B	SE B	T	P
<i>Paroxetine group</i>							
1	<i>c</i>	Time	Social anxiety	-2.45	0.37	-6.63	.001
2	<i>a</i>	Time	Depression	-0.38	0.07	-5.31	.001
3	<i>b</i>	Depression	Social anxiety	3.40	0.47	7.16	.001
	<i>c'</i>	Time	Social anxiety	-1.86	0.35	-5.36	.001
Sobel test of indirect effect of mediator: $ab = -0.03$						-3.25	.01
<i>Placebo group</i>							
1	<i>c</i>	Time	Social anxiety	-2.10	1.03	-2.05	.053
2	<i>a</i>	Time	Depression	-0.32	0.13	-2.50	.021
3	<i>b</i>	Depression	Social anxiety	1.68	0.58	2.89	.009
	<i>c'</i>	Time	Social Anxiety	-0.87	0.39	-2.24	.036
Sobel test of indirect effect of mediator: $ab = -0.16$						-1.76	.08

Results of the current investigation suggest that improvement in depression severity is driven by improvement in social anxiety severity. Paroxetine and other selective serotonin reuptake inhibitors have been shown to be effective in the treatment of both major depressive disorder and social anxiety independently [6]. Given the independent efficacy of paroxetine, one might assume that ameliorations of depressive and anxiety symptoms might be positively correlated, but not have a mediational relationship, when treated pharmacologically. Moscovitch and colleagues [1] suggested that amelioration of depression symptoms during social anxiety treatment may be the result of increased social interaction, subsequent to a reduction in social anxiety. However, the psychotherapy treatment used targeted social anxiety specifically, whereas paroxetine influences both depression and social anxiety; and yet, a mediational pattern is still maintained.

The placebo control group demonstrated improvements in both depression and social anxiety symptoms, although not at the magnitude seen in the paroxetine group. This is not uncommon, as it is well known that placebo medication can contribute to improvement in many medical and psychologic symptoms [20] and, more specifically, for social anxiety [7,21,22] and depression [8]. Of particular interest in the current investigation, the placebo group demonstrated a mediational pattern consistent with that observed in the paroxetine group. Specifically, in the placebo group, social anxiety symptoms fully mediated depression symptoms, accounting for 76% of the variance in the effect of placebo on depression scores. In the test of reverse mediation, consistent with the paroxetine group, depression symptoms were a significant partial mediator, accounting for about 33% of the variance in the effect of placebo on social anxiety. This seems to suggest that, among patients presenting with primary social anxiety, depression symptoms will be ameliorated regardless of treatment type, as long as the treatment is effective in reducing social anxiety severity. It should be noted, however, that the relationship between placebo and time was at an α of .053 and that the decrease in relationship between these variables, when accounting for the mediator, was at the trend level ($P = .08$).

The current investigation was consistent with that of Moscovitch and colleagues (2005), which is remarkable given that the 3 treatment modalities examined exert their effect through different pathways (eg, challenging dysfunctional cognitions vs increased availability of serotonin vs the “hope” of pharmacologic treatment). This makes it tempting to speculate that the observed relationships are fundamental to the specific form of psychopathology (ie, social anxiety). Supporting this speculation, interpersonal rejection sensitivity is particularly prevalent in the diagnostic assessment of depression among this comorbid population, suggesting overlap with social anxiety [4]. On the other hand, studies have shown that depression symptoms decrease after treatment of other anxiety

disorders as well. For example, treatments of posttraumatic stress disorder [23] and of generalized anxiety disorder [24] both result in reductions in depression. However, for these studies and others, it is unknown whether improving the anxiety disorder drives the reduction in depression or whether this phenomenon is specific to social anxiety disorder. The answer could have significant treatment implications.

It is important to note that, in the current investigation, few participants met diagnostic criteria for major depressive disorder (2% of each group). Although one might speculate a different pattern of mediational relationships among individuals with dual diagnoses vs subclinical depression, this does not appear to be the case. Moscovitch and colleagues [1] partialled their sample into 2 groups: those meeting dual diagnoses (clinical mood disorder and clinical social anxiety) and those with clinical social anxiety and subclinical symptoms of depression. The same pattern of mediational relationships was indicated for both groups, regardless of clinical status of depression.

There are some notable limitations of the current investigation. Specifically, the current investigation was a secondary analysis of a clinical trial that was not specifically designed to examine the question at hand. Furthermore, for the population in the current study, social anxiety disorder was a primary diagnosis; however, all patients also met diagnostic criteria for a comorbid alcohol use disorder. Given that the current investigation successfully replicated findings of a similar study [1], it seems unlikely that the comorbid alcohol use disorder substantially influenced the mediational relationship between social anxiety and depression symptoms. In addition, all participants explicitly sought treatment of social anxiety disorder rather than an alcohol use disorder. Thus, use of the current population for investigation of the mediational relationship between social anxiety and depression seems justifiable. However, because all were seeking treatment of social anxiety, it cannot be assumed that results would generalize to populations seeking treatment of depression.

In sum, the current investigation replicated previous findings of social anxiety symptoms fully mediating, and accounting for most of the variation of, secondary depression symptoms during the treatment of social anxiety. The current study extends upon previous research by documenting the same phenomenon while using a different treatment modality, pharmacologic treatment (paroxetine), as well as placebo. The fact that results agreed across 3 treatment modalities (psychotherapy, pharmacotherapy, placebo) suggests a fundamental relationship between social anxiety and depression in subjects seeking treatment of social anxiety—that is, successfully reducing severity of the former will likely improve the latter. Future research should be conducted to examine the mediational relationships between other comorbid primary and secondary mental health disorders. Current treatments may prove even more effective

through a better understanding of the relationships between comorbid psychiatric disorders and symptoms.

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