ORIGINAL ARTICLE

A Placebo-Controlled Trial of Phenelzine, Cognitive Behavioral Group Therapy, and Their Combination for Social Anxiety Disorder

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Context: Medication and cognitive behavioral treatment are the best-established treatments for social anxiety disorder, yet many individuals remain symptomatic after treatment.

Objective: To determine whether combined medication and cognitive behavioral treatment is superior to either monotherapy or pill placebo.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Research clinics at Columbia University and Temple University.

Participants: One hundred twenty-eight individuals with a primary *DSM-IV* diagnosis of social anxiety disorder.

Interventions: Cognitive behavioral group therapy (CBGT), phenelzine sulfate, pill placebo, and combined CBGT plus phenelzine.

Main Outcome Measures: Liebowitz Social Anxiety Scale and Clinical Global Impression (CGI) scale scores at weeks 12 and 24.

Results: Linear mixed-effects models showed a specific order of effects, with steepest reductions in Liebowitz Social Anxiety Scale scores for the combined group, followed by the monotherapies, and the least reduction in the placebo group (Williams test = 4.97, $P < .01$). The CGI response rates in the intention-to-treat sample at week 12 were 9 of 27 (33.3%) (placebo), 16 of 34 (47.1%) (CBGT), 19 of 35 (54.3%) (phenelzine), and 23 of 32 (71.9%) (combined treatment) ($\chi^2_1 = 8.76$, $P < .01$). Corresponding remission rates (CGI = 1) were 2 of 27 (7.4%), 3 of 34 (8.8%), 8 of 35 (22.9%), and 15 of 32 (46.9%) ($\chi^2_1 = 15.92$, $P < .01$). At week 24, response rates were 9 of 27 (33.3%), 18 of 34 (52.9%), 17 of 35 (48.6%), and 25 of 32 (78.1%) ($\chi^2_1 = 12.02$, $P = .001$). Remission rates were 4 of 27 (14.8%), 8 of 34 (23.5%), 9 of 35 (25.7%), and 17 of 32 (53.1%) ($\chi^2_1 = 10.72$, $P = .001$).

Conclusion: Combined phenelzine and CBGT treatment is superior to either treatment alone and to placebo on dimensional measures and on rates of response and remission.

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SOCIAL ANXIETY DISORDER (SAD) is a highly prevalent[1-3] chronic and disabling anxiety disorder associated with substantial impairment, decreased quality of life,[4-7] and psychiatric comorbidity.[8,9] Although cognitive behavioral therapy (CBT) and pharmacotherapy are the most efficacious treatments for SAD,[10-15] only two-thirds of patients who receive these treatments are considered responders, of which only half are considered remitters.[16] Most patients remain symptomatic after initial treatment.

Six controlled trials have examined the efficacy of combining medication and psychosocial treatments for SAD. The first study[17] compared social skills training plus propranolol hydrochloride with social skills training plus placebo. There were no significant differences in efficacy between the groups. The second study[18] compared buspirone hydrochloride, placebo, CBT plus buspirone, and CBT plus placebo; CBT resulted in improvement in SAD symptoms, but buspirone alone was not superior to placebo and did not augment the efficacy of CBT.

In the third study,[19] patients were randomized to receive sertraline hydrochloride or placebo and separately to receive exposure therapy or general medical care. Sertraline was associated with greater efficacy than was placebo, whereas exposure alone was not. The fourth study[15] examined the efficacy of fluoxetine hydrochloride, pill placebo, group CBT, CBT plus fluoxetine, and CBT plus pill placebo. All active treatments had greater efficacy than did pill placebo, but there were no differences among the active treatments.

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Two recent studies[20,21] examined the effect of administration of D-cycloserine before exposures in the context of CBT based on clinical and preclinical data on the effects of D-cycloserine on learning. Both studies found that D-cycloserine was superior to placebo as an adjunct to CBT. In a previous study,[10] our group compared the monoamine oxidase inhibitor phenelzine sulfate, cognitive behavioral group therapy (CBGT), pill placebo, and a psychosocial control treatment. We found that phenelzine and CBGT were superior to pill placebo and the psychosocial control on a variety of measures. At the end of the study, many patients in both active treatments were still symptomatic, suggesting the need for more efficacious treatments. The goal of the present study was to examine whether a combination of 2 partially efficacious treatments with different mechanisms of action—pharmacotherapy and CBGT—would be superior to each monotherapy in the treatment of SAD. We selected phenelzine as the medication because it was the best-established medication for the treatment of SAD at the time this study was initiated.

METHODS

DESIGN

This study was conducted at 2 academic centers with outpatient anxiety disorder programs and complementary expertise: the New York State Psychiatric Institute/Columbia University (pharmacotherapy expertise) (hereinafter New York) and the Adult Anxiety Clinic of Temple University (expertise in CBT) in Philadelphia (hereinafter Philadelphia). Enrollment began June 1, 1995, and continued through October 31, 2001. Biweekly conference calls were held to ensure homogeneity of procedures. The institutional review board at each site approved the protocol, and all the patients provided written informed consent.

The sample consisted of 128 patients referred by local mental health or medical practitioners or responding to advertisements in local media. Eighty-four patients were treated in New York and 44 in Philadelphia. The inclusion criteria were (1) a primary *DSM-IV* diagnosis of SAD and (2) age 18 to 65 years. To increase comparability with other treatment studies of SAD and to eliminate the possibility that improvements in SAD could be attributed to the antidepressant effects of phenelzine, the exclusion criteria were (1) a comorbid anxiety disorder more clinically salient for the patient; (2) a lifetime history of schizophrenia, bipolar disorder, or mental disorder due to a general medical condition; (3) major depressive disorder or substance use disorder in the past 6 months; (4) previous failure of treatment with phenelzine or CBT, defined as nonresponse to 60 mg or more of phenelzine (or the equivalent dose of another monoamine oxidase inhibitor) for at least 4 weeks or to 6 sessions of CBT for SAD; (5) concurrent psychiatric or psychological treatment; and (6) pregnancy, lactation, or inability or unwillingness to use contraceptive measures for the duration of the study.

At each site, patients were randomly assigned, in groups of 4 to 6, to 1 of 4 conditions: (1) phenelzine, (2) CBGT, (3) combined treatment (CBGT plus phenelzine), or (4) pill placebo. Patients were randomized according to a table of pseudorandom numbers by the New York site data manager (A.B.S.), who had no patient contact. Patient allocation was concealed from all other research personnel at both sites before randomization and from independent evaluators providing the clinician-administered assessments throughout the study. Medication or pill placebo was administered and monitored by a psychiatrist. All CBGT sessions were conducted by masters- or doctoral-level therapists. All CBGT sessions were audiotaped and evaluated by one of us (R.G.H.), who supervised therapists at both sites weekly.

The study had 4 phases. The first phase (acute treatment) lasted 12 weeks. Medication visits occurred weekly for 4 weeks, then every 2 weeks during this phase. The CBGT sessions took place weekly. Patients with at least minimal improvement on a modified version of the Clinical Global Impression Improvement Scale (CGI-I) that included anchors for each level of improvement[22] entered the second phase. In this 12-week intensive continuation phase, patients received the same treatment, with CBGT sessions taking place weekly and the frequency of medication visits reduced to once per month. At the end of the continuation phase, patients who were at least much improved on the CGI-I entered the third phase, a 28-week maintenance phase during which they received the same treatment modality but with monthly visits for both modalities. Patients who were at least much improved on the CGI-I at the end of the third phase entered a 12-month naturalistic follow-up. In this article, we present the results of the acute treatment phase and the main findings of the continuation phase.

TREATMENTS

Two therapists administered CBGT in twelve 2.5-hour sessions to groups of 4 to 6 participants. In the first 2 sessions, patients were taught to identify negative cognitions (automatic thoughts), to observe the covariation between anxiety and automatic thoughts, to challenge logical errors in automatic thoughts, and to formulate rational alternatives. Thereafter, they confronted increasingly difficult feared situations, first through role-playing in the session and then in real life, while applying cognitive skills. Patients worked on their personal target situations following a standard sequence: (1) identification of automatic thoughts, (2) identification of logical errors in automatic thoughts, (3) disputation of automatic thoughts and formulation of rational responses, and (4) establishment of observable behavioral goals. Patients practiced cognitive skills while completing behavioral tasks (eg, conversing with another group member). Goal attainment and use of cognitive skills were reviewed. Patients were given assignments for exposures between sessions and completed self-administered cognitive restructuring exercises before and after these assignments.

Pharmacotherapy patients began with phenelzine sulfate, 15 mg/d, or matching placebo for 3 days, then 30 mg/d for 4 days, 45 mg/d for week 2, and 60 mg/d for weeks 3 and 4. Depending on clinical progress and adverse effects, the dosage could be raised to 75 mg for week 5 and to 90 mg for weeks 6 to 12. Patients were instructed to expose themselves to anxiety-provoking situations and were told that the role of medication was to make such exposure easier. However, no systematic exposure instructions or programmed practice was offered. No other psychotropic medication was permitted except chloral hydrate, 500 to 1000 mg, and zolpidem, 5 to 10 mg, as needed for sleep. Patients were instructed about the dietary restrictions appropriate to phenelzine, symptoms that could occur if the restrictions were violated, and procedures to follow in that event.

Patients assigned to combined treatment received CBGT and phenelzine as described in the preceding paragraph beginning in the same week. To remove potential bias in the performance of treatments, neither pharmacotherapists nor CBGT therapists were informed as to whether a specific patient was also receiving the other treatment, and they could not consult

each other or attempt to integrate their treatment efforts. Patients were also coached to withhold information that would indicate whether they were receiving combined treatment. Although all patients undergoing combined treatment actually received phenelzine, they were told, with the approval of the institutional review board at each site, that they might receive either active medication or placebo.

ASSESSMENTS

Assessments were conducted at baseline (week 0) and at weeks 6, 12, and 24. Information was collected using clinician- and self-administered instruments.

Clinician-Administered Measures

Measures administered by independent evaluators blinded to treatment condition included (1) the Liebowitz Social Anxiety Scale (LSAS), a 24-item scale that assesses fear and avoidance of a range of social interaction and performance situations[12,23-25]; (2) the Anxiety Disorders Interview Schedule for *DSM-IV* Clinician's Severity Rating (ADIS), a rating from 0 to 8 of the severity of symptoms and impairment associated with SAD[26]; (3) the modified CGI with anchor points defined specifically in reference to SAD[22]; and (4) the 29-item version of the Hamilton Rating Scale for Depression.[27]

Self-report Measures

Patient-rated symptom measures included (1) the Fear Questionnaire Social Phobia Subscale,[28] a measure of the assessment of avoidance due to SAD; (2) the Social Interaction Anxiety Scale,[29-32] a measure of anxiety in dyads and groups; (3) the Social Phobia Scale, a measure of anxiety when being observed by others[28-30]; and (4) the Sheehan Disability Scale,[33] a 4-item scale to assess impairment in work, social life and leisure activity, family life and home responsibilities, and overall functioning as a result of a psychiatric disorder.

ADVERSE EFFECTS

The pharmacotherapist used a checklist (available on request) to inquire about the presence of 28 potential monoamine oxidase inhibitor adverse effects at each visit and rated the severity of each on a scale from 0 to 3 (none, mild, moderate, or severe). Emergent adverse effects were identified by an increase of at least 2 points from baseline to any of the assessment points.[15] Adverse effects were assessed in patients randomized to the placebo, phenelzine, and combined treatment groups but not in those randomized to the CBGT alone group.

STATISTICAL ANALYSES

The following hypotheses were tested: (1) phenelzine, CBGT, and combined treatment are superior to pill placebo in ameliorating the symptoms and disability of SAD and (2) there is a gradient of efficacy across the treatments, with combined treatment being superior to each monotherapy, which, in turn, is each superior to pill placebo.

To examine hypothesis 1 using continuous measures, outcomes at baseline and at weeks 6, 12, and 24 were modeled as a function of time, treatment, and the treatment × time interaction using linear mixed-effects models (LMMs),[34] which take into account baseline differences across groups and the intercorrelations of repeated observations, and a statistical software program (SAS Proc MIXED; SAS Institute Inc, Cary, North Carolina). Site effects were assessed by including site in the models and by examining the interactions of site with treatment, time, and treatment × time. Treatment group differences were assessed by the significance of the interaction term and the comparison of LMM estimates at the end point (week 12 for the acute treatment phase and week 24 for the maintenance phase). Response and remission rates were compared between groups using χ^2 tests of independence, using the last observation carried forward for individuals who dropped out before the end point. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to assess the magnitude of the differences in categorical outcomes for each treatment arm compared with placebo. Responder status was defined as a score of much improved or very much improved on the CGI-I at week 12 (ie, a score of 1 or 2). In accord with previous work, 2 definitions of remission were used: (1) an LSAS score of 30 or less, previously found to be the optimal value to discriminate between individuals in or outside of the clinical range,[24] and (2) a score of 1 on the CGI-I.[35]

To examine hypothesis 2 using categorical measures, we used the linear-by-linear association χ^2 test. In contrast to χ^2 tests of independence, this test assumes a specific gradation in the magnitude of responses.[36] To examine hypothesis 2 using continuous measures, we used the Williams test.[37] The linear-by-linear association test and the Williams test are part of a larger family of tests of constrained statistical inference.[38] The use of constrained statistical inference is indicated when the hypothesis to be tested implies an ordering of effects, as in the study of dose-response relationships or augmentation strategies, and has the advantage of providing more powerful tests in those situations.[38,39]

For both hypotheses, the primary outcome measures were change over time in the total LSAS score and responder classification using the CGI-I. Secondary measures were changes in scores on the ADIS, CGI Severity Scale, Fear Questionnaire Social Phobia Subscale, Social Interaction Anxiety Scale, Social Phobia Scale, and Sheehan Disability Scale. The Hamilton Rating Scale for Depression was included to determine whether effects of treatment were due to reductions in depression rather than to test differences across treatments in reducing depressive symptoms in individuals with SAD.

We calculated the slope of outcomes on each continuous measure for each participant using LMMs as implemented in SAS Proc MIXED.[40,41] We entered these individual slopes in the program ORIOGEN[42] to calculate the Williams test statistic and the *P* value. The critical value and the *P* value of the Williams test statistic are determined using nonparametric bootstrapping procedures. For each bootstrap sample, the Williams test statistic was computed and was compared with the Williams test statistic for the actual sample. This process was repeated 100 000 times. Then, the bootstrap *P* value was defined to be the proportion of times that the Williams test statistic for the bootstrap sample exceeded that for the actual sample. Note that unlike the original Williams test, which assumes that the data are normally distributed, ORIOGEN is distribution free.[42]

All tests were considered significant at $\alpha = .05$, 2-tailed. All analyses were based on the intention-to-treat sample, defined as those who received at least 1 dose of medication (or placebo) or attended at least 1 CBGT session. To examine the sensitivity of the results, we repeated the analyses with comorbidity as a predictor. Because comorbidity did not predict outcome, it was excluded from the final models. Power calculations for linear trends[43] and for continuous variables[44] under order restrictions indicated that the sample size provided 90% power to detect a linear trend in response rates and a linear trend in the change of LSAS score and 80% power to detect a linear trend in remission rates.

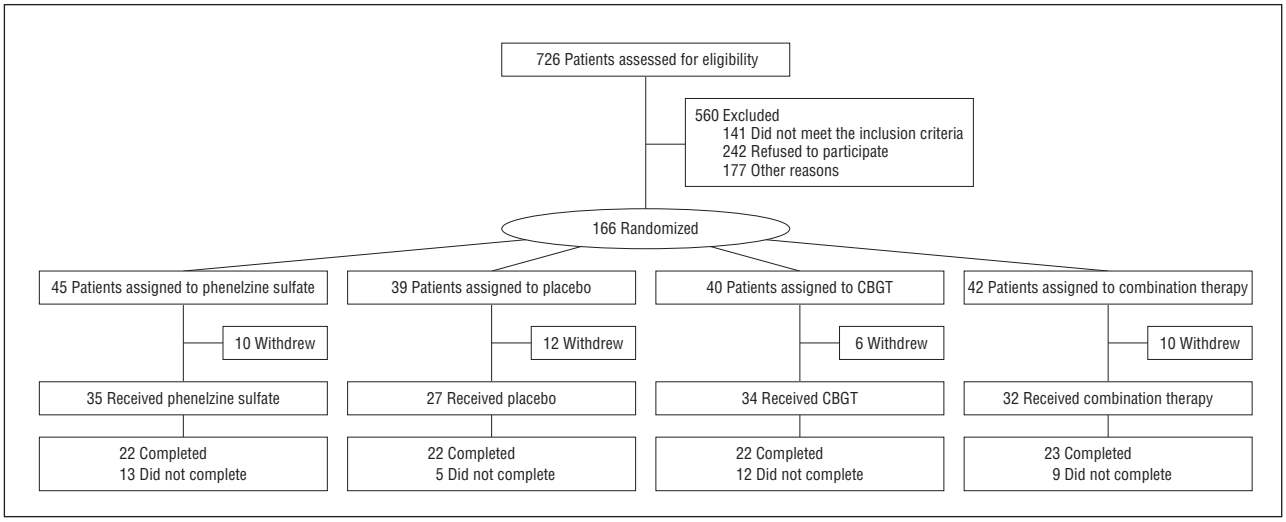

Figure 1. Consort diagram. CBGT indicates cognitive behavioral group therapy.

RESULTS

DISPOSITION AND BASELINE CHARACTERISTICS OF PATIENTS

Of 726 patients who were screened, 166 were randomized to 1 of the 4 treatment groups (**Figure 1**). The most common reasons for screening failure were not meeting the inclusion criteria (n=141) and lack of interest in participating in the research study due to time commitments or unwillingness to be randomized to treatment (n=242).

Of the 166 individuals randomized, 12 from the placebo group, 10 from the phenelzine group, 6 from the CBGT group, and 10 from the combined group withdrew from the study before receiving any treatment (χ^2_3=3.0, P=.40) and were excluded from the analyses. The remaining 128 participants composed the intention-to-treat sample as follows: phenelzine (n=35), CBGT (n=34), CBGT and phenelzine (n=32), and pill placebo (n=27). Groups did not differ significantly in demographic characteristics (**Table 1**). Differences between groups existed, however, in the baseline severity of SAD. Individuals randomized to the combined treatment group had significantly lower baseline values on the Fear Questionnaire Social Phobia Subscale, Social Interaction Anxiety Scale, and Social Phobia Scale than did those randomized to the other treatment conditions. Differences in baseline scores on the LSAS approached significance (**Table 2**). Some between-site differences were also observed. There were fewer married and Hispanic patients in Philadelphia than in New York. Mean age was lower in Philadelphia than in New York. Patients in Philadelphia had lower ADIS ratings than did those in New York. However, no site × treatment condition interactions were observed (data available on request). Of the 128 participants, 44 (34.4%) had at least 1 comorbid disorder, generally a comorbid anxiety disorder (26 patients [20.3%]) or dysthymia (19 [14.8%]).

Rates of discontinuation were 37.1% (13 of 35) in the phenelzine group, 35.3% (12 of 34) in the CBGT group, 28.1% (9 of 32) in the combined treatment group, and 18.5% (5 of 27) in the placebo group. Those rates were not significantly different when examining all groups jointly (χ^2_3=3.0, P=.40) or in pairwise treatment comparisons (P>.10 for all). There were no differences in demographic or baseline measures between patients who dropped out and those who completed the acute treatment phase (data available on request).

OUTCOME EVALUATION

Hypothesis 1

Mean scores and standard deviations for all primary and secondary continuous measures at the primary end point (week 12) are given in Table 2. Using LMM analyses, we found significant differences in the outcomes of the 4 treatment groups for most measures, as indicated by the F tests for the treatment × time interaction effects. Pairwise comparisons of each treatment group vs placebo showed that the slope of the LSAS score change was significantly greater in the combined treatment (t=4.3) and phenelzine (t=3.3) groups than in the placebo group (P=.001 for both), whereas there was no significant difference between the slopes of the CBGT and placebo groups (t=0.68, P=.50). The slope of change for the ADIS was significantly larger in the combined treatment group than in the placebo group (t=3.1, P=.002), whereas the slope of the Social Phobia Scale score change was larger in the phenelzine group than in the placebo group (t=2.1, P=.04). No other significant differences in slopes were seen between any of the treatment groups and placebo (data available on request).

Table 3 provides pairwise comparisons and corresponding effect sizes (Cohen d) of all the primary and secondary outcome measures at the acute phase end point for each treatment group vs the placebo group adjusting for baseline scores. Results were similar to the LMM findings. Phenelzine and combined treatment were superior to placebo on the LSAS, Fear Questionnaire Social Phobia Subscale, and Social Interaction Anxiety Scale. Combined treatment was also superior to placebo on the ADIS and the Social Phobia Scale. No significant differences

Table 1. Demographic Characteristics of Patients With SAD Treated With Placebo, CBGT, Phenelzine, and Their Combination

	Treatment Group[a]				
	Placebo (n=27)	CBGT (n=34)	Phenelzine Sulfate (n=35)	Combined (n=32)	*P* Value[b]
Women, No. (%)	10 (37.0)	18 (52.9)	11 (31.4)	13 (40.6)	.32
Age, y					
Mean (SD)	32.04 (8.73)	31.71 (9.63)	30.66 (7.98)	35.63 (9.84)	.14
Range	18-47	20-58	20-51	20-61	
Marital status, No. (%)					
Married	6 (22.2)	8 (23.5)	7 (20.0)	9 (28.1)	.55
Single, never married	18 (66.7)	24 (70.6)	27 (77.1)	23 (71.9)	
Divorced	3 (11.1)	2 (5.9)	1 (2.9)	0	
Ethnicity/race, No. (%)					
White	13 (48.1)	19 (55.9)	15 (42.9)	14 (43.8)	.91
Black	7 (25.9)	6 (17.6)	8 (22.9)	8 (25.0)	
Hispanic	6 (22.2)	6 (17.6)	7 (20.0)	8 (25.0)	
Other	1 (3.7)	3 (8.8)	5 (14.3)	2 (6.2)	
Employment, No. (%)					
Full-time employment	13 (48.1)	11 (32.4)	11 (31.4)	13 (40.6)	.37
Full-time student	3 (11.1)	4 (11.8)	3 (8.6)	2 (6.2)	
Part-time/homemaker/retired	11 (40.7)	14 (41.2)	20 (57.1)	13 (40.6)	
Unemployed	0	5 (14.7)	1 (2.9)	4 (12.5)	
Yearly family income, No. (%)					
≤$9999 or public assistance	5 (18.5)	10 (29.4)	5 (14.3)	10 (31.3)	.12
$10 000-$19 999	5 (18.5)	8 (23.5)	10 (28.6)	4 (12.5)	
$20 000-$39 999	13 (48.1)	4 (11.8)	8 (22.9)	6 (18.8)	
≥$40 000	4 (14.8)	8 (23.5)	7 (20.0)	8 (25.0)	
Failed to report	0	4 (11.8)	5 (14.3)	4 (12.5)	
Education, No. (%)					
College graduate	7 (25.9)	17 (50.0)	15 (42.9)	16 (50.0)	.06
Some college	15 (55.6)	8 (23.5)	10 (28.6)	5 (15.6)	
≤High school	5 (18.5)	7 (20.6)	9 (25.7)	10 (31.3)	
Failed to report	0	2 (5.9)	1 (2.9)	1 (3.1)	
Any previous treatment, No. (%)	6 (22.2)	11 (32.4)	12 (34.3)	7 (28.1)	.56
Any previous pharmacotherapy, No. (%)	6 (22.2)	8 (23.5)	9 (25.7)	7 (21.9)	.98
Any previous SSRIs, No. (%)	5 (18.5)	5 (14.7)	6 (17.1)	4 (12.5)	.92
Any previous benzodiazepines, No. (%)	1 (3.7)	2 (5.9)	2 (5.7)	1 (3.1)	.93
Any previous β-blockers, No. (%)	0	1 (2.9)	1 (2.9)	2 (6.2)	.59
Any previous psychotherapy, No. (%)	2 (7.4)	7 (20.6)	4 (11.4)	1 (3.1)	.13
Treated at each site, No. (%)					
Philadelphia	9 (33.3)	12 (35.3)	14 (40.0)	9 (28.1)	.78
New York	18 (66.7)	22 (64.7)	21 (60.0)	23 (71.9)	

Abbreviations: CBGT, cognitive behavioral group therapy; SAD, social anxiety disorder; SSRI, selective serotonin reuptake inhibitor.
[a] Because of rounding, percentages may not total 100.
[b] Differences across groups were compared using analysis of variance for continuous variables and χ^2 tests for categorical variables.

were seen between the CBGT and placebo groups on any of the outcome measures. Effect sizes were generally small for CBGT, medium for phenelzine, and large for combined treatment.

Categorical measures yielded similar results. Patients randomized to receive combined treatment were significantly more likely than those randomized to receive placebo to be classified as responders (OR, 5.11; 95% CI, 1.68-15.52). There were no significant differences in the probability of response in patients randomized to receive phenelzine (OR, 2.38; 95% CI, 0.84-6.72), CBGT (1.78, 0.63-5.06), or placebo. Rates of remission were also significantly higher for patients randomized to combined treatment than for those randomized to placebo (**Figure 2**). Using the definition of CGI-I=1, 46.9% of patients who received combined treatment were classified as remitters compared with 7.4% taking placebo (OR, 11.03; 95% CI, 2.23-54.57). In contrast, the percentage of CGI-I remitters was 22.1% in the phenelzine group (OR, 3.70; 95% CI, 0.82-19.14) and 8.8% in the CBGT group (1.21, 0.19-7.81), neither significantly different from the rate in the pill placebo group. When remission was defined by an LSAS score of 30 or less, 59.4% of patients in the combined treatment group and 11.1% in the placebo group were classified as remitters (OR, 11.69; 95% CI, 2.91-47.05). The percentage of remitters was 20.0% in the phenelzine group (OR, 2.00; 95% CI, 0.47-8.60) and 20.6% in the CBGT group (2.07, 0.48-8.93). Here again, the monotherapies did not distinguish themselves from placebo.

Hypothesis 2

Table 4 provides mean slopes of change for all continuous measures and rates of response and remission for all the treatment groups. Across all measures, the results of

Table 2. Outcome Measures in the Treatment of Social Anxiety Disorder at Baseline and at Week 12 by Treatment Group

	Treatment Group[a]					
	Placebo	CBGT	Phenelzine Sulfate	Combined	F[b]	P Value
LSAS						
Week 0	75.96 (24.80)	77.12 (27.34)	80.09 (19.82)	64.06 (27.80)	2.58	.06
Week 12	63.29 (27.51)	62.71 (24.78)	47.80 (26.22)	24.14 (17.28)	7.85	<.001
ADIS						
Week 0	5.96 (0.85)	6.03 (0.95)	6.15 (0.93)	5.87 (1.12)	0.47	.71
Week 12	4.70 (1.69)	4.70 (1.16)	4.38 (1.88)	3.43 (1.57)	4.60	.005
CGI-S						
Week 0	5.44 (0.58)	5.34 (0.70)	5.51 (0.70)	5.19 (0.74)	1.39	.25
Week 12	4.63 (1.31)	4.71 (1.23)	4.35 (1.38)	3.64 (1.36)	3.48	.02
HAM-D						
Week 0	6.07 (4.60)	6.75 (4.52)	6.63 (5.58)	6.41 (4.54)	0.11	.96
Week 12	5.43 (4.64)	5.73 (5.05)	5.60 (4.83)	4.26 (4.37)	0.59	.62
FQ						
Week 0	23.56 (7.78)	22.13 (8.23)	24.88 (7.17)	18.61 (7.75)	3.62	.02
Week 12	19.24 (9.57)	15.39 (8.64)	13.64 (8.59)	7.26 (4.93)	3.71	.02
SIAS						
Week 0	41.42 (12.46)	42.87 (13.09)	45.06 (9.91)	34.71 (18.22)	3.20	.03
Week 12	34.52 (14.72)	29.94 (15.43)	25.96 (17.57)	16.04 (14.95)	3.44	.02
SPS						
Week 0	35.96 (11.11)	35.38 (17.84)	39.91 (16.25)	25.64 (14.63)	4.63	.01
Week 12	28.95 (14.66)	21.22 (13.00)	21.32 (18.68)	8.61 (8.01)	1.89	.14
CGI-I						
Week 12	3.00 (1.14)	2.45 (0.60)	2.35 (1.06)	1.78 (0.85)	6.55	<.01
SDS						
Week 0	15.56 (4.67)	15.50 (5.90)	17.35 (6.63)	14.74 (7.18)	1.01	.39
Week 12	11.33 (5.92)	10.35 (5.72)	9.09 (7.03)	5.78 (7.29)	2.56	.06

Abbreviations: ADIS, Clinician's Severity Rating of the Anxiety Disorders Interview Schedule for *DSM-IV*; CBGT, cognitive behavioral group therapy; CGI-I, Clinical Global Impression Improvement Scale; CGI-S, Clinical Global Impression Severity Scale; FQ, Fear Questionnaire Social Phobia Subscale; HAM-D, 29-item Hamilton Rating Scale for Depression; LSAS, Liebowitz Social Anxiety Scale (total score); SDS, Sheehan Disability Scale; SIAS, Social Interaction Anxiety Scale; SPS, Social Phobia Scale.

[a] All values are given as mean (SD) score.

[b] Differences in the mean at baseline were compared using analysis of variance. Differences between baseline and week 12 were compared using linear mixed-effects models.

Table 3. 12-Week Pairwise Differences Between the Placebo Group and Patients Receiving CBGT, Phenelzine, and Combined Treatment

	Treatment Group					
	CBGT		Phenelzine Sulfate		Combined	
	Mean (SE)	ES	Mean (SE)	ES	Mean (SE)	ES
ADIS	−0.26 (0.42)	0.15	−0.70 (0.39)	0.42	−1.33 (0.40)[a]	0.79
LSAS	−2.28 (5.77)	0.08	−17.24 (5.52)[a]	0.60	−30.19 (5.82)[a]	1.05
CGI-S	0.08 (0.30)	0.06	−0.44 (0.28)	0.32	−0.56 (0.30)	0.41
HAM−D	0.31 (1.24)	0.07	0.35 (1.20)	0.07	−1.30 (1.22)	0.28
FQ	−2.88 (2.14)	0.32	−5.21 (1.97)[a]	0.58	−8.11 (2.13)[a]	0.90
SIAS	−5.20 (3.96)	0.31	−9.10 (3.61)[b]	0.54	−11.56 (3.81)[a]	0.68
SPS	−5.67 (3.61)	0.36	−6.61 (3.32)	0.42	−12.87 (3.65)[a]	0.81
SDS	−0.58 (1.69)	0.09	−2.95 (1.56)	0.43	−4.25 (1.59)[a]	0.63

Abbreviations: ES, effect size (Cohen d). For other definitions, see Table 2.

[a] $P<.01$.

[b] $P<.05$.

the Williams test were highly significant. Examination of categorical measures produced similar results.

Because in a previous study[10] phenelzine was superior to CBGT on several continuous measures after acute treatment, in the exploratory analyses of the present study, we reexamined the models hypothesizing the following order: combined treatment, phenelzine, CBGT, and placebo. The results also support this ordering of treatment effects (Table 4). Additional analyses restricted the sample to responders to examine whether responders to each treatment differed in magnitude of improvement. The mean slope of the LSAS score change was significantly larger for combined treatment than for the monotherapies considered separately or pooled (**Table 5**).

MEDICATION DOSE AND ADVERSE EFFECTS

The mean (SD) daily dose of phenelzine sulfate at the end of week 12 in the medication group (65.9 [22.5] mg/d) and in the combined group (62.0 [24.6] mg/d) did not differ significantly ($t = 0.7$, $P = .11$). However, significant differences in rates of treatment-emergent events were noted for 7 symptoms: insomnia, lightheadedness, dry mouth, weight gain, constipation, anorgasmia, and nervousness (**Table 6**). For 3 symptoms, incidence was highest in the combined group; the incidence of 3 other symptoms was highest in the phenelzine group; and the incidence of 1 symptom was highest in the placebo group.

Continuation Phase

At week 24, mean (SD) LSAS scores were 59.3 (23.5) for the placebo group, 51.0 (22.9) for the CBGT group, 52.6 (24.0) for the phenelzine group, and 32.0 (19.6) for the combined group, resulting in effect sizes (Cohen d) of 0.36, 0.35, and 0.91 respectively. The Williams test statistic was 4.7 ($P < .001$). The proportion of responders at week 24 was 9 of 27 (33.3%) in the placebo group, 35 of 69 (50.7%) in those receiving monotherapy (18 of 34 [52.9%] for CBGT and 17 of 35 [48.6%] for phenelzine), and 25 of 32 (78.1%) in those randomized to combined treatment, yielding a linear-by-linear $\chi^2_1 = 12.02$ ($P = .001$). Rates of remission were 4 of 27 (14.8%), 17 of 69 (24.6%; 8 of 34 [23.5%] and 9 of 35 [25.7%]), and 17 of 32 (53.1%), respectively, resulting in a linear-by-linear $\chi^2_1 = 10.72$ ($P = .001$), when remission was defined as an LSAS score of 30 or less. Rates of remission were 2 of 27 (7.4%), 14 of 69 (20.3%; 5 of 34 [14.7%] and 9 of 35 [25.7%]), and 15 of 32 (46.9%), with a linear-by-linear $\chi^2_1 = 12.78$ ($P < .001$), when remission was defined as CGI-I = 1.

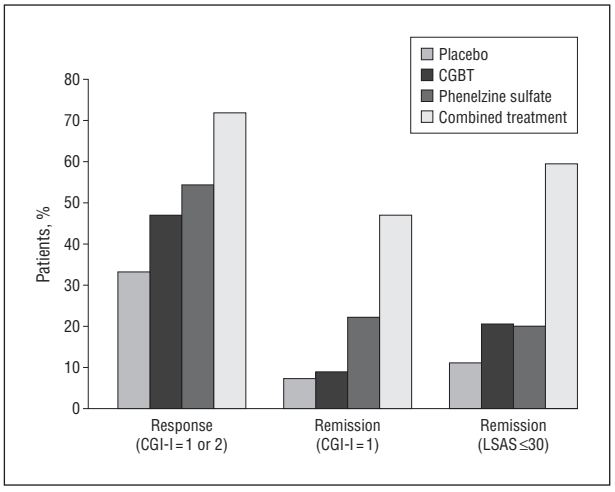

Figure 2. Response and remission rates by treatment group at week 12. CBGT indicates cognitive behavioral group therapy; CGI-I, Clinical Global Impression Improvement Scale; and LSAS, Liebowitz Social Anxiety Scale.

COMMENT

To our knowledge, this is the first study to show the superiority of a combined treatment over medication, psychotherapy, and placebo in the acute treatment of SAD. In addition, we found that phenelzine, but not CBGT alone, was superior to placebo. These results were consistent across several outcome measures and analytic strategies and were maintained throughout the 12-week continuation phase.

Supporting the main hypothesis, combined treatment was superior to both monotherapies and to placebo. Two mechanisms could explain the higher efficacy of combined treatment: (1) distinct groups of patients with SAD could respond to only phenelzine or CBGT (by receiving both, patients in the combined treatment group would have increased their chances of receiving at least 1 treatment that was efficacious for them) and (2) combined treatment may exert a truly additive or synergistic effect in the treatment of SAD beyond the effects of either monotherapy alone.

If only the first mechanism was at work, responders in the combined group would not have had larger aver-

Table 4. Statistical Inference Under Order Restrictions for Patients With SAD[a]

	Placebo	Phenelzine Sulfate or CBGT	Combined	Statistic[b]	*P* Value	Placebo	CBGT	Phenelzine	Combined	Statistic[b]	*P* Value
CGI-I score, mean (SD)	3.00 (1.10)	2.41 (0.88)	1.79 (0.86)	4.45	<.01	3.00 (1.10)	NA	NA	1.79 (0.86)	NA	NA
Slope, mean (SE), change per mo											
LSAS	−1.82 (0.45)	−2.07 (0.59)	−2.59 (0.48)	4.97	<.01	−1.82 (0.45)	−1.93 (0.51)	−2.24 (0.60)	−2.59 (0.48)	5.07	<.01
ADIS	−0.12 (0.06)	−0.14 (0.06)	−0.18 (0.07)	3.15	<.01	−0.12 (0.06)	0.13 (0.04)	−0.14 (0.07)	−0.18 (0.07)	3.21	<.01
CGI-S	−0.07 (0.06)	−0.08 (0.06)	−0.12 (0.06)	2.50	<.01	−0.07 (0.06)	−0.07 (0.05)	−0.09 (0.06)	−0.12 (0.06)	2.53	<.01
HAM-D	−0.10 (0.05)	−0.09 (0.05)	−0.12 (0.05)	NA	NA	−0.10 (0.05)	−0.09 (0.06)	−0.09 (0.04)	−0.12 (0.05)	NA	NA
FQ	−0.62 (0.19)	−0.72 (0.18)	−0.81 (0.11)	3.78	<.01	−0.62 (0.19)	−0.68 (0.17)	−0.75 (0.18)	−0.81 (0.11)	3.80	<.01
SIAS	−1.03 (0.36)	−1.26 (0.42)	−1.40 (0.35)	3.14	<.01	−1.03 (0.36)	−1.15 (0.29)	−1.33 (0.48)	−1.40 (0.35)	3.22	<.01
SPS	−1.09 (0.16)	−1.17 (0.17)	−1.23 (0.14)	2.91	<.01	−1.09 (0.16)	−1.16 (0.15)	−1.18 (0.18)	−1.23 (0.14)	2.99	<.01
SDS	−0.58 (0.05)	−0.60 (0.06)	−0.62 (0.06)	2.15	.02	−0.58 (0.05)	−0.59 (0.05)	−0.61 (0.07)	−0.62 (0.06)	2.18	.02
Rate, No. (%)											
Response	9/27 (33.3)	35/69 (50.7)	23/32 (71.9)	8.92	<.01	9/27 (33.3)	16/34 (47.1)	19/35 (54.3)	23/32 (71.9)	8.76	<.01
Remission, CGI-I = 1	2/27 (7.4)	11/69 (15.9)	15/32 (46.9)	14.00	<.01	2/27 (7.4)	3/34 (8.8)	8/35 (22.9)	15/32 (46.9)	15.92	<.01
Remission, LSAS ≤30	3/27 (11.1)	14/69 (20.3)	19/32 (59.4)	17.78	<.01	3/27 (11.1)	7/34 (20.6)	7/35 (20.0)	19/32 (59.4)	15.53	<.01

Abbreviations: CBGT, cognitive behavioral group therapy; NA, not applicable; SAD, social anxiety disorder. For other definitions, see Table 2.
[a] The left side of the table describes the main analyses, that is, collapsing the phenelzine and CBGT groups into one. The right side of the table describes the exploratory analyses, in which the phenelzine and CBGT groups are examined separately.
[b] Williams test for slope and linear-by-linear χ^2 tests for categorical measures.

Table 5. Overall Liebowitz Social Anxiety Scale Slope for Responders: Williams Test

	Mean (SD)	Patients, No.	Statistic	*P* Value
Hypothesis 1: combined ≤ phenelzine sulfate or CBGT ≤ placebo				
Placebo	−2.27 (0.27)	9	2.01	.03
Phenelzine or CBGT	−2.38 (0.44)	35		
Combined	−2.60 (0.42)	23		
Hypothesis 2: combined ≤ phenelzine ≤ CBGT ≤ placebo				
Placebo	−2.27 (0.27)	9	2.23	.006
CBGT	−2.15 (0.42)	16		
Phenelzine	−2.57 (0.38)	19		
Combined	−2.60 (0.42)	23		

Abbreviation: CBGT, cognitive behavioral group therapy.

Table 6. Significant Differences in Adverse Effects by Treatment Group

	Treatment Group, %				
	Placebo	Phenelzine Sulfate	Combined	χ^2_2	*P* Value
Insomnia	0	2.9	28.6	8.1	.001
Lightheadedness	7.7	35.3	28.6	6.3	.04
Dry mouth	0	8.9	25.0	8.7	.01
Weight gain	0	0	14.3	9.0	.01
Constipation	7.7	35.3	7.1	10.9	.004
Anorgasmia	7.7	29.4	7.1	7.6	.02
Nervousness	11.5	0	0	7.4	.03

age improvements than responders in the monotherapy groups. However, individuals receiving combined treatment had larger average improvements than did those receiving phenelzine or CBGT alone. This finding suggests an additive or synergistic effect of these treatment modalities, possibly due to their different mechanisms of action or by mutually facilitating the other's effect. For example, phenelzine may reduce anxiety and increase the chances of successful exposures to feared situations, whereas the skills learned through CBGT may help those taking phenelzine profit more from their exposures.

The present findings of the superiority of combined treatment are at variance with those of previous studies[15,17,18] of combination treatment for SAD but in accord with some other studies and meta-analyses[45-48] that have shown the superiority of combined treatment over monotherapies in other mood and anxiety disorders. Discrepancies in the SAD results may be due in some cases to the use of medications with a mixed[15] or poor record of efficacy in the treatment of SAD.[17,18]

The findings of Blomhoff and colleagues[19] are more difficult to interpret. Although the study did not find an additional benefit of combined treatment over sertraline monotherapy, this result may have been due to the use of pairwise comparisons rather than tests for ordered responses implied in the design. We reanalyzed the rates of response from that study assuming a gradation of response from placebo to monotherapies to combined treatment using a linear-by-linear test, which yielded χ^2_1=8.0 (*P*=.005). An even more significant result was obtained when the gradation was assumed to be placebo, exposure therapy, sertraline, and combined treatment (χ^2_1=9.9, *P*=.002). More recent work by the same group,[49] although not formally tested for ordered responses, also suggests a gradient of efficacy in the acute treatment of SAD, with placebo having the lowest degree of response, followed by monotherapies (exposure therapy and sertraline), and combined treatment having the highest efficacy at week 24. Taken together, the available evidence seems to support the superiority of combined treatment over medication or exposure and CBT alone for the treatment of SAD.

Consistent with previous studies,[10,50-52] we found that phenelzine was superior to placebo on most measures, providing additional documentation of its efficacy. Phenelzine and CBGT, however, were less efficacious than in previous studies,[10] and CBGT was generally not superior to placebo in pairwise comparisons, although it was superior to placebo in the analyses using tests of constrained statistical inference, was not different from phenelzine monotherapy in pairwise comparisons at week 12, and achieved the same efficacy as phenelzine at week 24. The lower efficacy of CBGT in this study is surprising to us and may be due to sample differences (R.G. H. moved from Albany to Philadelphia between the time of the previous trial[10] and the present one). However, there were no site × treatment interactions in either study, making this explanation less likely. Furthermore, in another 2-site trial[53] conducted since the time of the study reported herein, CBT proved highly efficacious. Recent meta-analyses[54-56] and qualitative reviews[57] continue to support the efficacy of CBT for SAD.

The present study has the limitations common to most efficacy trials. First, treatments were provided by experts and may show lower efficacy in less specialized settings. Second, participants had to be willing to be randomized to any of the 4 treatment conditions. Individuals who dropped out of the study after randomization but before receiving any treatment were not included in the analyses. These results may not generalize to them. Similarly, because individuals were recruited from advertisements and word of mouth, the results may not be generalizable to all patients with SAD. Third, because the study lacked a CBGT plus pill placebo group, the nonspecific effects of phenelzine in the combined treatment cannot be ruled out. Fourth, because self-exposure was neither assessed nor explicitly discouraged in the pill-only groups, it is possible that more spontaneous exposure occurred in the phenelzine group, which may have contributed to their improvement. Fifth, the study examined only 1 medication, 1 psychotherapy, and their combination rather than a broader array of treatments. Thus, these findings may not extend to individuals treated with selective serotonin reuptake inhibitors or selective noradrenergic reuptake inhibitors. However, the reanalysis of the study by Blomhoff et al[19] and the findings of Haug et al[49] suggest that a gradation of response from placebo to

monotherapy to combined treatment may extend to other medications and empirically supported psychotherapies. Further research is needed to confirm those findings. Sixth, there were some baseline differences across treatment groups and sites. However, the results remained significant after appropriate statistical adjustments, suggesting the robustness of the findings.

In summary, this study is the first, to our knowledge, to provide an empirical rationale for the use of combined treatment for SAD. Future studies should prospectively examine whether the combination of a selective serotonin reuptake inhibitor plus behavioral therapy or CBT is superior to either treatment alone and the acceptability, efficacy, and cost-effectiveness of combined vs sequentially administered or augmented treatments.

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