

Fluoxetine, Comprehensive Cognitive Behavioral Therapy, and Placebo in Generalized Social Phobia

Jonathan R. T. Davidson, MD; Edna B. Foa, PhD; Jonathan D. Huppert, PhD; Francis J. Keefe, PhD; Martin E. Franklin, PhD; Jill S. Compton, PhD; Ning Zhao, PhD; Kathryn M. Connor, MD; Thomas R. Lynch, PhD; Kishore M. Gadde, MD

Background: Generalized social phobia is common, persistent, and disabling and is often treated with selective serotonin reuptake inhibitor drugs or cognitive behavioral therapy.

Objective: We compared fluoxetine (FLU), comprehensive cognitive behavioral group therapy (CCBT), placebo (PBO), and the combinations of CCBT/FLU and CCBT/PBO.

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

Setting: Two academic outpatient psychiatric centers.

Patients: Subjects meeting a primary diagnosis of generalized social phobia were recruited via advertisement. Seven hundred twenty-two were screened, and 295 were randomized and available for inclusion in an intention-to-treat efficacy analysis; 156 (52.9%) were male, 226 (76.3%) were white, and mean age was 37.1 years.

Interventions: Treatment lasted for 14 weeks. Fluoxetine and PBO were administered at doses from 10 mg/d to 60 mg/d (or equivalent). Group comprehensive cognitive behavioral therapy was administered weekly for 14 sessions.

Main Outcome Measures: An independent blinded evaluator assessed response with the Brief Social Phobia

Scale and Clinical Global Impressions scales as primary outcomes. A videotaped behavioral assessment served as a secondary outcome, using the Subjective Units of Distress Scale. Adverse effects were measured by self-rating. Each treatment was compared by means of χ^2 tests and piecewise linear mixed-effects models.

Results: Clinical Global Impressions scales response rates in the intention-to-treat sample were 29 (50.9%) (FLU), 31 (51.7%) (CCBT), 32 (54.2%) (CCBT/FLU), 30 (50.8%) (CCBT/PBO), and 19 (31.7%) (PBO), with all treatments being significantly better than PBO. On the Brief Social Phobia Scale, all active treatments were superior to PBO. In the linear mixed-effects models analysis, FLU was more effective than CCBT/FLU, CCBT/PBO, and PBO at week 4; CCBT was also more effective than CCBT/FLU and CCBT/PBO. By the final visit, all active treatments were superior to PBO but did not differ from each other. Site effects were found for the Subjective Units of Distress Scale assessment, with FLU and CCBT/FLU superior to PBO at Duke University Medical Center, Durham, NC. Treatments were well tolerated.

Conclusions: All active treatments were superior to PBO on primary outcomes. Combined treatment did not yield any further advantage. Notwithstanding the benefits of treatment, many patients remained symptomatic after 14 weeks.

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Author Affiliations:

Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC (Drs Davidson, Keefe, Compton, Connor, Lynch, and Gadde); and the Department of Psychiatry, University of Pennsylvania, Philadelphia, Pa (Drs Foa, Huppert, Franklin, and Zhao).

SOCIAL PHOBIA, NOW OFTEN referred to as social anxiety disorder, is widespread with prevalence rates as high as 14% in the United States,¹ begins early in life, and rarely remits.² Of the 2 types of social phobia, generalized social phobia (GSP) is believed to be more severe than nongeneralized.³ A recent study of GSP in a health maintenance organization setting showed an 8% prevalence rate, along with raised incidence of suicide attempts, greater health seeking, and reduced earning capacity; physician

recognition of GSP was no more than 0.5% of all cases.⁴

Controlled trials suggest benefit from medication and psychosocial approaches. Among medications, the selective serotonin reuptake inhibitor (SSRI) group is the most extensively studied.⁵ Cognitive behavioral treatments (CBTs) are also effective in social phobia, especially a form of group CBT, which includes cognitive restructuring, exposure to simulated situations in sessions, and in vivo exposure homework assignments.⁶ Group CBT has been found to be more ef-

Table 1. Demographic Characteristics*

| | FLU Group | CCBT Group | CCBT/FLU Group | CCBT/PBO Group | PBO Group | Test | P Value |
|-------------------|-------------|------------|----------------|----------------|-------------|--------------------|---------|
| No. of subjects | 57 | 60 | 59 | 59 | 60 | | |
| Women | 42.9 | 53.3 | 54.2 | 36.2 | 45.8 | $\chi^2_4 = 5.33$ | .26 |
| White | 71.4 | 71.2 | 84.7 | 75.9 | 82.8 | $\chi^2_4 = 5.30$ | .26 |
| Age, y, mean (SD) | 36.3 (11.1) | 36.7 (9.1) | 38.2 (10.7) | 37.8 (10.2) | 36.9 (10.6) | $F_{4,283} = 0.31$ | .87 |

Abbreviations: CCBT, comprehensive cognitive behavioral therapy; FLU, fluoxetine; PBO, placebo.

*Values are expressed as percentages unless otherwise indicated.

fective than psychoeducation,⁶ atenolol,⁷ and buspirone hydrochloride⁸ and equivalent to phenelzine sulfate.⁶ Comprehensive cognitive behavior therapy (CCBT) was developed by Foa et al (unpublished data, 1994) for GSP. In this group CBT, social skills training is added to exposure therapy and cognitive restructuring, because social skills deficits are a pertinent part of GSP and may not respond well to programs if skill training is absent.⁹

With the emergence of SSRIs as frontline and proven pharmacotherapy for GSP, we considered it important to compare an SSRI with CCBT. To our knowledge, this is 1 of only 2 completed GSP studies to include a combination cell in which subjects received both CCBT and an SSRI.¹⁰ Our project had 5 overall goals: (1) to compare the effects of 14 weeks' treatment with fluoxetine (FLU) alone, group alone (CCBT), combined CCBT/FLU, CCBT/placebo (PBO) (to take into account nonspecific pill taking), and PBO alone; (2) to evaluate maintenance of treatment effects following completion of treatment; (3) to demonstrate transportability of treatments (ie, that CCBT can be successfully implemented in a center specializing in pharmacotherapy [Duke University Medical Center, Durham, NC] and vice versa for a center specializing in medication [University of Pennsylvania, Philadelphia, Pa]); (4) to investigate mechanisms of therapeutic change by examining the relationship between cognitive distortions and social skills deficits; and (5) to explore predictors of treatment response. This report will focus on the first goal, short-term effects of the 5 treatments.

METHODS

OVERALL DESIGN

The study was conducted at 2 academic medical centers with outpatient programs specializing in anxiety disorder research. At each research center, FLU, CCBT, CCBT/FLU, CCBT/PBO, and PBO were all compared, with FLU and PBO being administered on a double-blind basis. An independent rater, blinded to treatment assignments, conducted the primary outcome assessments. Eligible subjects met *DSM-IV* criteria for primary GSP, assessed by the Structured Clinical Interview for *DSM-IV*.¹¹ Subjects underwent psychiatric and medical evaluation to establish inclusion and exclusion criteria. Subjects were assigned to treatment by block randomization, which was generated by computer program at Duke University Medical Center, in groups of 10, with 2 subjects assigned to each of the 5 conditions. There were some exceptions to the implementation of this process because of a small number of prerandomization dropouts. We balanced CCBT groups to include at least 2 women and 2 men and typically had a male and a female thera-

pist. The study coordinator at each site enrolled and allocated subjects to their treatment groups. This individual was blind to the sequence prior to assignment.

Medication was administered and monitored by a psychiatrist. Medication sessions were audiotaped, and tapes were audited at random by 1 of the investigators at each site. Pharmacotherapy was provided according to the study manual and adherence rated according to a standardized checklist (available on request) to assure that no CCBT was being conducted and that medication was being provided in a standard way. Medication visits occurred weekly for 4 weeks, then every 2 weeks. Study investigators (E.B.F., F.J.K., and M.E.F.) videotaped and evaluated CCBT at each site and provided feedback to therapists in weekly supervision sessions (adherence rating scale available by request). Early in the trial, the sites provided feedback to therapists via weekly supervisory conference calls to ensure consistency of treatment across sites. Group CCBT was administered at weekly intervals.

Enrollment began in early 1995 and continued until September 2001. Regular conference calls were held between the 2 sites throughout. The protocol was approved by the institutional review board at each site, and all subjects provided written informed consent.

SAMPLE

Inclusion criteria were: (1) *DSM-IV* diagnosis of GSP; (2) age between 18 and 65 years; (3) fluency in English; and (4) provision of written informed consent. Exclusion criteria were: (1) a primary comorbid anxiety disorder (defined by which disorder was the more debilitating and clinically salient); (2) lifetime history of schizophrenia, bipolar disorder, or organic brain syndrome; (3) major depression within the last 6 months; (4) substance abuse or dependence within the past year; (5) mental retardation or pervasive developmental disability; (6) unstable medical condition; (7) prior failure of response to fluoxetine at 60 mg/d for at least 4 weeks or to 12 weekly sessions of CCBT for GSP; (8) concurrent psychiatric treatment or other psychoactive medications; (9) positive urine drug screen results; (10) inability to maintain 2 weeks' psychotropic drug-free washout; and (11) pregnancy or lactation.

Table 1 presents demographic characteristics by treatment group, showing no group differences. Between-site demographic differences were observed for ethnicity, marital status, and employment, with fewer African American subjects and more married and employed subjects in the Duke University Medical Center site sample, as compared with the University of Pennsylvania site sample. Baseline symptom scores for each treatment group are shown in **Table 2**.

TREATMENT ADMINISTRATION

Fluoxetine was started at 10 mg/d, increasing on day 8 to 20 mg/d, on day 15 to 30 mg/d, and on day 29 to 40 mg/d. Unless adverse effects became problematic, the goal was for subjects to reach 40 mg/d. At days 43 and 57, the dose could be raised to 50 mg/d and 60 mg/d, respectively, if subjects failed to achieve

Table 2. Effects of Treatment and Response Rates: Raw Posttreatment and Linear Mixed-Effects Models (LMM) Analyses*

| | FLU Group | CCBT Group | CCBT/FLU Group | CCBT/PBO Group | PBO Group | Test | P Value |
|---------------------------------|-------------|--------------|----------------|----------------|--------------|--------------------|---------|
| Effects of Treatment | | | | | | | |
| No. of subjects | | | | | | | |
| Week 0 | 57 | 60 | 59 | 59 | 60 | | |
| Week 14 | 39 | 48 | 42 | 46 | 36 | | |
| BSPS score | | | | | | | |
| Week 0 | 38.4 (9.6) | 39.2 (10.4) | 39.1 (9.9) | 37.6 (9.9) | 37.3 (8.5) | $F_{4,274} = 0.49$ | .75 |
| Week 0-4 | | | | | | $F_{4,654} = 4.13$ | .003 |
| Week 4-14 | | | | | | $F_{4,647} = 2.89$ | .02 |
| Week 14† | 20.8 (13.2) | 20.6 (9.9) | 21.6 (12.6) | 20.5 (12.1) | 26.7 (13.5) | | |
| CGI-S score | | | | | | | |
| Week 0 | 4.4 (0.1) | 4.5 (0.1) | 4.4 (0.1) | 4.4 (0.1) | 4.3 (0.1) | $F_{4,274} = 0.33$ | .86 |
| Week 0-4 | | | | | | $F_{4,654} = 4.08$ | .003 |
| Week 4-14 | | | | | | $F_{4,647} = 3.46$ | .01 |
| Week 14‡ | 2.7 (1.2) | 2.9 (1.2) | 2.7 (1.2) | 2.8 (1.2) | 3.3 (1.3) | | |
| SPAI score | | | | | | | |
| Week 0§ | 97.5 (24.8) | 106.1 (21.3) | 109.9 (23.8) | 111.3 (21.0) | 112.0 (21.0) | $F_{4,274} = 3.63$ | .007 |
| Week 0-4 | | | | | | $F_{4,654} = 1.03$ | .39 |
| Week 4-14 | | | | | | $F_{4,647} = 2.3$ | .05 |
| Week 14† | 69.3 (37.2) | 77.1 (28.7) | 76.1 (31.5) | 75.4 (32.0) | 94.8 (28.0) | | |
| Response Rate at Week 14 | | | | | | | |
| ITT sample, % | 50.9 | 51.7 | 54.2 | 50.8 | 31.7 | $\chi^2_4 = 8.03$ | .09 |
| Completer sample, %¶ | 64.1 | 64.6 | 66.7 | 58.7 | 38.9 | $\chi^2_4 = 8.09$ | .09 |

Abbreviations: BSPS, Brief Social Phobia Scale; CCBT, comprehensive cognitive behavioral therapy; CGI-S, Clinical Global Impressions Severity scale; FLU, fluoxetine; ITT, intention to treat; PBO, placebo; SPAI, Social Phobia and Anxiety Inventory.

*Values are expressed as mean (SD) unless otherwise indicated. Statistics and *P* values were calculated by LMM analyses.

†All individual treatments were superior to PBO at week 14 (*P* < .05).

‡All individual treatments were superior to PBO, except CCBT/PBO, at week 14 (*P* < .05).

§At week 0, FLU treatment was superior to CCBT/FLU, CCBT/PBO, and PBO (*P* < .05).

||All individual treatment response rates were superior to PBO at week 14 (*P* < .05).

¶All individual treatment response rates were superior to PBO, except CCBT/PBO, at week 14 (*P* < .05).

a Clinical Global Impressions (CGI) Improvement¹² score of 1 or 2 and were tolerating medication. Compliance was monitored by reviewing daily medication logs and pill counts at each visit. Normally, the dose was given in the morning.

Comprehensive cognitive behavioral therapy is a 14-week group treatment that combines in vivo exposure, cognitive restructuring, and social skills training. Derived in part from a treatment developed by Heimberg et al,¹³ CCBT differs from Heimberg group CBT in that CCBT includes specific social skills training (eg, how to begin a conversation with a stranger) and improves specific behaviors (eg, eye contact), the role-plays are much shorter, and CCBT is 2 sessions longer than group CBT. Two therapists (1 male, 1 female) who received extensive training prior to this study conducted the treatment; each group consisted of 5 to 6 subjects. The first 2 sessions were educational, with therapists presenting a cognitive behavioral model of social anxiety and explaining treatment techniques. Sessions 3 and 4 were devoted to social skills training; patients received instruction and role-played short (30-60 second), repeated (5-7 times) scenarios devoted to initiating, maintaining, and ending conversations, as well as compromise/negotiation. In sessions 5 through 13, patients participated in longer (3-4 minute) role-plays tailored to their specific social concerns. Prior to each role-play, subjects identified a core dysfunctional thought associated with that situation and a relevant rational response to replace it. Next, social skills training instructions were provided before the role-play, and specific aspects of each role-play were repeated to facilitate skills acquisition. Between sessions, subjects completed homework assignments designed to help them confront fearful social situations using the techniques learned in therapy. Session 14 included a discussion of treatment gains and recommendations for future practices.

INDEPENDENT EVALUATOR RATINGS AND SELF-REPORT MEASURE

Primary outcome assessments by the blinded independent evaluator (IE) were as follows: (1) CGI Improvement scale, a 7-point rating measured improvement wherein response is defined as having a CGI Improvement score of 1 (very much improvement) or 2 (much improvement), and the 7-point CGI Severity scale¹² and (2) the Brief Social Phobia Scale (BSPS), an 18-item scale comprised of fear, avoidance, and physiological symptoms.¹⁴ Independent evaluator ratings were conducted at baseline and at weeks 4, 8, and 14. Success of the blinding procedure was not evaluated. Altogether, 8 IEs were associated with this trial from start to finish (3 at Duke University Medical Center and 5 at University of Pennsylvania). Intraclass correlation pairwise agreement coefficients for between raters ranged from 0.77 to 0.98.

The Social Phobia and Anxiety Inventory,¹⁵ which is reliable, valid, and sensitive to treatment effects,¹⁶ served as a secondary measure.

ADVERSE EFFECTS

Symptoms possibly attributable to treatment were evaluated by means of the Severity of Symptoms Scale,¹⁷ which was given to subjects at each visit, regardless of treatment assignment.

BEHAVIORAL ASSESSMENT

A role-play test evaluated social skills before and after treatment. The subject was videotaped in each of 3 social scenarios: initiating a conversation with a stranger; expression of

negative assertiveness; and an impromptu speech. Subjects were asked to indicate their level of anxiety using the Subjective Units of Distress Scale (SUDS), an analogue scale ranging from 0 (relaxed and calm) to 100 (extremely fearful). The SUDS ratings were assessed 7 times: immediately after receiving role-play instructions (ie, at baseline); before each of the 3 role-play scenarios (to measure anticipatory anxiety); and after each scenario (to measure "aftermath"). An experimenter and a confederate, both blinded to the subject's treatment status, were present during the test. Each scenario lasted 3 minutes.

STATISTICAL ANALYSIS

The following hypotheses were tested: (1) all active treatments would be superior to PBO and (2) combined CCBT/FLU treatment would be superior to other active treatments. Post hoc, exploratory, 2-tailed pairwise contrasts were performed to determine whether the active treatments differed from one another. Sample size was calculated based on pilot data obtained earlier. Three power estimates were made for the primary contrasts, with a single pooled estimate of the error term and 1-tailed hypothesis testing. Power to detect a difference for 60 subjects per group, with an effect size of 0.30 at $\alpha = .05$, ranged from 0.7 to 0.9 in the combined site sample according to comparison.

First, to detect possible pretreatment differences among conditions, 1-way analyses of variance were performed on pretreatment data for the BSPS, CGI, Social Phobia and Anxiety Inventory, and SUDS ratings. Second, the differential efficacy of the conditions at 14 weeks or an earlier end point was analyzed using (1) χ^2 tests to compare the proportion of subjects who achieved treatment response status within each treatment and (2) linear mixed-effects models (LMM), from SAS procedure MIXED,¹⁸ to assess differences in course of treatment response. For these analyses, piecewise linear growth curve models, with a change point at week 4, provided the best fit for the data. An unstructured variance model best fit the data for all analyses. We applied this piecewise LMM to each of the 3 continuous outcome measures. These analyses were followed by pairwise analyses to determine whether treatments differed in how fast they induced change. In addition, piecewise LMMs were applied to each outcome variable to determine whether each treatment induced change across the 14 treatment weeks. Site effects were examined by including a binary indicator and its interactions with treatment and time in the piecewise LMMs mentioned earlier. When the interaction of site by treatment or site by time was significant, we conducted follow-up analyses to explain these interactions. Sex, age, marital status, ethnicity, and employment status were all examined to determine whether they differentially affected treatment outcome. None of these variables had significant interactions with treatment condition by time and were therefore not included in final analyses.

Linear mixed-effect model analyses included all randomized subjects and were conducted using pretreatment and post-treatment behavioral measures, with the behavioral measure as the dependent variable.

Responder analyses were conducted separately for all randomized subjects for whom any data were available (ITT) and subjects who completed 14 weeks (completer sample).

Effect size, along with 95% confidence intervals, was calculated according to the Cohen formula¹⁹ for a difference between groups of m_1 (postactive treatment) – m_2 (post-PBO)/pooled standard deviation ($m_1 m_2$), in order to determine effect sizes of active treatments at posttreatment.

RESULTS

A total of 4306 subjects were screened by telephone, of whom 722 were invited for a full study assessment. The

most common reasons for exclusion at this stage were the presence of major depression, social phobia being non-generalized, presence of another primary anxiety disorder, and substance abuse. Of these, 295 were randomized to 1 of the 5 treatments, with the following dispositions: 16 (5%) dropped out prior to receiving treatment; 68 (23%) dropped out between week 1 and week 14; and 211 (72%) completed 14 weeks of treatment. Randomized subjects who were analyzed composed the ITT ($n = 265$) and completer ($n = 211$) samples, respectively, as follows: FLU ($n = 57, 39$), CCBT ($n = 60, 48$), CCBT/FLU ($n = 59, 42$), CCBT/PBO ($n = 59, 46$), and PBO ($n = 60, 36$). **Figure 1** provides details of subject disposition. The overall significance for rate of dropout by treatment type was not statistically significant ($\chi^2_4 = 8.22$; $P = .08$). However, in pairwise contrasts, the PBO group had significantly more dropouts than the CCBT group ($\chi^2_1 = 6.53$; $P = .01$) and the CCBT/PBO group ($\chi^2_1 = 4.48$; $P = .03$), respectively.

The proportion of subjects who discontinued prematurely did not differ statistically across site ($\chi^2_8 = 9.67$; $P = .29$). Reasons for early discontinuation are provided in Figure 1.

There were no significant differences among groups in respect of mean medication doses. For the combined PBO groups (CCBT/PBO and PBO), mean (SD) maximum and final attained visit doses were 49.3 (15.2) mg equivalents per day and 46.4 (17.9) mg equivalents per day, respectively. For the combined FLU groups (CCBT/FLU and FLU), they were 47.3 (13.9) mg/d and 43.6 (16.4) mg/d, respectively.

INDEPENDENT EVALUATIONS

The ITT response rates determined by a CGI Improvement score of 1 or 2 were as follows: FLU, 50.9%; CCBT, 51.7%; CCBT/FLU, 54.2%; CCBT/PBO, 50.8%; and PBO, 31.7%. The overall χ^2 test showed a trend toward significance ($\chi^2_4 = 8.03$; $P = .09$), and pairwise significance was found for all treatment comparisons against PBO: FLU vs PBO ($\chi^2_1 = 4.46$; $P = .03$); CCBT vs PBO ($\chi^2_1 = 4.94$; $P = .03$); CCBT/FLU vs PBO ($\chi^2_1 = 6.19$; $P = .01$); and CCBT/PBO vs PBO ($\chi^2_1 = 4.52$; $P = .03$). For the completer sample, response rates were as follows: FLU, 64.1%; CCBT, 64.6%; CCBT/PBO, 59.6%; CCBT/FLU, 66.7%; and PBO, 40.5%. The overall χ^2 test showed a trend toward significance ($\chi^2_4 = 8.09$; $P = .09$). Pairwise significance was found for the following treatment comparisons against PBO: FLU vs PBO ($\chi^2_1 = 4.77$; $P = .03$); CCBT vs PBO ($\chi^2_1 = 5.46$; $P = .02$); and CCBT/FLU vs PBO ($\chi^2_1 = 6.02$; $P = .01$); CCBT/PBO vs PBO showed a trend toward significance ($\chi^2_1 = 3.17$; $P = .08$). There were more subjects in the responder sample in the CCBT/PBO group at Duke University Medical Center than at the University of Pennsylvania. No other site differences were detected.

Effect sizes (95% confidence interval) for each comparison vs PBO, based on the ITT analysis of variance, provided the following results on the BSPS: 0.40 (0.02 to 0.77) for FLU; 0.30 (–0.07 to 0.66) for CCBT; 0.24 (–0.13 to 0.60) for CCBT/FLU, and 0.52 (0.14 to 0.89) for CCBT/PBO vs PBO.

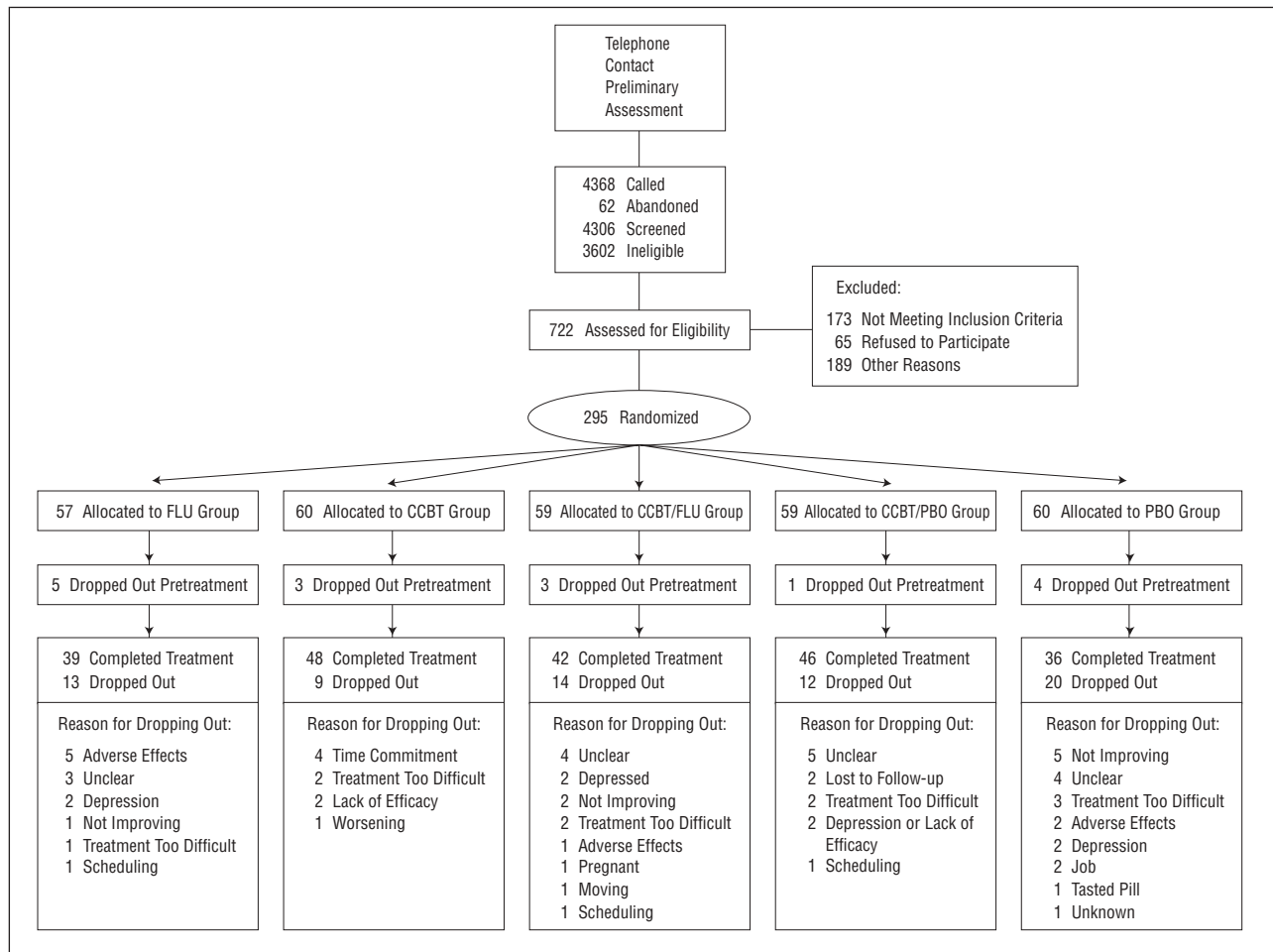


Figure 1. Flowchart of subject progress through the phases of the study. There were 295 subjects in the intention-to-treat analysis and 211 subjects in the completer analysis. CCBT indicates comprehensive cognitive behavioral therapy; FLU, fluoxetine; PBO, placebo.

For the CGI Severity scale, effect size (95% confidence interval) results for each treatment relative to PBO were as follows: 0.42 (0.04 to 0.80) for FLU; 0.27 (-0.10 to 0.64) for CCBT; 0.30 (-0.07 to 0.67) for CCBT/FLU; and 0.42 (0.04 to 0.79) for CCBT/PBO.

LMMS ANALYSIS

At week 14, significant differences existed in favor of all active treatments compared with PBO on the BSPS and Social Phobia and Anxiety Inventory ($P < .05$) (Table 2). The CGI Severity scale evidenced the same pattern, with FLU and CCBT/FLU both being superior to PBO ($P = .01$) but not reaching significance for CCBT or CCBT/PBO ($P < .10$).

For the BSPS, treatment by time models (ie, slope or rate of change) was significant for weeks 0 to 4 ($P = .002$) and for weeks 4 to 14 ($P = .02$) (Figure 2). Pairwise analysis suggested that FLU alone produced more change than PBO, CCBT/FLU, and CCBT/PBO from weeks 0 to 4 ($P < .01$), while CCBT evidenced more change than CCBT/FLU and CCBT/PBO ($P < .05$) and a trend toward superiority over PBO ($P = .10$). From weeks 4 to 14, CCBT/FLU and CCBT/PBO conditions produced more change than PBO ($P < .05$), and CCBT evidenced a trend in the same direction ($P = .09$). Furthermore, CCBT/FLU showed

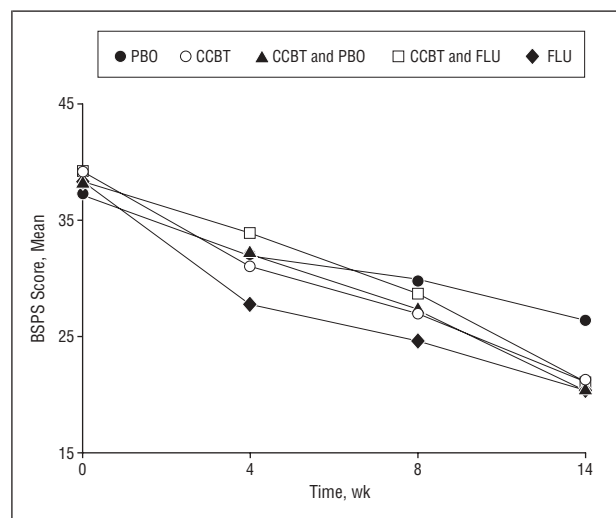


Figure 2. Mean Brief Social Phobia Scale (BSPS) score by treatment group (n=295). Piecewise linear mixed-effects models analysis. CCBT indicates comprehensive cognitive behavioral therapy; FLU, fluoxetine; PBO, placebo.

more change than FLU in the last 10 weeks ($P = .03$), and CCBT/PBO showed a trend in the same direction ($P = .07$). Similar results were found for the CGI Severity scale. In summary, FLU demonstrated the fastest onset of action

followed by CCBT. By the final visit, combined treatments were not different from monotherapies, and all active treatments were superior to PBO.

BEHAVIORAL RATINGS

Posttreatment SUDS ratings are presented in **Table 3**. The multiple tests were combined to produce average ratings for all 3 scenarios. For each treatment, we provide the average postinstruction, anticipatory, and aftermath scores for all 3 scenarios. Significant time \times treatment \times site interactions emerged for all 3 analyses ($P < .05$), leading us to break down the treatment comparisons by site. At the University of Pennsylvania, no comparisons were significant. At Duke University Medical Center, subjects in the FLU group reported significantly less anxiety than the PBO group on all behavioral measures. Comprehensive cognitive behavioral therapy/fluoxetine was superior to PBO in anticipatory anxiety before scenarios but not in baseline anxiety. Fluoxetine was associated with significantly lower anticipatory distress than CCBT, and CCBT/PBO was associated with less distress than CCBT at anticipatory and posttest tasks.

Further examination of Table 3 indicates a difference in outcome between those who received CCBT in any form and those who did not. While there were no differences in outcome per se, the pattern of SUDS scores from postinstruction to anticipatory to aftermath is consistent at week 0 across conditions; at each step, there is an increase in anxiety. However, at week 14, subjects who participated in CCBT evidenced, on average, no change or even a decrease in SUDS score from anticipatory to aftermath, while the PBO and FLU subjects continued to show an increase in anxiety from anticipatory to aftermath. This difference in SUDS ratings was significant ($P < .05$). These data provide some evidence that exposure during group therapy did have an effect on behavioral ratings.

ADVERSE EFFECTS

Significantly higher rates of treatment emergent events were noted on 4 symptoms (**Table 4**). Insomnia and headache both occurred more often in the PBO and CCBT/PBO groups relative to CCBT alone and in the CCBT/FLU and FLU groups relative to CCBT alone. Nausea occurred more frequently in the PBO and CCBT/PBO groups relative to the group undergoing CCBT alone and in the FLU group relative to the CCBT and CCBT/PBO groups. Relative to the PBO group, anorgasmia was more commonly seen in the CCBT/PBO, CCBT/FLU, and FLU groups, as well as in the FLU vs CCBT/PBO groups.

COMMENT

In adults with GSP, this study demonstrated efficacy for FLU and CCBT relative to PBO but no evidence for greater benefit of combined treatment over monotherapies. Response rates indicated a treatment vs placebo difference ranging from 15% to 24%. A comparison of our findings with the study of phenelzine and group CBT by Heimberg et al⁶ indicates that the 2 studies have a similar PBO

response rate (31% and 33%, respectively) and broadly comparable rates of response to group therapy (52% and 58%, respectively). Response rates to FLU and phenelzine were 51% and 65%, respectively. Given a very broad spectrum of activity for monoamine oxidase inhibitors, it is conceivable that phenelzine carries greater benefit than an SSRI, a hypothesis consistent with a recent meta-analysis by Hidalgo et al.⁵

One SSRI, sertraline hydrochloride, has been studied in conjunction with CBT in a Swedish primary care setting.^{10,20} Sertraline/CBT and sertraline alone, but not CBT/PBO, exceeded the response from PBO alone. Combined sertraline/CBT tended to produce greater benefits. However, on 28-week posttreatment follow-up, initial CBT alone was associated with further gain, whereas sertraline alone or combined with CBT was associated with deterioration. This study differed from ours in sample characteristics, type of CBT, and lack of a CBT-alone group, which may account for some of the different findings.

The IE and self-report analyses consistently demonstrated an advantage of all active treatments over PBO, other than the CGI Severity scale, on which only FLU and CCBT/FLU were superior to PBO at end point. Effect sizes (which were not derived from the LMM analyses) indicate a moderate effect of all treatments, with CCBT/PBO and FLU tending to be the highest. The fact that CCBT/PBO had a large effect size on the BSPS but only a trend toward superiority over PBO on the CGI measures suggests that the CGI scale may be somewhat less sensitive to changes in social anxiety symptoms. Alternatively, the BSPS may detect subtle changes in social anxiety that do not reflect the global impairment as well as the CGI scale.

Measures of social interaction were evaluated in vivo, in the form of a series of videotaped social interactions and speech delivery. These assessments proved generally robust in picking up treatment effects relative to PBO at Duke University Medical Center but not at the University of Pennsylvania. This is because at the University of Pennsylvania, but not at Duke University Medical Center, the patients treated with PBO responded well to the behavioral task, even though their symptoms did not change substantially. We do not understand why CCBT alone should have failed to distinguish from PBO, although a numerically superior effect was observed in the posttest evaluation.

Mixed-effects models have become well accepted for interpretation of clinical trial data and include all data without imputing missing values.²¹ We used a 2-level approach (piecewise linear growth model) and found FLU generated a faster response than the other treatments; at week 4, FLU showed superiority to CCBT/FLU, CCBT/PBO, and PBO. However, the degree of change at posttreatment did not differ between FLU and CCBT. Thus, our findings are similar to Heimberg et al,⁶ who reported an earlier advantage for phenelzine over CBT, with the 2 treatments being comparable by week 12. Such a finding suggests that greater advantage would accrue from a strategy of initial treatment with an SSRI, followed by augmentation with psychosocial treatment after 4 to 8 weeks. This indeed was found in a study of posttraumatic stress disorder,²² and we are now planning such a study in social anxiety disorder. Besides taking advan-

Table 3. Effects of Treatment on Behavioral Measure (Subjective Units of Distress Scale) at Weeks 0 and 14 by Site: Raw Posttreatment and Linear Mixed-Effects Models (LMM) Analyses*

| | FLU Group | CCBT Group | CCBT/FLU Group | CCBT/PBO Group | PBO Group | Test | P Value |
|---------------------------------------|-------------|-------------|----------------|----------------|-------------|--------------------|---------|
| No. of subjects | | | | | | | |
| University of Pennsylvania | | | | | | | |
| Week 0 | 27 | 29 | 28 | 27 | 29 | | |
| Week 14 | 20 | 22 | 20 | 21 | 17 | | |
| Duke University Medical Center | | | | | | | |
| Week 0 | 27 | 30 | 30 | 29 | 27 | | |
| Week 14 | 21 | 24 | 25 | 25 | 21 | | |
| University of Pennsylvania | | | | | | | |
| Postinstruction score | | | | | | | |
| Week 0 | 31.0 (18.7) | 29.5 (21.4) | 28.7 (19.4) | 27.4 (20.4) | 35.6 (22.5) | $F_{4,123} = 0.62$ | .65 |
| Week 14 | 24.3 (18.1) | 33.4 (17.9) | 30.5 (17.6) | 26.1 (14.0) | 25.0 (21.0) | $F_{4,81} = 0.64$ | .63 |
| Anticipatory score | | | | | | | |
| Week 0 | 45.1 (16.8) | 44.8 (18.3) | 47.9 (23.7) | 39.2 (19.8) | 47.8 (16.2) | $F_{4,123} = 0.87$ | .48 |
| Week 14 | 30.3 (16.4) | 37.0 (15.0) | 34.9 (19.2) | 34.2 (17.7) | 35.4 (21.3) | $F_{4,81} = 0.92$ | .45 |
| Aftermath score | | | | | | | |
| Week 0 | 49.1 (21.0) | 50.4 (20.1) | 54.6 (24.2) | 44.2 (19.8) | 52.5 (20.6) | $F_{4,123} = 0.91$ | .46 |
| Week 14 | 36.8 (18.2) | 33.3 (17.8) | 35.6 (18.9) | 36.3 (20.6) | 44.0 (22.1) | $F_{4,81} = 0.95$ | .44 |
| Duke University Medical Center | | | | | | | |
| Postinstruction score | | | | | | | |
| Week 0† | 33.9 (21.4) | 29.4 (20.5) | 42.8 (24.1) | 28.2 (14.5) | 29.6 (15.4) | $F_{4,135} = 2.68$ | .03 |
| Week 14‡ | 21.5 (12.6) | 32.3 (20.2) | 33.7 (17.8) | 28.5 (18.1) | 36.6 (22.7) | $F_{4,106} = 2.05$ | .09 |
| Anticipatory score | | | | | | | |
| Week 0 | 43.1 (18.9) | 43.2 (19.2) | 54.4 (23.7) | 46.6 (18.8) | 45.6 (16.6) | $F_{4,135} = 1.60$ | .18 |
| Week 14§ | 25.0 (16.9) | 36.4 (20.7) | 30.8 (13.1) | 31.8 (14.2) | 44.6 (21.1) | $F_{4,106} = 3.60$ | .009 |
| Aftermath score | | | | | | | |
| Week 0 | 48.1 (22.7) | 47.4 (21.5) | 60.1 (22.8) | 51.7 (15.9) | 52.7 (15.2) | $F_{4,135} = 1.84$ | .13 |
| Week 14 | 31.1 (21.5) | 38.1 (22.1) | 28.0 (13.7) | 31.3 (16.7) | 47.9 (20.2) | $F_{4,106} = 3.52$ | .01 |

Abbreviations: CCBT, comprehensive cognitive behavioral therapy; FLU, fluoxetine; PBO, placebo.

*Values are expressed as mean (SD) unless otherwise indicated. Statistics and P values were calculated by LMM analyses. Given the treatment time by site interaction, data are presented separately for each site. Final Subjective Units of Distress Scale scores given (0 = relaxed and calm; 100 = extremely fearful). Pairwise differences were significant at $P < .05$, 2-tailed.

†At week 0, CCBT/FLU treatment was superior to PBO, CCBT, and CCBT/PBO treatments ($P < .05$).

‡At week 14, FLU treatment was superior to PBO, CCBT/FLU, and CCBT treatments ($P < .05$).

§At week 14, CCBT/FLU, FLU, and CCBT/PBO treatments were superior to PBO; FLU treatment was superior to CCBT treatment ($P < .05$).

||At week 14, CCBT/FLU, FLU, CCBT/PBO treatments were superior to PBO treatment ($P < .05$).

Table 4. Significant Differences in Adverse Effects by Treatment Group*

| Parameter | FLU Group (n = 48) | CCBT Group (n = 44) | CCBT/FLU Group (n = 53) | CCBT/PBO Group (n = 55) | PBO Group (n = 52) | χ^2 | P Value |
|---------------------------|--------------------|---------------------|-------------------------|-------------------------|--------------------|----------|---------|
| Insomnia†‡§ | 47.9 (33.3-62.8) | 13.6 (5.0-27.3) | 45.3 (31.6-59.6) | 41.8 (28.7-55.9) | 42.3 (28.7-56.8) | 14.82 | .005 |
| Headaches†‡§ | 31.2 (18.7-46.2) | 6.8 (1.4-18.7) | 34.3 (21.5-48.3) | 27.3 (16.1-41.0) | 38.5 (25.3-53.0) | 13.76 | .008 |
| Nausea†‡§ ¶ | 18.8 (9.0-32.6) | 0.0 (0.0-8.0) | 17.0 (8.1-29.8) | 9.1 (3.0-22.0) | 15.4 (6.9-28.1) | 10.08 | <.04 |
| Anorgasmia‡§ #**††‡‡ | 32.4 (22.2-50.5) | 4.6 (0.86-15.5) | 28.3 (16.8-42.4) | 7.3 (2.0-17.6) | 9.6 (3.2-21.0) | 26.79 | <.001 |
| Erectile dysfunction‡ ** | 10.4 (3.5-22.7) | 0.0 (1.0-8.0) | 5.7 (1.2-15.7) | 14.6 (6.5-26.7) | 1.9 (0.04-10.3) | 11.55 | <.02 |

Abbreviations: CCBT, comprehensive cognitive behavioral therapy; FLU, fluoxetine; PBO, placebo.

*Values are expressed as rate percentage (95% confidence interval). Adverse effect identified by an increase of at least 2 points (on a 0-3 scale) relative to baseline at any assessment point and counted only once per patient.

†Significant pairwise control PBO vs CCBT; PBO was worse.

‡Significant pairwise control CCBT/PBO vs CCBT; CCBT/PBO was worse.

§Significant pairwise control CCBT/FLU vs CCBT; CCBT/FLU was worse.

||Significant pairwise control FLU vs CCBT; FLU was worse.

¶Significant pairwise control CCBT/FLU vs FLU; CCBT/FLU was worse.

#Significant pairwise control CCBT/FLU vs PBO; CCBT/FLU was worse.

**Significant pairwise control FLU vs PBO; FLU was worse.

††Significant pairwise control CCBT/FLU vs CCBT/PBO; CCBT/FLU was worse.

‡‡Significant pairwise control FLU vs CCBT/PBO; FLU was worse.

tage of the therapeutic impact of an SSRI, when psychosocial treatment is added to established SSRI therapy, its effects would not be obfuscated by issues of pill taking

and adverse effects or pseudo adverse effects that may appear early in the course of treatment. Our findings about adverse effects are interesting in this regard, because they

indicate that pill taking itself (whether drug or PBO) is associated with a high rate of headaches and insomnia, which occurred in 27% to 42% of subjects. Thus, a person who is in therapy and taking a pill may be initially distracted by somatic concerns such as impaired sleep and headaches. The same was true to a lesser extent for erectile dysfunction and nausea. Anorgasmia occurred more frequently in patients receiving FLU than PBO; we do not know if this in any way compromised the integrity of the double-blind design. Although the IEs were instructed not to discuss adverse effects and to remind subjects only to address symptoms of social phobia, adverse effects were discussed in the medication management sessions.

Similar to the findings of Heimberg et al,⁶ we did not detect a site \times treatment effect, indicating that medication and psychosocial treatments, as well as PBO, can be given in a consistent manner at sites that differ in their therapeutic allegiance. It is possible that the between-site differences on the behavioral test were related to the fact that less attention was devoted to intersite standardization of test delivery, relative to medication and CBT.

Some limitations of our study need to be acknowledged. First, group treatment restricted flexibility of schedule for potential subjects, some of whom may have been deterred through fear of the group itself. Second, some subjects declined to take part in treatment after being randomized, since they did not want to receive medication alone. This issue has been addressed in a separate report by our group²³ and is partly taken care of in the ITT analysis. It could be questioned whether FLU was the most appropriate drug, particularly since there are 2 reports demonstrating no difference between FLU and PBO.^{24,25} Given that SSRIs as a class have very broad-spectrum anxiolytic properties but are not invariably positive in all trials, we are as yet unpersuaded that this argument has great merit. However, we do not know if other SSRIs might have been more effective (eg, paroxetine hydrochloride or sertraline).^{10,26-30} No published head-to-head comparisons of SSRIs exist to our knowledge. As in most social phobia/social anxiety disorder trials to date, we excluded subjects with a diagnosis of major depression. Data from a subsection of the subject screens administered at the University of Pennsylvania suggest that depression was the most frequent reason for study exclusions, comprising approximately one third of the patients excluded. It is essential that the next generation of studies determine effective treatment strategies for subjects with comorbid social phobia and depression, especially given their impairing effects.²³ We did not assess the success of IE binding, as recommended by the CONSORT guidelines.³¹ As such, this could be seen as a limitation. On the other hand, our experience from a similar previous trial suggests that "guessing" increases attention and/or sensitivity to the matter of what treatment is being administered. As to the increased anorgasmia in subjects receiving FLU, the IE was instructed not to discuss or encourage reports of adverse events, which formed part of the pharmacotherapy assessment.

To conduct and complete a trial of this magnitude is a considerable undertaking, representing approximately 10 years of work from inception of the idea, to

acquisition of funding, recruitment into the study, and subsequent analysis of data. Such trials can be successfully accomplished, and this one has demonstrated that widely used treatments (ie, CBT and FLU) are effective for individuals with generalized social phobia, many of whom are significantly impaired. Although FLU and CCBT were more successful than PBO, substantial symptoms still remained after 14 weeks' treatment. We therefore wonder whether longer-term pharmacological treatment is necessary and if changes in the delivery of CCBT would improve results. Furthermore, recent evidence suggests that individual CBT produces better results than group CBT in GSP.³² Finally, combining FLU with CCBT did not provide any greater therapeutic benefit. One possible contributing reason may be the distracting physical complaints that arise early with medication and may be a reason for sequential treatment rather than simultaneous initiation.

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