Paroxetine Treatment of Generalized Social Phobia (Social Anxiety Disorder)

A Randomized Controlled Trial

Murray B. Stein, MD; Michael R. Liebowitz, MD; R. Bruce Lydiard, PhD, MD; Cornelius D. Pitts, RPh; William Bushnell, MS; Ivan Gergel, MD

Context.—The generalized type of social phobia (social anxiety disorder) is a severe and often disabling form of social anxiety that affects approximately 5% of the general population. Earlier research has shown monoamine oxidase inhibitors or benzodiazepines to be effective in treating this condition, but neither has achieved widespread use.

Objective.—To compare the efficacy of paroxetine, a selective serotonin reuptake inhibitor, with placebo in adults with generalized social phobia.

Design.—Twelve-week, multicenter, randomized, double-blind trial.

Setting.—Thirteen centers across the United States and 1 in Canada.

Participants.—Between April 13, 1995, and February 28, 1996, 187 persons meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for generalized social phobia were randomized (and 183 returned for at least 1 efficacy assessment) to treatment.

Intervention.—After a 1-week, single-blind, placebo, run-in period, patients received a double-blind, 11-week course of either paroxetine or matching-image placebo. The initial daily dosage of paroxetine (or placebo) was 20 mg with increases of 10 mg/d weekly (flexible dosing to a maximum of 50 mg/d) permitted after the second week of treatment.

Main Outcome Measures.—Number of responders based on the Clinical Global Impression Global Improvement Item (“much improved” or “very much improved”); mean change from baseline on the Liebowitz Social Anxiety Scale total score.

Results.—Fifty (55.0%) of 91 persons taking paroxetine and 22 (23.9%) of 92 persons taking placebo were much improved or very much improved at the end of treatment (odds ratio [OR], 3.88; 95% confidence interval [CI], 2.81-5.36). Mean Liebowitz Social Anxiety Scale total scores were reduced by 39.1% (the mean baseline score of 78.0 declined by a mean of 30.5 points at follow-up) in the paroxetine group compared with 17.4% (the mean baseline score of 83.5 declined 14.5 points at follow-up) in the placebo group, a difference of 21.7% (95% CI, 8.7%-34.7%) favoring paroxetine.

Conclusions.—Paroxetine is an effective treatment for patients with generalized social phobia. Short-term (ie, 11-week) treatment results in substantial and clinically meaningful reductions in symptoms and disability. Future research should test whether these may be further reduced by extended treatment or supplementation with specific educational-cognitive-behavioral techniques.

From the Department of Psychiatry, University of California at San Diego, La Jolla (Dr Stein); Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY (Dr Liebowitz); Department of Psychiatry, Medical University of South Carolina, Charleston (Dr Lydiard); and Clinical Research, Development, and Medical Affairs, North America, SmithKline Beecham Pharmaceuticals, Collegeville, Pa (Messrs Pitts and Bushnell and Dr Gergel).

Reprints: Murray B. Stein, MD, Department of Psychiatry (0985), University of California, San Diego, 9500 Gilman Dr, La Jolla, CA 92037-0985 (e-mail: mstein@ucsd.edu).

SOCI AL PHOBIA, also known as social anxiety disorder, is characterized by the fear of being observed or evaluated by others.1 In such situations, individuals with social phobia fear that they will say or do something to embarrass or humiliate themselves or that others will notice that they are anxious. Consequently, people with social phobia often avoid situations where such scrutiny might take place or they endure them with intense distress. Not surprisingly, this can result in impaired functioning and reduced quality of life.2-4 Patients with social phobia may have few friendships, experience trouble dating, drop out of school, reject promotions at work, become demoralized and depressed, abuse alcohol, and develop other psychiatric comorbidities.2-7

Most clinicians associate the term social phobia with a fear of public speaking. Indeed, social phobia often involves public speaking and, in some cases, does so exclusively.8 However, it has recently been recognized that there is a subgroup of social phobic people whose social anxiety is far more pervasive and usually far more disabling. Persons with this variant of the disorder, known as generalized social phobia (GSP), typically fear and avoid a broad array of situations that most people take for granted.9,5,7 Examples might include speaking in small groups (eg, at work or school), attending social gatherings, talking to people in authority (eg, teachers, employers), or interacting with peers in informal settings (eg, talking to colleagues over lunch).

Previously believed to be a rare disorder based on prevalence estimates from psychiatric clinics, recent epidemiologic surveys have demonstrated that social phobia is highly prevalent.1-12 After major depression and alcohol dependence, social phobia is the third most common psychiatric disorder in the gen-
eral population with lifetime, 12-month, and 30-day prevalence rates of 13.3%, 7.9%, and 4.5%, respectively. Although precise rates of GSP are lacking, it is estimated that approximately two thirds of people with social phobia in the community would fall into this category. It is this 4% to 5% of persons in the community who warrant our attention as suffering from a public health problem of considerable importance.

Social phobia, like many other anxiety disorders, is highly prevalent in the primary care setting but goes largely undiagnosed and untreated. In a recent primary care study, social phobia was noted to be associated with meaningfully reduced role functioning and sense of well-being. In the only in-depth study to date of social phobia in the general medical health care system, investigators found a 1-month prevalence of 4.9% in a French primary care clinic but poor recognition of the disorder on the part of general practitioners. Unfortunately, the low rate of recognition and appropriate treatment reflect the fact that social phobia remains a largely neglected anxiety disorder.

This neglect also extends into the area of treatment. Whereas most physicians equate treating social phobia with the prescription of as-needed β-blockers or benzodiazepines (which can be useful in treating social phobia limited to public speaking or other kinds of performance situations on a daily, often unpredictable basis), the use of occasional “as needed” medications for GSP is not an option. Treatment options for generalized social phobia include monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase A (RIMAs), and benzodiazepines. However, these treatment choices are associated with dietary restrictions (MAOIs), potential difficulties with withdrawal and dependence (benzodiazepines), and questionable efficacy in some studies (RIMAs).

Specific psychotherapies focused on changing maladaptive thoughts and behaviors (ie, cognitive and behavioral therapies) have also shown considerable promise in the treatment of social phobia. Access to these psychotherapies is often limited, however, by an inadequate supply of trained therapists, insurance barriers, and other cost factors.

Based on their success in the treatment of many mood and other anxiety disorders, the selective serotonin reuptake inhibitors (SSRIs) have been investigated in the treatment of social phobia. Case reports and open-label trials have suggested considerable potential for the treatment of this condition. In the 2 double-blind, comparative, single-site studies published to date, sertraline hydrochloride and fluvoxamine maleate were more effective than placebo with relatively small sample sizes of 12 patients and 30 patients, respectively.

Based on these encouraging preliminary reports, the first double-blind, randomized, multicentered trial of paroxetine in patients with social phobia was undertaken. The trial was limited to patients with the generalized subtype of social phobia (GSP) because of its greater severity and more specific response (ie, lower placebo-response rate) compared with nongeneralized social phobia in prior treatment trials.

METHODS

Study Design

This was a double-blind, placebo-controlled trial in patients diagnosed as having GSP under the guidelines of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Investigators at 13 centers in the United States and Canada (see acknowledgement) participated in this 12-week study. The protocol was approved by the institutional review boards at all centers. After a complete description of the study to the patients, written, informed consent was obtained prior to enrollment. A total of 213 patients entered the screening phase of this study (although additional subjects were excluded at the prescreening phase based on obvious ineligibility for the protocol). A Structured Clinical Interview for the DSM-IV (SCID) (modified by M.B.S. and Andrea L. Hazen, PhD), which has been shown to reliably distinguish between generalized vs nongeneralized subtypes (k = 0.84; M.B.S. and Andrea L. Hazen, PhD, unpublished observations, July 1996), was used to confirm that GSP was the predominant diagnosis. In addition to meeting DSM-IV criteria for social phobia, patients were required to exhibit fear and/or avoidance of at least 4 social situations. At least 2 of these were required to involve interpersonal interactions.

Patient Eligibility

Eligible patients were 18 years of age or older; adults older than 65 years were permitted if they were able to tolerate a starting paroxetine dose of at least 20 mg/d. Patients who required concurrent psychoactive medication (except chloral hydrate for insomnia), narcotic analgesics, warfarin sodium, digitalis glycosides, phenytoin, cinetidine, or sulfonylurea derivatives were excluded. Patients who had taken any psychotropic agent or β-blockers within 14 days prior to the study were ineligible, as were those who...
had received depot neuroleptics within the previous 12 weeks. Also excluded were patients with any other Axis I diagnosis that was considered to be clinically predominant within the previous 6 months. Patients who met DSM-IV criteria for substance abuse or dependence within 3 or 6 months prior to this study, respectively, were excluded, as were those judged to be serious suicidal or homicidal risks. Additional reasons for exclusion were body dysmorphic disorder, history of seizure disorder, schizophrenia or bipolar affective disorder, any serious or uncontrolled medical illness or condition that precluded paroxetine use, electroconvulsive therapy within the previous 3 months, investigational drug use or participation in a clinical trial within the previous 12 months, and previous intolerance of or lack of response to paroxetine (no subject was excluded on this basis). Women who were pregnant, lactating, or not using a clinically acceptable method of birth control also were ineligible. Finally, patients with clinically significant abnormal laboratory or electrocardiographic findings that could not be resolved prior to baseline evaluations were not included.

### Blinding, Randomization, and Treatment

Following initial screening procedures, potential subjects entered a 1-week, single-blind, placebo run-in period, after which a baseline Clinical Global Impression (CGI) Global Improvement rating was performed. Patients who were rated no more than minimally improved (CGI Improvement rating >2) and who continued to meet all inclusion criteria were randomized to receive paroxetine or placebo (identical in appearance). Patients were randomly assigned in a balanced fashion to the 2 treatment groups (in blocks of 4) using a computer-generated randomization code for up to 300 patients. For the purposes of blinding, dosage was referred to as level 1 (20 mg), level 2 (30 mg), level 3 (40 mg), or level 4 (50 mg). Patients received an initial dose of level 1 medication once daily. After 2 weeks, the dosage could be increased to the next level (ie, in 10-mg increments) up to level 4 (ie, 50 mg/d) based on clinical response as determined by the treating physician. Dosage could be reduced to a minimum of level 1 (ie, 20 mg/d) at any time if the physician felt that adverse effects warranted this adjustment.

### Efficacy and Safety Evaluation

Patients were evaluated for safety and efficacy at weeks 1, 2, 3, 4, 6, 8, and 12. Adverse events were also assessed by telephone at week 10. The primary efficacy variables were (1) the percentage of responders at end point, defined as those rated on the CGI Global Improvement Item as 1 (very much improved) or 2 (much improved) and (2) the mean change from baseline at end point on the Liebowitz Social Anxiety Scale total score, which is a 24-question assessment of fear and avoidance of public and social situations. Secondary efficacy variables included mean changes from baseline at end point in the Social Avoidance and Distress Scale (a measure of social anxiety and discomfort); the Sheehan Disability Inventory for work, social life, and family life (a measure of quality of life); and the fear/anxiety and avoidance subscales of the Liebowitz Social Anxiety Scale. Safety analyses included routine adverse-event monitoring and vital-sign assessment.

### Statistical Methods

The proportion of patients achieving a dichotomous response (CGI Global Improvement rating of 1 or 2) and who continued to meet all inclusion criteria were randomized to receive paroxetine or placebo (identical in appearance). Patients were randomly assigned in a balanced fashion to the 2 treatment groups (in blocks of 4) using a computer-generated randomization code for up to 300 patients. For the purposes of blinding, dosage was referred to as level 1 (20 mg), level 2 (30 mg), level 3 (40 mg), or level 4 (50 mg). Patients received an initial dose of level 1 medication once daily. After 2 weeks, the dosage could be increased to the next level (ie, in 10-mg increments) up to level 4 (ie, 50 mg/d) based on clinical response as determined by the treating physician. Dosage could be reduced to a minimum of level 1 (ie, 20 mg/d) at any time if the physician felt that adverse effects warranted this adjustment.

### Efficacy and Safety Evaluation

Patients were evaluated for safety and efficacy at weeks 1, 2, 3, 4, 6, 8, and 12. Adverse events were also assessed by telephone at week 10. The primary efficacy variables were (1) the percentage of responders at end point, defined as those rated on the CGI Global Improvement Item as 1 (very much improved) or 2 (much improved) and (2) the mean change from baseline at end point on the Liebowitz Social Anxiety Scale total score, which is a 24-question assessment of fear and avoidance of public and social situations. Secondary efficacy variables included mean changes from baseline at end point in the Social Avoidance and Distress Scale (a measure of social anxiety and discomfort); the Sheehan Disability Inventory for work, social life, and family life (a measure of quality of life); and the fear/anxiety and avoidance subscales of the Liebowitz Social Anxiety Scale. Safety analyses included routine adverse-event monitoring and vital-sign assessment.

### Statistical Methods

The proportion of patients achieving a dichotomous response (CGI Global Improvement rating of 1 or 2) and who continued to meet all inclusion criteria were randomized to receive paroxetine or placebo (identical in appearance). Patients were randomly assigned in a balanced fashion to the 2 treatment groups (in blocks of 4) using a computer-generated randomization code for up to 300 patients. For the purposes of blinding, dosage was referred to as level 1 (20 mg), level 2 (30 mg), level 3 (40 mg), or level 4 (50 mg). Patients received an initial dose of level 1 medication once daily. After 2 weeks, the dosage could be increased to the next level (ie, in 10-mg increments) up to level 4 (ie, 50 mg/d) based on clinical response as determined by the treating physician. Dosage could be reduced to a minimum of level 1 (ie, 20 mg/d) at any time if the physician felt that adverse effects warranted this adjustment.
Improvement score of 1 or 2) was analyzed by logistic analysis using the categorical modeling procedure of the SAS system (SAS Statistical Software, Cary, NC); this model included treatment and investigator effects. Changes from baseline scores of the various efficacy scales were analyzed using parametric analysis of variance. The general linear model of the SAS system, including treatment and investigator effects, was used. Type III sums of squares were used. The treatment-by-investigator interaction was not significant for any variable and subsequently was removed from the models.

All statistical tests comparing paroxetine with placebo were 2-tailed and performed at an α of .05. Using a power (1-β) of 0.90 to detect a difference between paroxetine and placebo responders on the CGI Global Improvement Item, the target recruitment for the study was set at 180 patients with 90 per group. Efficacy analyses were carried out on the sample of patients with at least 1 postbaseline efficacy evaluation and those who had received at least 1 dose of double-blind medication (N = 183, referred to herein as the efficacy population). For patients who did not complete the entire study, the last evaluation during treatment was used as an estimate of the missing data (ie, last observation carried forward). Data are reported as mean values (SE), and 95% confidence intervals (CIs) are reported where appropriate.

RESULTS

Of the 213 patients who were screened, 187 patients were enrolled and randomized to either paroxetine (n = 94) or placebo (n = 93) treatment arms (Figure 1). The typical patient was relatively young (mean age, approximately 36 years) and white. No statistically significant differences between groups were detected with regard to demographic characteristics or mean baseline rating scale scores (Table 1). Though not excluded by the protocol, few subjects had current comorbid major depressive or panic disorder (Table 1).

Of the 187 patients randomized in this study, 4 patients received the drug but were lost to follow-up prior to the first efficacy evaluation. Therefore, the efficacy data for the remaining 183 patients (ie, the efficacy population) are reported. Safety assessments were obtained for all 187 patients who were randomized.

Premature Discontinuation

In the paroxetine group, 62 (66%) of 94 patients completed the 12-week trial. The most common reasons for patient withdrawal were adverse events (15% [14/94]) or lost to follow-up (13% [12/94]). In the placebo group, 72 (77%) of 93 patients (P = .03 vs paroxetine) completed the trial. The most common reason for discontinuation was lack of efficacy (11% [10/93]) (Table 2).

Efficacy Results

Fifty (55.0%) of 91 persons who received paroxetine and 22 (23.9%) of 92 persons who received placebo were much or very much improved at the end of treatment (odds ratio [OR], 3.88; 95% CI, 2.81-5.36). The proportion of paroxetine responders (ie, CGI Global Improvement score of 1 or 2) was significantly greater than placebo beginning at week 4 and continuing through week 12 (Figure 2). No interactions were found between sex and response (either on the CGI or on the measures listed below).

The mean change from baseline on the Liebowitz Social Anxiety Scale total score was more than twice as large in the paroxetine group (−30.5 ± 2.66; 39.1% decrease from mean baseline total score of 78.0) than in the placebo group (−14.5 ± 2.63; 17.4% decrease from mean baseline total score of 83.5), a difference of 21.7% (95% CI, 8.7%-34.7%) favoring paroxetine. Significant differences that were apparent by week 2 continued through the end of the study (Figure 3).

Paroxetine was significantly superior to placebo on 5 of 6 secondary efficacy measures (Liebowitz Social Anxiety Scale, avoidance and fear/anxiety subscales; Social Avoidance and Distress Scale; and Sheehan Disability Inventory, work and social life) (Table 3). Although the improvement from baseline at end point for the Sheehan Disability Inventory family life item was numerically greater with paroxetine (−1.0) than with placebo (−0.6), this difference was not statistically significant.

Medication Dosages

The mean dose of paroxetine at study end point was 36.6 mg (SD, 12.1 mg); mean dose of placebo at study end point was dose level 3.5 (SD, 0.90) (equivalent to 45 mg [SD, 18 mg]).

Adverse Experiences

The reported incidence and severity of adverse experiences in paroxetine-treated patients were as expected, and no unusual experiences were reported (Table 4). The most frequently occurring adverse experiences in paroxetine-treated patients were headache (37.2%), delayed ejaculation (36% of males), somnolence (26.6%), and nausea (25.5%).
placebo-treated patients, these events occurred at the rates of 32.2%, 0%, 9.7%, and 11.8%, respectively. Most adverse experiences were of mild to moderate intensity.

COMMENT

This is the first multicenter, double-blind, randomized study of an SSRI in social phobia (social anxiety disorder). The results clearly demonstrate that paroxetine treatment effectively reduces the symptoms and avoidance associated with generalized social phobia. Paroxetine was statistically superior to placebo on both primary efficacy criteria and on 5 of 6 secondary efficacy variables. Among the latter, it is noteworthy that disability associated with generalized social phobia improved significantly as demonstrated by significantly greater reductions in the Sheehan Disability Inventory work and social life subscales compared with placebo. Given the early age at onset and chronicity of this disorder, detecting a reduction in disability after a 12-week trial is noteworthy. It is hoped, but remains to be shown in future studies, that longer duration of treatment might result in even further consolidation of gains and reduction of functional impairment.

Paroxetine was well tolerated in this study as evidenced by the relatively low incidence of withdrawal because of adverse experiences (15%) and the lack of serious adverse experiences. The adverse-event profile is in concordance with the findings of other efficacy and safety studies of paroxetine and other SSRIs.

As reported in this study, paroxetine was clearly effective for generalized social phobia. The response to paroxetine therapy among patients with this most serious and recalcitrant form of social phobia is a rigorous demonstration of efficacy. Unfortunately, the lack of direct, comparative studies precludes between-treatment efficacy comparisons. To the extent that indirect comparisons are valid, the response rate to paroxetine in this generalized social phobia study (55% in the efficacy population) compares favorably with double-blind, placebo-controlled study response rates of 52% for moclobemide (severely ill subset), 68% for phenelzine sulfate (GSP subset), and 78% for clonazepam. The response rate to paroxetine in this study is particularly notable when the fact that this was a 13-center study is taken into account. In such studies, drug-placebo differences often tend to be less robust than those in the hands of highly experienced investigators at single-center sites.

Although the benzodiazepines, MAOIs, and other pharmacological treatments have been shown to be effective for generalized social phobia, there are some relative disadvantages as well. High-potency benzodiazepines have limited antidepressant effects, which is an important consideration in a disorder for which major depression is commonly comorbid. The benzodiazepines have the potential for abuse or misuse and can also cause physical dependence with long-term use. Nonselective MAOIs sometimes cause unpleasant activation or a hypomania-like effect, postural hypotension, and other adverse effects and require dietary restriction to avoid hypertensive reactions; all of these can limit clinical acceptance by physicians and patients. In this study, paroxetine had a side effect profile consistent with its use in other mood and anxiety disorders. In general, these side effects tend to be benign, leading to good patient tolerance (with the possible exception of the relatively high rate of abnormal ejaculation in men; although only 2 of 16 men with this side effect elected to discontinue treatment prematurely as a result). Based on its efficacy, safety, and relatively good tolerability, paroxetine can be considered among the first-line treatments for social phobia.

Given the experience that all SSRIs tend to be effective for those conditions in which any have demonstrated efficacy, we would surmise that efficacy for the treatment of generalized social phobia will eventually be shown to extend to other SSRIs as well.

There are a number of limitations to this study. Social phobia is a chronic, potentially disabling disease that may require long-term therapy. By design, this study did not assess treatment effects beyond the acute, 12-week treatment period. It is possible, albeit not yet proven, that a longer course of therapy could result in continued and even greater reductions in impairment and in improvement in quality of life. A previous study suggested that relapse rates may be very high when treatment with paroxetine is discontinued after only 12 weeks of treatment. Further studies of long-term treatment with paroxetine are warranted to determine optimal duration of therapy, efficacy in sustaining remission, and the role of concomitant psychotherapy (eg, cognitive behavioral therapy), which can be effective for many patients with this condition.

Another limitation of this study is its inability to definitively demonstrate that reductions in social phobic symptoms were not merely a secondary manifestation of an antidepressant effect. Although few patients (4.8%) in this study had co-morbid major depressive disorder at the time of entry into the study, it is possible that other patients may have had subsyndromal symptoms that could be antidepressant responsive. The next study with an SSRI for social phobia should measure depressive symptoms throughout the trial to determine whether or not these appear to drive the reduction in social anxiety symptoms.

In conclusion, this controlled clinical trial confirmed the suggestions from earlier reports and demonstrated that paroxetine is an effective and well-tolerated treatment for patients with generalized social phobia. Future research should address questions of optimal dose and duration of treatment, as well as the potential utility of educational and psychotherapeutic strategies to augment response and/or reduce relapse.

Financial support for this study was provided by SmithKline Beecham Pharmaceuticals, Collegeville, Pa.

The authors are grateful to the following investigators at the 13 sites who participated in this study: Bijan Bastani, MD (Comprehensive Psychiatric Services, Beachwood, Ohio), Catheryn Clary, MD (Clary Research Associates, New Castle, Del), Larry Davis, MD (The Davis Clinic, Indianapolis, Ind), Eugene DuBoff, MD (Center for Behavioral Medicine, Denver, Colo), Robert DuPont, MD (Institute for Behavior and Health, Rochville, Md), James Ferguson, MD (Pharmacology Research Corporation, Salt Lake City, Utah), James Jefferson, MD (The Dean Foundation for Health Research and Education, Madison, Wis), Richard Kavoussi, MD (Eastern Pennsylvania Psychiatric Institute, Philadelphia), Michael Liebowitz, MD (New York State Psychiatric Institute, New York), R. Bruce Lydiard, PhD, MD (Medical University of South Carolina, Charleston), Robin Renshon, MS (Western Canada Behavioural Research Centre, Calgary, Alberta), Edward Schweizer, MD (University of Pennsylvania, Philadelphia), and Murray Stein, MD (University of California-San Diego, La Jolla).

References


