Efficacy of Sertraline in Severe Generalized Social Anxiety Disorder: Results of a Double-Blind, Placebo-Controlled Study

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Background: Generalized social anxiety disorder is an early onset, highly chronic, frequently disabling disorder with a lifetime prevalence of approximately 13%. The goal of the current study was to evaluate the efficacy and tolerability of sertraline for the treatment of severe generalized social anxiety disorder in adults.

Method: After a 1-week single-blind placebo lead-in period, patients with DSM-IV generalized social phobia were randomly assigned to 12 weeks of double-blind treatment with flexible doses of sertraline (50–200 mg/day) or placebo. Primary efficacy outcomes were the mean change in the Liebowitz Social Anxiety Scale (LSAS) total score and the responder rate for the Clinical Global Impressions-Improvement scale (CGI-I), defined as a CGI-I score ≤ 2. Data were collected in 2000 and 2001.

Results: 211 patients were randomly assigned to sertraline (intent-to-treat [ITT] sample, 205), and 204 patients, to placebo (ITT sample, 196). At week 12, sertraline produced a significantly greater reduction in LSAS total score compared with placebo (mean last-observation-carried-forward [LOCF] change from baseline: –31.0 vs. –21.7; p = .001) and a greater proportion of responders (CGI-I score ≤ 2: 55.6% vs. 29% among week 12 completers and 46.8% vs. 25.5% in the ITT-LOCF sample; p < .001 for both comparisons). Sertraline was well tolerated, with 7.6% of patients discontinuing due to adverse events versus 2.9% of placebo-treated patients.

Conclusion: The results of the current study confirm the efficacy of sertraline in the treatment of severe social anxiety disorder.

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Social anxiety disorder (social phobia) is one of the most common of all the anxiety disorders, with a 1-year prevalence estimated to range from approximately 1.7% (95% CI: 1.5% to 1.9%)[1] to 7.4% (6.6% to 8.2%)[2] and a lifetime prevalence of 13.3%.[2,3]

DSM-IV identifies 2 subtypes of social phobia, generalized and specific.[4] Generalized social phobia is typically chronic with an onset in early adolescence.[2,5] Its course is frequently complicated by comorbidity with other mood and anxiety disorders, though social phobia tends to have the earlier age at onset and to represent a risk factor for subsequent development of other mood and anxiety disorders.[1,2,5–8] In one study,[7] the onset of social phobia preceded the first episode of depression by a mean of 12 years and represented a 3-fold increased morbid risk. Compared with nongeneralized social phobia, the generalized subtype is more likely to have a genetic/familial diathesis[9–11] and to be associated with significantly greater functional and quality of life (QOL) impairment, including lower educational attainment, lower social support and marriage, and lower income.[2,7,12–17] Despite extensive negative psychosocial consequences, the proportion of patients who seek treatment tends to be much lower than

for other mood and anxiety disorders,[1,18–20] accounting for less than 20% of individuals with social phobia.[1,2,19]

The past decade has witnessed the transformation of social phobia from a disorder with low diagnostic recognition and a dearth of treatment research to an illness that has engendered numerous placebo-controlled clinical trials. To date, evidence for efficacy exists for 4 classes of treatment: (1) monoamine oxidase inhibitors[21–26]; (2) benzodiazepines (and gabapentin)[21,27–29]; (3) selective serotonin reuptake inhibitor (SSRI) antidepressants (most notably paroxetine,[30–33] fluvoxamine,[34] and sertraline[35–37]); and (4) cognitive-behavioral therapy.[21,35,38]

Earlier treatment studies tended to include both generalized and nongeneralized social phobia subtypes, resulting in a relatively heterogeneous treatment sample. More recently, study entry has been restricted to patients meeting criteria for the generalized subtype. As noted above, sertraline has established efficacy based on the results of 2 previous placebo-controlled trials in generalized social phobia.[35,36] Few available studies have examined patients suffering from the more severe and disabling end of the social anxiety spectrum.

The goals of the current study were to further establish the efficacy of sertraline among patients with severe generalized social anxiety disorder and to examine QOL outcomes associated with the more severely socially phobic patients.

METHOD

Patients

The study was conducted at 20 psychiatric outpatient clinics in the United States. Study entry criteria required patients to be aged 18 years or over with a primary diagnosis of generalized social phobia of at least 2 years' duration and a Liebowitz Social Anxiety Scale (LSAS)[39] score ≥ 68 at baseline. Social phobia was diagnosed using the Structured Clinical Interview for DSM-IV.[40] 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 involving interpersonal interactions). Women of childbearing potential were required to have negative results on a serum β–human chorionic gonadotropin pregnancy test and to be using a medically accepted form of contraception. Patients were excluded if they met DSM-IV criteria in the previous 6 months for substance abuse or substance dependence, body dysmorphic disorder, major depressive disorder, dysthymia, panic disorder, posttraumatic stress disorder, or an eating disorder; if they reported any current or past diagnosis of schizophrenia, psychotic disorder, bipolar disorder, or obsessive-compulsive disorder (OCD); or if they met criteria for a primary diagnosis of generalized anxiety disorder. Patients were also excluded for the following reasons: (1) 17-item Hamilton Rating Scale for Depression (HAM-D)[41] score of ≥ 14 or item 1 (depressed mood) rating moderate or greater in severity; (2) currently reporting serious suicidal or homicidal risk; (3) currently receiving specific behavioral or supportive therapy for social phobia or another anxiety disorder; (4) any history of seizure disorder; (5) any serious or uncontrolled medical illness or condition that precludes sertraline use; (6) women who were pregnant, nursing, or lactating; (7) receiving any concomitant therapy with any psychotropic drug or with any drug with a psychotropic component, except zolpidem for insomnia.

Study procedures were explained to patients, and written informed consent was obtained. The study and the consent form were approved by the institutional review board at each study site.

Study Design

After screen evaluation, study patients completed 1 week of single-blind placebo treatment. Patients who continued to meet all inclusion and exclusion criteria were then randomly assigned in a double-blind fashion to 12 weeks of double-blind treatment with flexible doses of sertraline or matching placebo. Sertraline treatment was initiated at a daily dose of 25 mg, which was increased at week 1 to 50 mg. After 2 weeks at a daily dose of 50 mg, patients with insufficient clinical response (based on the clinical judgment of the investigator) but good tolerability were permitted to increase to 100 mg, and then by 50-mg increments per week to a maximum dose of 200 mg/day.

Efficacy and Safety Evaluations

Patients were evaluated for medication safety and efficacy at weeks 1, 2, 3, 4, 6, 8, and 12. The primary efficacy variables consisted of (1) the percentage of responders at endpoint, defined by a Clinical Global Impressions-Improvement scale (CGI-I)[42] score ≤ 2 ("very much" or "much" improved), and (2) mean change from baseline to endpoint on the LSAS total score.[39] The LSAS is a 24-item scale that evaluates both the fear and anxiety evoked by a range of social situations such as eating in public places, speaking up at a meeting, or talking to people in authority, as well as the degree of avoidance associated with each situation. Investigators received training in completion of the LSAS that included consensus ratings of videotaped LSAS interviews. The lead author (M.L.) reviewed videotaped LSAS interviews to provide additional quality assurance.

Secondary efficacy variables included mean changes from baseline to endpoint on the following investigator-rated scales: (1) fear/anxiety and avoidance subscales of the LSAS, (2) Clinical Global Impressions-Severity of Illness scale (CGI-S),[42] (3) HAM-D,[41] (4) Hamilton Rating Scale for Anxiety (HAM-A),[43] and (5) Duke Brief Social Phobia Scale (BSPS),[44,45] an 11-item scale assessing the severity of social phobia symptoms across 3 domains, fear, avoidance, and physiologic.

The effect of study treatment on functional status and QOL was evaluated using 3 patient-rated measures: (1) the Sheehan Disability Scale,[46] which evaluates the severity of impairment in 3 dimensions, work, social life, and family life, on a 10-point scale; (2) the Endicott Work Productivity Scale[47]; and (3) the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[48] which measures satisfaction with common domains of work and social function.

At each study visit, patients were questioned and data were recorded regarding any perceived adverse effects, which were rated as to severity and date and time of onset and offset. Vital signs and weight were also recorded at each study visit. Electrocardiograph (ECG) and laboratory tests were performed prior to randomization and at the end of double-blind treatment, or earlier if the patient discontinued prematurely.

Statistical Methods

Efficacy analyses were carried out on the intent-to-treat (ITT) group, which was defined as subjects who had received at least 1 dose of double-blind medication and at least 1 postbaseline primary efficacy evaluation.

The number of patients calculated to be necessary to ensure 85% power, at an alpha level of .05 (2-sided), to detect a 10-point difference in the change from baseline to endpoint in LSAS score (assuming SD = 30) and a 20% difference in response rate (CGI-I score of 1 or 2) was approximately 200 per treatment group.

Center-stratified Cochran-Mantel-Haenszel methods and analysis of variance were used to compare baseline characteristics of the patients receiving sertraline or placebo. The main efficacy analyses were performed by using an analysis of covariance (ANCOVA), with baseline measures as covariates. ANCOVA models included the effects of treatment and site. All statistical tests were 2-sided and assumed a .05 level of significance. The frequency of adverse events and the proportion of patients who discontinued due to adverse events were compared between treatment groups with Fisher exact tests. Changes in vital signs were compared between treatment groups with Wilcoxon rank sum tests.

Repeated-measures analysis was performed to examine treatment difference over time for change from baseline in LSAS total score and for CGI-I score. Generalized estimating equation methodology using an exchangeable correlation model was employed to fit repeated-measures models. These methods accurately account for correlations among observations measured across visits on the same patient.

RESULTS

Patient Characteristics

The typical study patient (Table 1) was a well-educated, employed male in his thirties who was not currently married and who had experienced several decades of social anxiety dating back to early adolescence. The global severity of illness was rated as being in the markedly ill range (CGI-S score, 4.8 ± 0.7). Patient characteristics were similar in both treatment groups, though there was a somewhat ($p < .10$) higher likelihood for patients in the sertraline treatment group to have never been married.

Table 1. Demographic and Clinical Information on Patients With Severe Generalized Social Anxiety Disorder

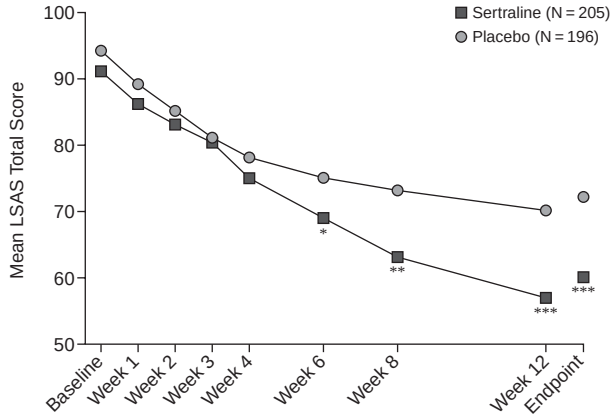
Patient Variable	Sertraline (N = 211)	Placebo (N = 204)
Female, %	39.8	41.2
Age, mean ± SD, y	35.1 ± 10.6	35.0 ± 10.6
Ethnicity, %[a]		
White	66.8	76.5
Black	12.8	11.3
Hispanic	13.3	5.4
Other	7.1	6.9
Marital status, %		
Married or living with partner	36.5	44.6
Never married	48.3	39.2
Divorced, separated, or widowed	15.2	16.2
Current occupational status, %		
Employed	82.5	86.3
Unemployed	6.6	5.4
Student, homemaker, or retired	10.9	7.8
Previous history of depression, %	15	20
Previous history of anxiety disorder, %	3	3
Age at onset of social phobia, mean ± SD, y	13.4 ± 6.8	13.0 ± 7.3
Duration of social phobia, mean ± SD, y	20.8 ± 12.0	21.5 ± 11.8
Baseline LSAS total score, mean ± SD[a]	91.3 ± 15.9	93.9 ± 16.0
Q-LES-Q		
Baseline score, mean ± SD	68.9 ± 10.8	71.0 ± 10.1
Proportion of patients within 10% of community norms, %	28	37
Proportion of patients ≥ 2 SD units below community norms, %	22	20

[a]Based on intent-to-treat sample, sertraline N = 205; placebo N = 196.
Abbreviations: LSAS = Liebowitz Social Anxiety Scale, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

Study Treatment and Patient Disposition

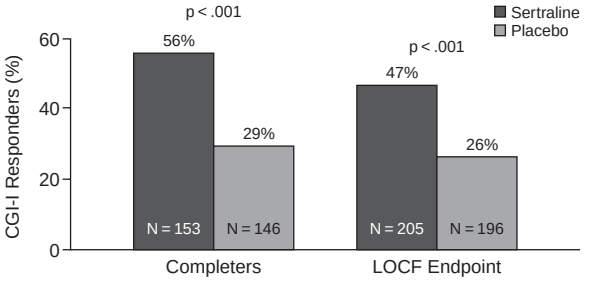
A total of 520 patients were screened to obtain 415 who met all study entry criteria and were randomly assigned to sertraline (N = 211) or placebo (N = 204). The ITT–last-observation-carried-forward (LOCF) sample evaluated for efficacy was composed of 205 patients receiving sertraline and 196 patients receiving placebo. One hundred fifty-two (72%) of the 211 patients treated with sertraline and 141 (69%) of the patients treated with placebo completed 12 weeks of double-blind treatment. Reasons for premature discontinuation during treatment with sertraline and placebo, respectively, included the following: withdrawal of consent, 11 (5.2%) versus 17 (8.3%); lost to follow-up, 17 (8.1%) versus 10 (4.9%); adverse events, 16 (7.6%) versus 6 (2.9%); insufficient clinical response, 5 (2.4%) versus 9 (4.4%); protocol

Figure 1. Liebowitz Social Anxiety Scale (LSAS) Mean Total Score for Intent-to-Treat Sample of Patients With Severe Generalized Social Anxiety Disorder[a]



[a]Endpoint value based on analysis of covariance with treatment, baseline, and center as covariates; all other significance testing based on generalized estimating equation repeated-measures analysis.
*p = .029.
**p = .003.
***p < .001.

Figure 2. CGI-I Responder Status (CGI-I score ≤ 2) at Week 12 Endpoint Among Patients With Severe Generalized Social Anxiety Disorder



Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, LOCF = last observation carried forward.

violation, 3 (1.4%) versus 3 (1.5%); and miscellaneous other reasons, 7 (3.3%) versus 18 (8.8%).

Consistent with the gradual titration schedule mandated by the protocol, the mean ± SD daily dose of sertraline was 49.6 ± 1.9 mg at week 3 and 114.0 ± 21.1 mg at week 6. The mean maximal daily dose of sertraline was 158.8 ± 54.0 mg, with 71% of patients using a maximal dose ≥ 150 mg. The mean equivalent dose of placebo (1 tablet = 50 mg) was 174.9 ± 29.2.

Treatment Response

Primary outcome measures. Sertraline showed statistically significant superiority on both a priori primary outcome parameters based on an LOCF and a completer analysis. Treatment with sertraline resulted in a clinically significant (mean change score, –12.1 ± 1.2) reduction in the LSAS total score by week 3 that reached statistical significance at week 6 compared with placebo based on a repeated-measures analysis (Figure 1). At 12-week endpoint, significantly more patients treated with sertraline had achieved CGI-I responder status compared with those receiving placebo using both LOCF and completer analyses (Figure 2). An LOCF endpoint comparison of mean CGI-I scores also found sertraline to have significantly greater efficacy than placebo (Table 2). The effect size for sertraline based on the LSAS change score was 0.43.

Secondary outcome measures. Sertraline demonstrated significantly superior efficacy across most of the secondary outcome variables in the ITT-LOCF sample (Table 2) including the LSAS-fear/anxiety, LSAS-avoidance, and BSPS. Percentage reductions in score (compared with baseline severity) for sertraline versus placebo, respectively, were 24% versus 19% for LSAS-fear at week 6 and 36% versus 22% at week 12. Similarly, percentage reductions for LSAS-avoidance were 26% versus 21% at week 6 and 40% versus 24% at week 12. The physiology subscale of the BSPS showed a 40% reduction at endpoint with sertraline compared with a 32% reduction with placebo, but this difference did not achieve significance (Table 2).

Functional and QOL Measures

In the ITT-LOCF sample, improvement in symptoms of social anxiety was associated with significant improvements in both QOL, as measured by the Q-LES-Q, and social functioning, as measured by the Sheehan Disability Scale (Table 3). Improvement was seen on the Endicott Work Productivity Scale, but it did not achieve statistical significance versus placebo. Q-LES-Q scores were also obtained at week 6 and showed significant improvement at this early timepoint; mean ± SE change from baseline was +4.0 ± 0.67 versus +1.8 ± 0.69 (p = .022). A subgroup (N = 87) identified post hoc as having the highest level of QOL impairment, based on a baseline Q-LES-Q total score that was at least 2 standard deviations below normative community mean values, showed highly significant improvement on sertraline treatment (+12.83 ± 15.69) compared with placebo treatment (+5.17 ± 8.66), with mean week 12 Q-LES-Q scores of 67.23 ± 14.01 versus 61.53 ± 9.67 (p < .05). Thirty-seven percent of patients in this severely impaired subgroup who were treated with sertraline achieved normative QOL at the end of acute treatment, compared with 11% of those receiving placebo (p < .05).

Treatment Tolerability

Treatment-emergent adverse events occurring at a rate of > 10% were as follows for sertraline and placebo,

Table 2. Efficacy Variables at Baseline and Endpoint for Patients With Severe Generalized Social Anxiety Disorder (ITT-LOCF)[a]

Efficacy Variable	Sertraline (N = 205)	Placebo (N = 196)	p Value
LSAS			
Total score			
Baseline	91.3 ± 15.9	93.9 ± 16.0	
Endpoint	60.3 ± 28.1	72.2 ± 27.8	.001
Fear/anxiety			
Baseline	46.3 ± 8.2	47.7 ± 8.0	
Endpoint	31.3 ± 14.1	37.4 ± 13.7	.001
Avoidance			
Baseline	45.0 ± 8.5	46.2 ± 8.9	
Endpoint	29.0 ± 14.6	34.8 ± 14.6	.001
BSPS			
Total score			
Baseline	48.1 ± 8.6	48.5 ± 8.6	
Endpoint	32.6 ± 14.5	37.8 ± 14.5	.001
Fear			
Baseline (total score)	19.8 ± 3.7	19.9 ± 3.7	
Endpoint	13.5 ± 6.1	15.9 ± 6.0	.001
Avoidance			
Baseline (total score)	20.4 ± 3.8	20.8 ± 3.9	
Endpoint	14.2 ± 6.4	16.5 ± 6.3	.001
Physiological			
Baseline (total score)	7.8 ± 3.6	7.7 ± 3.6	
Endpoint	4.9 ± 3.8	5.4 ± 3.8	.129
HAM-A			
Baseline	10.5 ± 6.1	9.3 ± 5.8	
Endpoint	7.4 ± 5.0	8.1 ± 5.3	.041
HAM-D			
Baseline	6.4 ± 3.3	6.2 ± 3.4	
Endpoint	5.3 ± 3.9	6.0 ± 4.0	.042
CGI-Severity of Illness			
Baseline	4.8 ± 0.7	4.8 ± 0.7	
Endpoint	3.6 ± 1.2	4.0 ± 1.2	.004
CGI-Improvement (endpoint)	2.6 ± 1.1	3.1 ± 1.1	.001

[a]Values are shown as mean ± SD.
Abbreviations: BSPS = Duke Brief Social Phobia Scale, CGI = Clinical Global Impressions scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, ITT = intent to treat, LOCF = last observation carried forward, LSAS = Liebowitz Social Anxiety Scale.

Table 3. Quality of Life/Functional Impairment Measures at Baseline and 12-Week Endpoint: Results for Sertraline Versus Placebo in Patients With Severe Generalized Social Anxiety Disorder[a]

Efficacy Variable	Sertraline (N = 205)	Placebo (N = 196)	p Value[b]
Q-LES-Q			
Baseline	68.9 ± 10.8	71.0 ± 10.1	
Endpoint	74.9 ± 11.9	72.5 ± 11.1	.001
SDS			
Work			
Baseline	4.9 ± 2.8	5.0 ± 2.8	
Endpoint	3.1 ± 2.5	4.0 ± 2.6	.002
Social life/leisure activities			
Baseline	6.6 ± 2.6	6.6 ± 2.7	
Endpoint	4.4 ± 3.1	5.1 ± 2.8	.040
Family life/home responsibilities			
Baseline	3.9 ± 2.6	3.6 ± 2.6	
Endpoint	2.6 ± 2.3	3.1 ± 2.4	.009
Endicott Work Productivity Scale			
Baseline	32.4 ± 14.4	29.8 ± 16.9	
Endpoint	26.5 ± 15.1	28.0 ± 15.8	.070

[a]Values are shown as mean ± SD. Results are based on an intent-to-treat, last-observation-carried-forward analysis.
[b]Based on an analysis of covariance model including treatment, center, and baseline terms.
Abbreviations: Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SDS = Sheehan Disability Scale.

respectively: insomnia (24.4% vs. 10.1%), loose stools (20.6% vs. 4.0%), nausea (16.7% vs. 6.5%), dizziness (16.7% vs. 5.5%), dry mouth (14.4% vs. 3.5 %), sweating (11.5% vs. 1.5%), and ejaculatory dysfunction (men, 14.3% vs. 0%).

There were no significant differences between sertraline and placebo in the incidence of clinically significant laboratory test results, ECG findings, vital signs, or weight change. Over 3 months of study treatment, 1 patient on sertraline treatment and 6 patients on placebo treatment gained ≥ 7% over their baseline body weight.

DISCUSSION

The results of the current study confirm the efficacy of sertraline for the treatment of social anxiety disorder established in 2 previous double-blind, placebo-controlled trials.[35,36] Use of a stringent symptom severity criterion (baseline LSAS score ≥ 68) for study entry resulted in a study sample with a higher degree of illness severity (mean LSAS score = 93) than has been reported in most previous double-blind, placebo-controlled trials, in which the baseline LSAS score is typically in the mid-80s.[29–33,49] The specificity of social anxiety as a distinct disorder is underscored by the low baseline scores on the HAM-A (mean total score = 10) and the HAM-D (mean total score = 6), despite a mean baseline LSAS score that was severe. In contrast, treatment studies of generalized anxiety disorder that similarly exclude patients with major depressive disorder typically report baseline HAM-D scores in the range of 12 to 15.

In this severely ill patient group, sertraline treatment showed consistently significant efficacy compared with placebo across all primary outcome measures (Figures 1 and 2) and most secondary outcome measures (Tables 2 and 3). The reduction in symptom severity on the LSAS achieved by sertraline was equivalent in magnitude (approximately 33%) across the 3 major social phobia outcome domains: social anxiety/fearfulness, physiologic symptoms of anxiety, and behavioral avoidance (Table 2).

Despite the baseline symptom severity of the current treatment sample, the degree of QOL impairment reported by patients was relatively low (mean Q-LES-Q score = 69; Table 1), in the same range as for panic disorder.[50,51] The explanation for this is uncertain. We speculate that it may be due to the fact that the QOL instrument used in the current study is based on self-perception and self-ratings: because of the early age at onset (mean = 13 years), patients have largely adapted to their illness and perceive it as part of their personality. This hypothesis is consistent

with other research that finds early age at illness onset to be associated with low medical help-seeking in anxiety disorders.[52,53] With these caveats in mind, improvement in social phobic symptoms was associated with significant functional and QOL improvement for subjects treated with sertraline versus those treated with placebo (Table 3). The magnitude of the improvement in QOL was in the same range that has been reported in previous acute treatment studies.[30–33] This magnitude of improvement (30%–40%, for example, on the Sheehan Disability Scale) is notably less than the improvement reported during panic disorder treatment studies of comparable duration, which typically is in the range of 50% to 65% on the Sheehan Disability Scale.[54,55] This somewhat lower/slower improvement in QOL has been noted in previous reviews of QOL across anxiety disorders.[17] It should be emphasized that the patients in the current treatment sample were typically very severely and chronically ill. In the subgroup reporting the most severe baseline impairment in QOL (≥ 2 standard deviations below the community norm), 12 weeks of sertraline treatment was still associated with attainment of QOL community norms in 37% of patients compared with 11% of placebo-treated patients ($p < .05$).

The effect size achieved by sertraline in the current study, 0.43, is comparable to the effect sizes previously reported for paroxetine.[30–32] The combined results from the large placebo-controlled trials of SSRIs that are now available[30–37,56] provide an emerging perspective on social phobia as a treatable illness, but one in which the magnitude of symptomatic and QOL response to acute treatment is somewhat less than what is observed for such illnesses as major depressive disorder or panic disorder. It is unusual for the average endpoint improvement in the severity of social anxiety symptoms to be greater than 50%. While this degree of improvement after acute pharmacologic therapy is substantial and is associated with significant corollary improvement in functional and QOL measures, it should be emphasized that significant residual symptoms remain, with mean LSAS scores typically > 50. In light of this, the management of social anxiety disorder might usefully be compared with the management of OCD, another chronic illness in which acute treatment can only be considered a first step on the road to remission. For example, in a large recent OCD trial,[56] patients treated with sertraline improved from a mean Yale-Brown Obsessive Compulsive Scale (YBOCS) score of 26.1 ± 4.2 at baseline to a score of 15.9 ± 7.3 at the end of 16 weeks of acute treatment. Continuation pharmacologic treatment with sertraline and no psychotherapy resulted in substantial further improvement on the YBOCS.

Given the degree of residual symptoms in social phobia, there is a need for similar long-term treatment studies, not simply to establish the relapse prevention benefits of treatment, but more pressingly to determine the extent to which initial response might convert to remission given more time. The only available study of an SSRI for the long-term treatment of social phobia[57] found sertraline to have highly significant relapse prevention efficacy. The study also found that patients continued to have reductions in social anxiety symptoms, even after 20 weeks of initial treatment: the BSPS total score showed an additional 11% improvement during the course of 24 weeks of continued long-term treatment. The improvement in the BSPS-avoidance factor showed the most late-onset improvement (24%), suggesting that this clinical outcome domain may well require very long term therapy to overcome decades-long ingrained behavioral patterns. It should be noted, though, that this study was designed as a relapse prevention study and enrollment was limited to patients who had achieved a significant response during acute treatment. The design, therefore, does not fully address whether continuation therapy is an effective strategy for optimizing the efficacy of acute treatment.

Other strategies for optimizing acute response also need to be evaluated, including dose escalation, addition of adjunctive therapies, and switching treatment. A previous placebo-controlled study[35] found that adjunctive behavioral therapy was associated with an approximately 10% to 15% higher rate of full response than was achieved by sertraline monotherapy. The parallel-group design of this study, though, did not address the question of whether the addition of adjunctive therapy would convert partial responders to full responders, or responders to remitters.

Sertraline was generally well tolerated in the current study, resulting in a relatively low discontinuation rate due to adverse events (7.6%) that was no different from that of placebo. The lack of weight gain on sertraline during this 12-week trial is consistent with the lack of weight gain reported in previous long-term treatment studies in both social anxiety disorder[36,37] and depression.[58] Weight gain has been shown to be one of the most common reasons for medication discontinuation during the long-term treatment of anxiety disorders.[59] The lack of clinically meaningful weight gain on sertraline treatment, in conjunction with its overall efficacy and tolerability profile, makes it a good first-line treatment for social anxiety disorder.

In conclusion, the results of the current study confirm the efficacy of sertraline in the treatment of generalized social phobia, among a group of highly chronic patients whose illness was at the marked-to-severe end of the clinical spectrum. Treatment with sertraline was well tolerated and was associated not only with improvement in symptoms, but also with improvement in functional and QOL measures.

Drug names: fluvoxamine (Luvox and others), gabapentin (Neurontin), paroxetine (Paxil), sertraline (Zoloft), zolpidem (Ambien).

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